Setting the Stage: New Directions for Low-Dose Radiation Research

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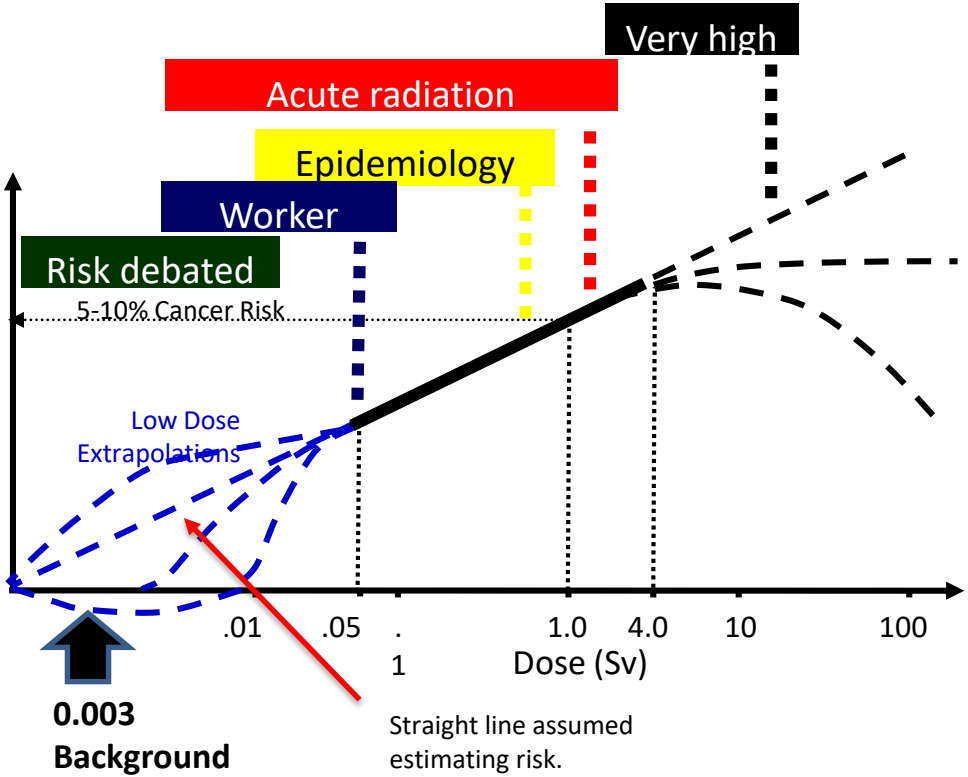
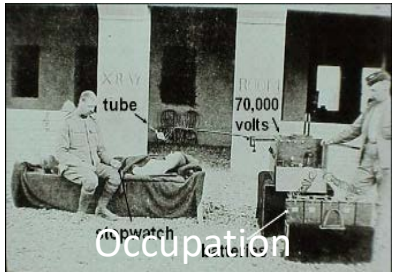
This talk addresses the following questions:

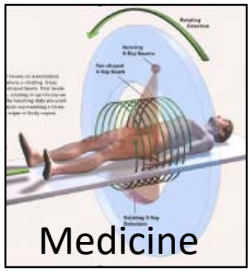
- How can epidemiology contribute to further understanding risks?
- What are some limitations and how can these be overcome?
- What are your views on research priorities for low dose radiation research?

The sources of radiation exposures vary and the magnitude of health risks from low-dose radiation exposure is uncertain



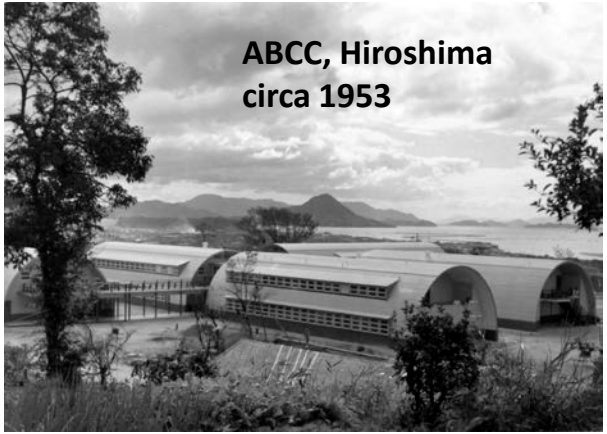
Graphic courtesy N Coleman





Images courtesy L Dauer

RERF cohorts have been the primary sources for determining health risks of radiation exposure



1946 Children's Cohort: 80,000 "F1"

Clinic: 12,000 (2002)

1945 In utero Cohort: 3,600

Clinic: 1,100 (1958)

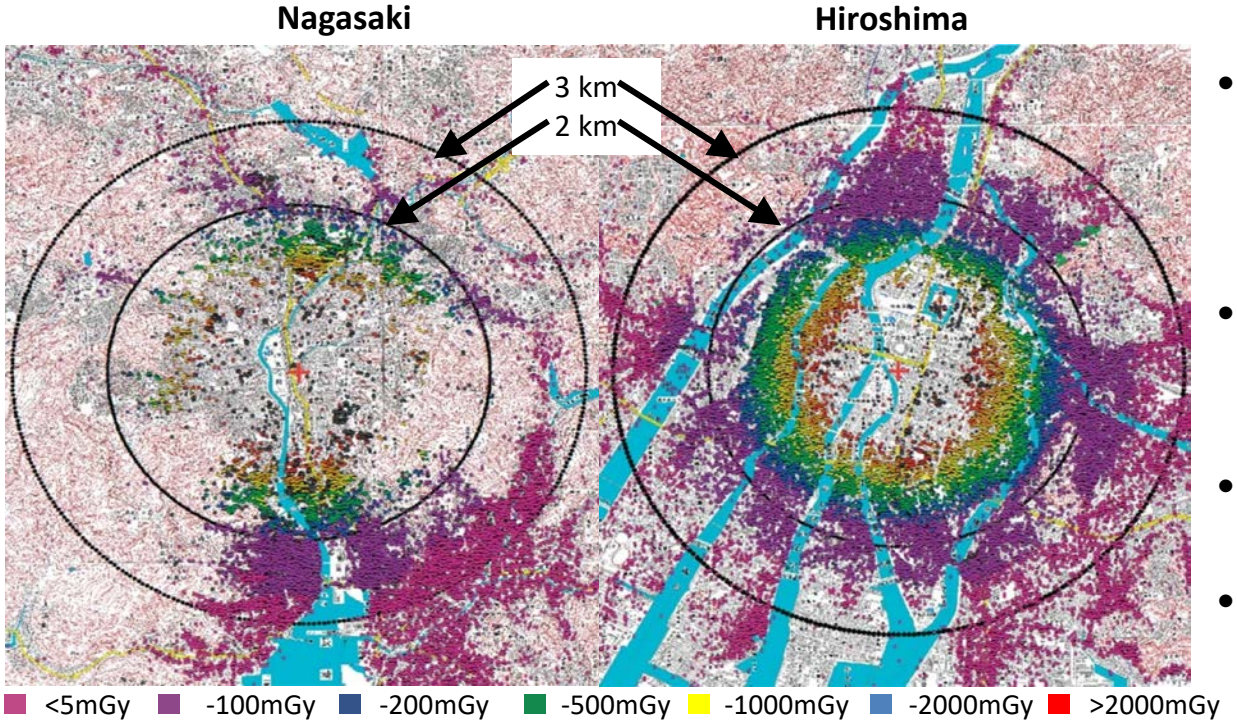
1950 Life Span Study: 120,000 "LSS"

Clinic: 20,000 (1958) Adult Health Study "AHS"

Images courtesy of E Grant

放影研 RERF

RERF cohort studies have informed low dose radiation protection standards issues of extrapolating risk from war-torn Japan



- Radiation is acute high dose rate with geocoded location for all cohort members at time of bombing
- Large nationwide cohort across age span with long-term follow-up
- Sensitivities in biospecimen sharing
- Difficulties in extrapolating risk from war-torn Japan

Funding: RERF is a public interest foundation funded by the Japanese Ministry of Health, Labor and Welfare (MHLW) and the US Department of Energy (DOE).

放影研
RERF

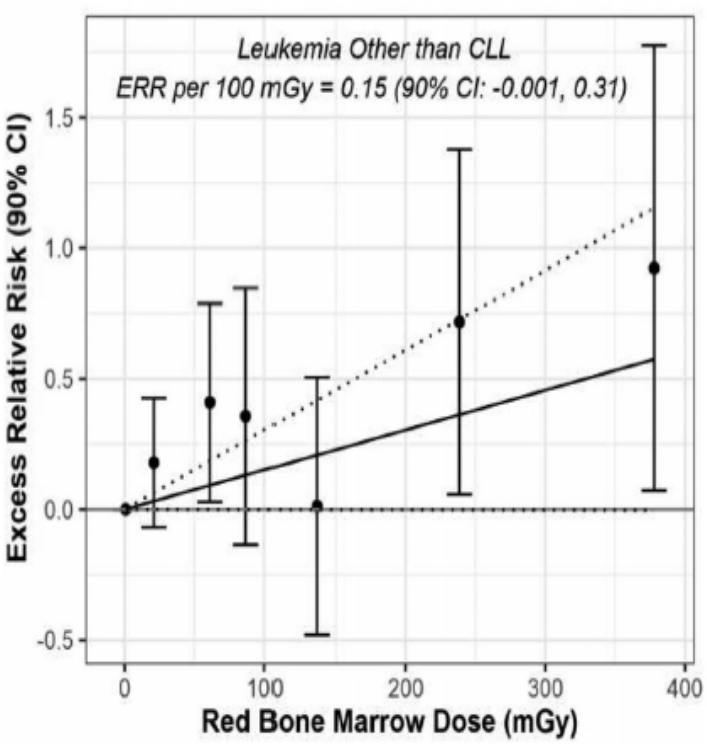
The Million Person Study (MPS): a nation-wide study of one Million U.S. Radiation Workers and Veterans

• Manhattan Project and beyond (DOE)	260,000
• Atomic Veterans (DOD, US Navy)	115,000
• Nuclear Power Plant Workers (NRC)	135,000
• Industrial Radiographers (NRC)	130,000
• Medical Radiation Workers (NASA)	>110,000
• Nuclear Submariners & other (US Navy)	>200,000
• Radium Dial Workers (DOE)	3,200

Funding: DOE (DE-AU0000042,DE-AU0000046), NASA(80NSSC17M0016, 80NSSC19M0161), U.S. Navy (N00024-17-C-4322), CDC (5 NUE1EH001315), NRC-HQ-60-14-G-0011

Boice et al. *The Million Person Study, Whence it Came and Why*. IJRB March 2019, Slide courtesy of L Dauer

The MPS a cohort of cohorts provides risk estimates by type of exposure, but lacks individual level risk factor data



Data Collection: Assembly of 34 established radiation exposed workers from 1913-present => 1,000,000+ workers.

Dosimetry: Records, registries, Landauer. Average absorbed dose over time

Biospecimens: Limited, N/A for majority

Outcome: Vital status thru NDI, linkage with CMS (Medicare/Medicaid claims data)

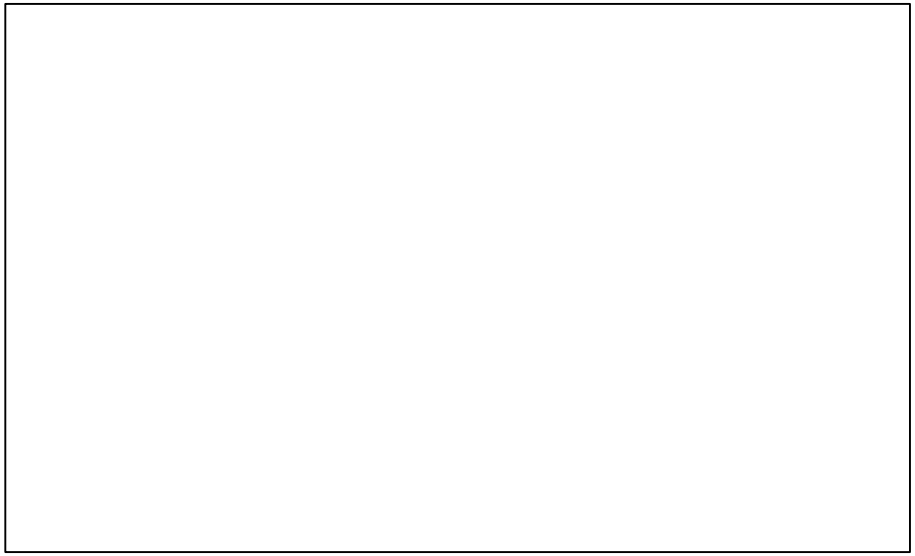
Comments

- Large comprehensive occupational study
- Data is mostly retrospective
- No individual risk factor data. Included adults only

Boice et al. Mortality among nuclear power plant workers. IJRB 2021 (in press)

Funding: DOE (DE-AU0000042,DE-AU0000046), NASA (80NSSC17M0016, 80NSSC19M0161), U.S. Navy (N00024-17-C-4322), CDC (5 NUE1EH001315)

WECARE Study specifically designed to examine joint effects of radiation and genetics in the etiology of breast cancer



25+ Center, population-based, international case-control

1521 Cases are women with contralateral breast cancer (CBC)

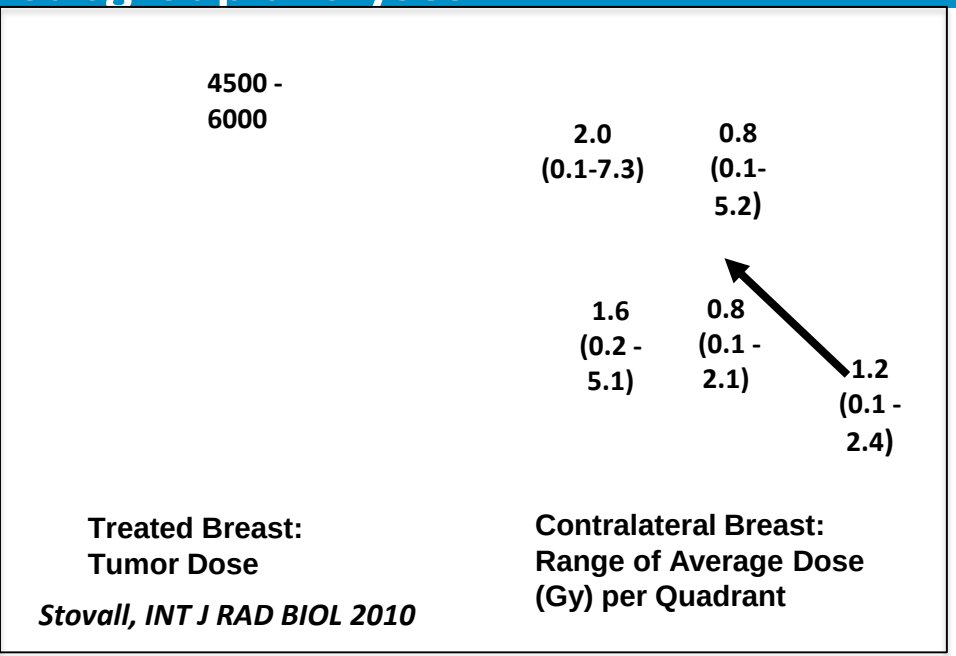
2212 Controls are women with unilateral breast cancer (UBC)

Hypothesis

Women who are carriers of certain genetic mutations will be more susceptible to radiation-induced breast cancer than are non-carriers.

Bernstein et al, Br Ca Res 2004

WECARE Study includes individual level risk factor data, dosimetry and biospecimens but sample size is limited for subgroup analyses



Stovall, INT J RAD BIOL 2010

Data Collection: 3733 women w/ breast cancer

Epi: questionnaire, detailed treatment information (radiation dosimetry, chemo, tamoxifen), mammographic density

Biospecimens: blood, cryopreserved lymphocytes, cell lines, tissue

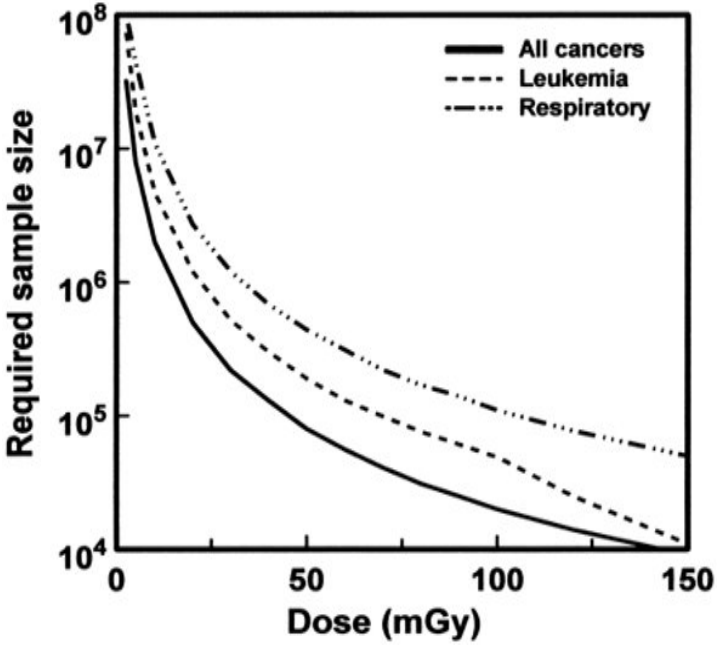
Mutation screening: ATM, CHEK2, PALB2, BRCA1/2, GWAS, WES, WGS, tumor characteristics

Comments

- Individual dosimetry from radiotherapy
- Biospecimens on all participants
- Limited sample size for subgroup analyses

NCI Funding: R01CA129639, U01CA083178, R01CA097397, R01CA114236, R01CA168339, R01CA206464, R21CA234752, R03CA139583

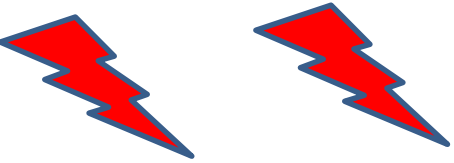
Priority: Strong epidemiological methods and accurate dose assessment require individual level data at baseline (ideally) and over the course of follow-up



Graph courtesy of L Dauer

- *Capturing the data-- anticipate future needs*
  - Key individual level risk factors (e.g., smoking)
  - Individual radiation exposure information (with dosimetry)
  - Allow for multiple outcome data (cancer and non-cancer, intermediary effects)
  - Longitudinal follow-up (radiation effects have a long latency)
  - Large sample sizes needed to capture small effects from low dose exposure

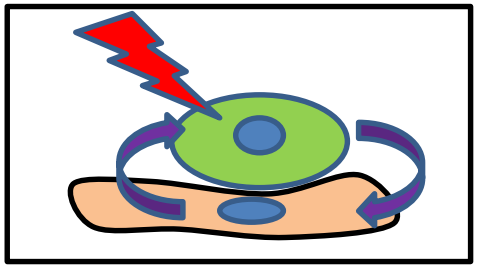
Priority: Understanding the role of genetics and biology in radiation response



DNA damage

Biochemical changes

Gene induction



Damage detection

Cell cycle arrest

Mitotic cell death

DNA repair

Cell survival

Residual damage

Too much damage

Mutated cell

Programmed cell death

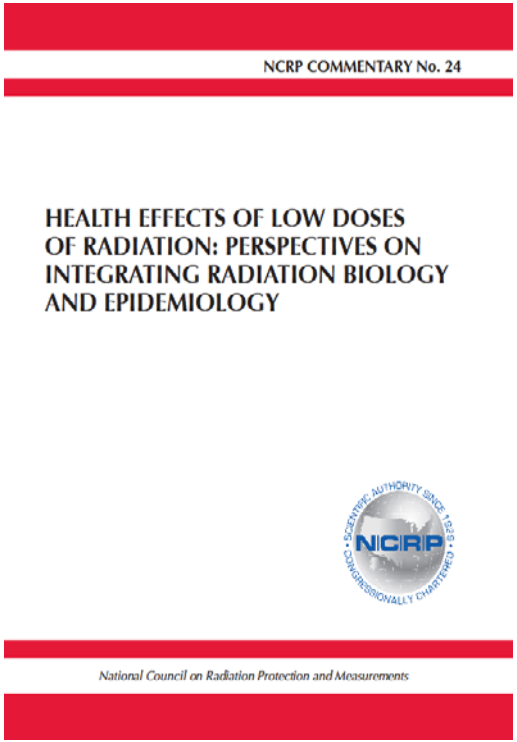
Neighboring cells influence the outcome. Cells communicate that they were radiated (bystander effect)

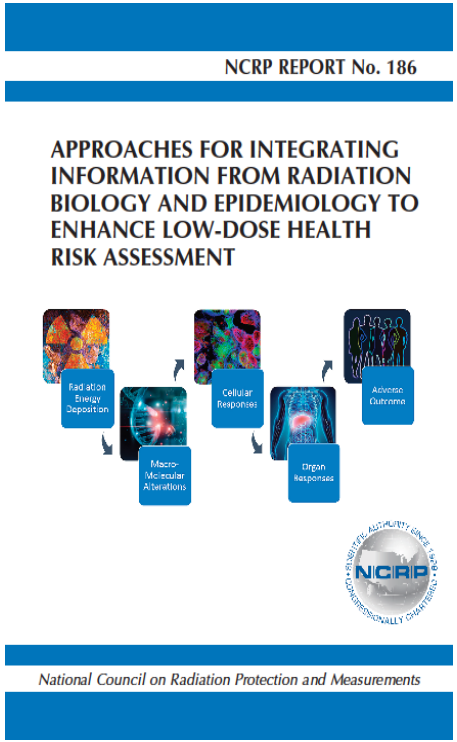
Graphic courtesy N Coleman

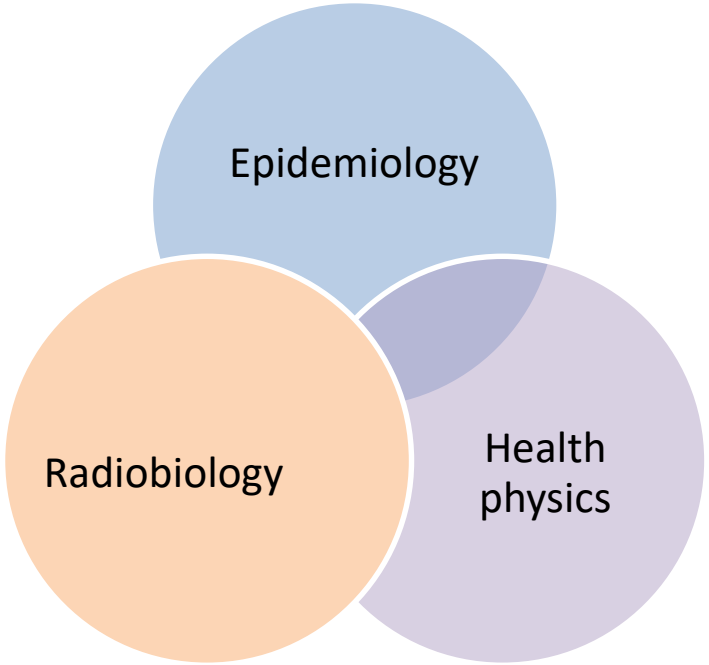
Priority: Include genetic factors in radiation epidemiology studies

- Including biospecimens to examine genetic effects requires
  - Both prospective and retrospective data collection with consent
  - Long-term storage
  - Anticipating genetic analyses that might be coming down the pike
  - Flexibility for a variety of types of specimens (saliva, blood, microbiome)

Priority: Need to take an integrated approach to incorporating epidemiology research with radiation biology and health physics







"Blue-Sky" Proposal: Create a *Universal Digital Cohort and Biobank*

Large-scale nation-wide longitudinal digital cohort of:

Patients
(pediatric and adult)

Radiation Workers
And Veterans

Outcomes

- Serial collections: risk exposures, health histories, behaviors, biospecimens (blood, saliva)
- Complete digital annotation (exposure, risk factor, genomic, imaging, clinical, behavioral)
- Linked radiation exposure data (e.g., health systems, Landauer database)

Challenges: Real world epidemiologic issues in establishing a *Universal Digital Cohort and Biobank*

5. Entire age span needed: pediatric recruitment necessary

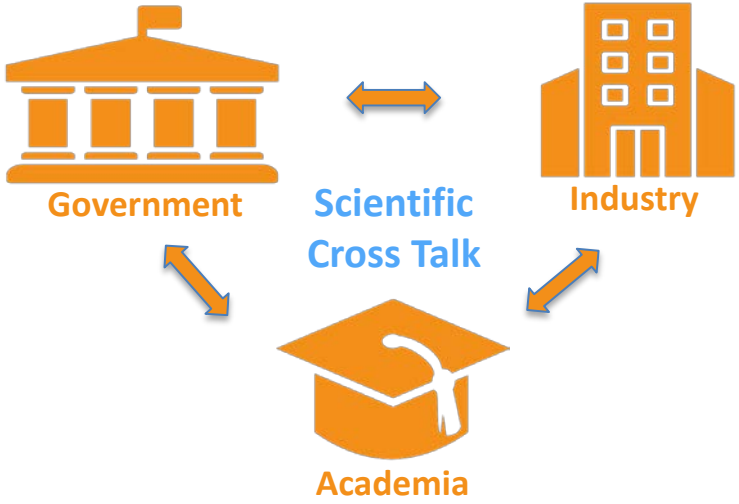
4. Risk factor, dosimetry, and outcome data requires linkage with medical records and PHI

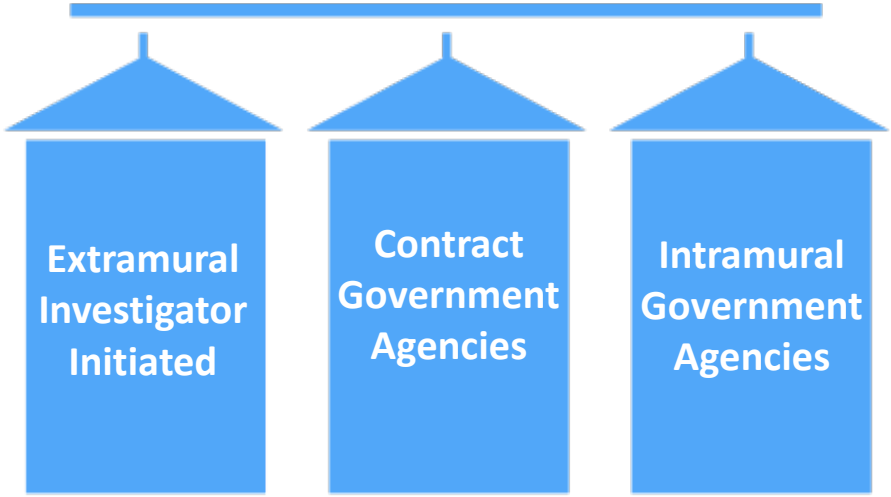
3. Including biospecimens requires living cohort and/or informed consent

2. It's possible to include non-radiation cohorts

1. Cohort includes: range of doses, long-term follow up, and large numbers

Setting priorities: Large low dose studies are $$$, need national research goals that are coordinated across individual investigators and government agencies





- Establish expert interdisciplinary scientific advisory team, and be inclusive
- Allocate research funding according to priority areas
- Coordinate the mission-driven research
- Share the data and findings for innovation

In Summary…Priority setting strategy needs to be based on the big picture

Chronic low-dose radiation studies need to take an integrated interdisciplinary approach and incorporate epidemiology, radiation dosimetry, biology and genetics.

- Can use data from higher dose studies to inform studies of low dose
- Important to include exposed individuals across the lifespan
- Funding needs to be coordinated across federal agencies and partnered with academia and industry
- Model after successful interdisciplinary studies/research platforms, here and abroad
- Integrate interdisciplinary training of the next gen of radiation scientists
- CONSIDER initiating a digital cohort of exposed workers/patients

Thank You

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Acknowledgements

John D. Boice Jr, Sc.D.

C. Norman Coleman, M.D.

Lawrence T. Dauer, Ph.D.

Eric J. Grant, Ph.D.

Mark P. Little, D.Phil

David J. Pawel, Ph.D.