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BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY
BARDA

Biodosimetry – challenges to product development and regulatory approval

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Diagnostics (Dx) for Biodosimetry

- Based on Radiation Biomarkers
- Measure host response to estimate absorbed dose of IR
- Inform patient management - useful for clinical evaluation, management of victims, appropriate treatment, proper use of scarce resources
- Expected clinically relevant cut-points: ~ 2 Gy (cytokine treatment), ~ 6 Gy (bone marrow transplant), ~ 8 Gy (palliative care)

Biodosimetry Dx - Key Requirements

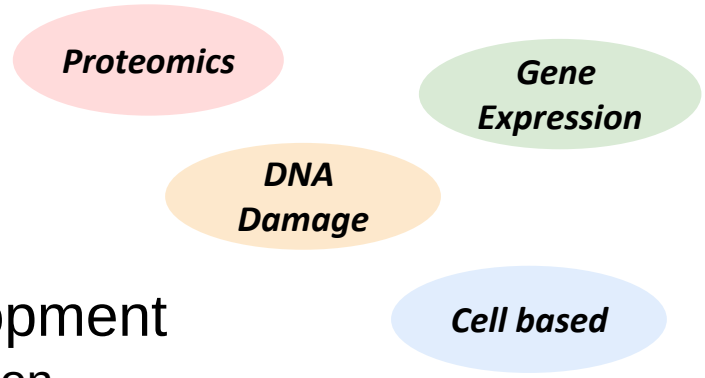
- Target Product Profile (PHEMCE working group 2009) for POC, HT Dx

Point of Care (POC) and High-throughput (HT) Biodosimetry Test Characteristics

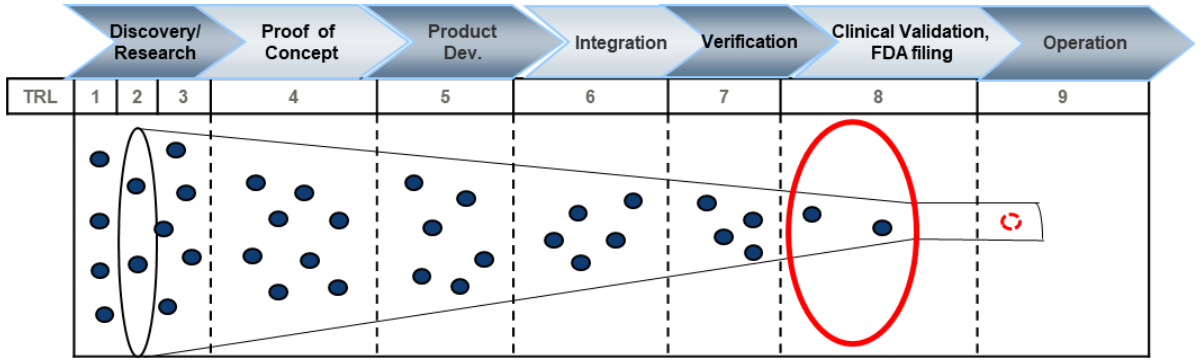
	POC device	HT device
Type of result	Screening/qualitative	Quantitative/semi-quantitative
Concept of operations	Initial triage/sorting	Injury assessment/treatment tool
Exposure level	2 Gy–threshold	Range: 0–10 Gy
Ease of operations	Easy to operate, minimal complexity, requires minimal training, CLIA waived	Laboratory instrument; more labor intensive, requires training
Device characteristics	Integrated components; no separate sample preparation.	May include separate components as needed. High automation desired.
Intended use	Tents, shelters, open settings	Laboratories, hospitals, fixed facilities
No. of patients/event	Up to 1,000,000 within 7 days	Up to 400,000 within 7 days (may need multiple assessments)
Time to result	Rapid but individual sample result (15 to 30 min)	Up to 24 h

Satyamitra M, Reyes Turcu FE, Pantoja-Galicia N, Wathen L.
Challenges and Strategies in the Development of Radiation Biodosimetry Tests for Patient Management. Radiat Res. 2021

BARDA Biodosimetry Program Overview



- Awarded 11 R&D projects in 2009-2010 (laboratory, POC)
- 4 projects funded by Project BioShield for advanced development
  - 2 completed initial verification, 1 pEUA submission, 1 now in validation



- One more project funded in 2022 (R&D project, 2019 BAA)

Lessons Learned

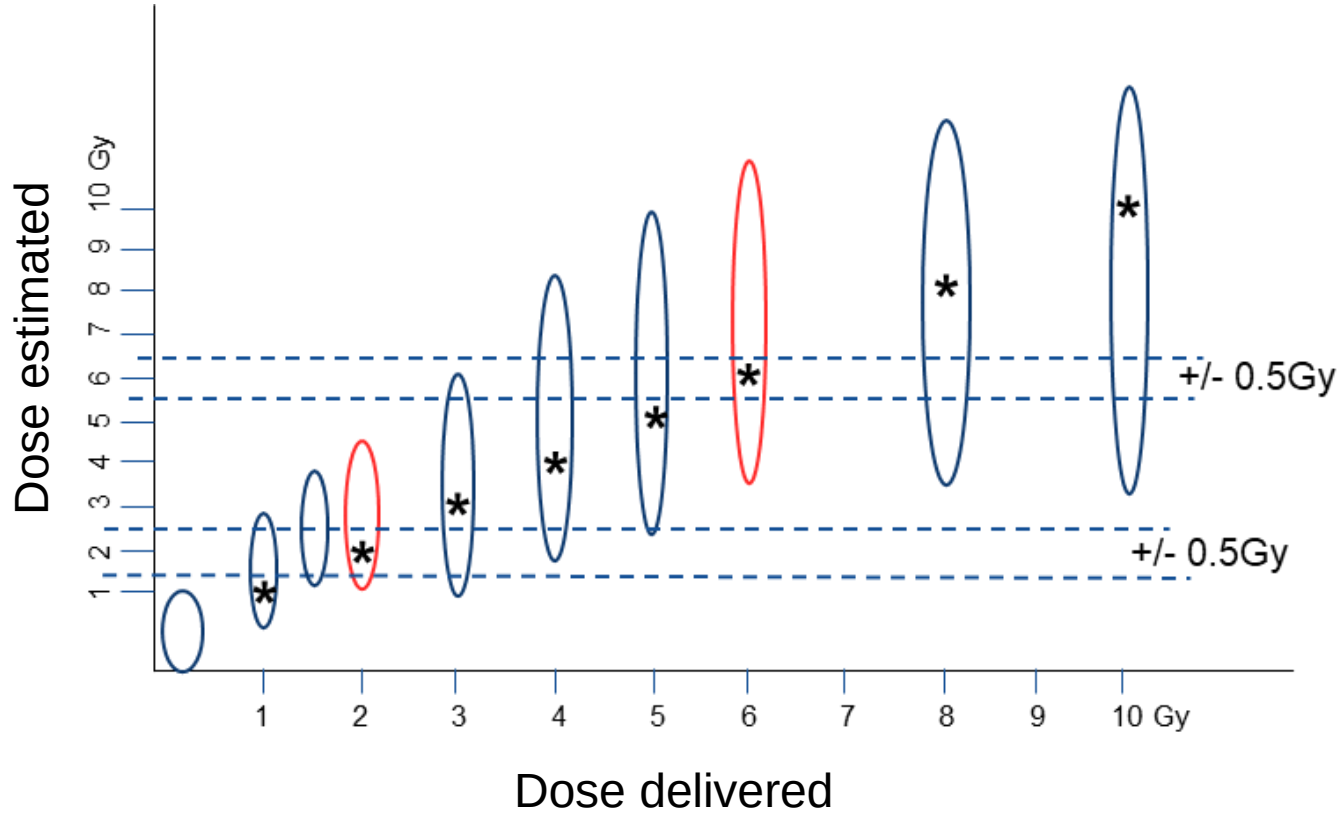
- Overview
  - Interindividual variability, biomarker's sensitivity, specificity
  - Dose response, time dependency
  - Bridging studies
    - Animal models
    - Unirradiated controls and radiotherapy patients

(*all figures in following slides are for illustrative purposes only and are not representative of any particular biomarker*)

Lessons Learned –variability and performance

- Desired performance goals:
  - dose estimated = dose absorbed +/- 0.5 Gy

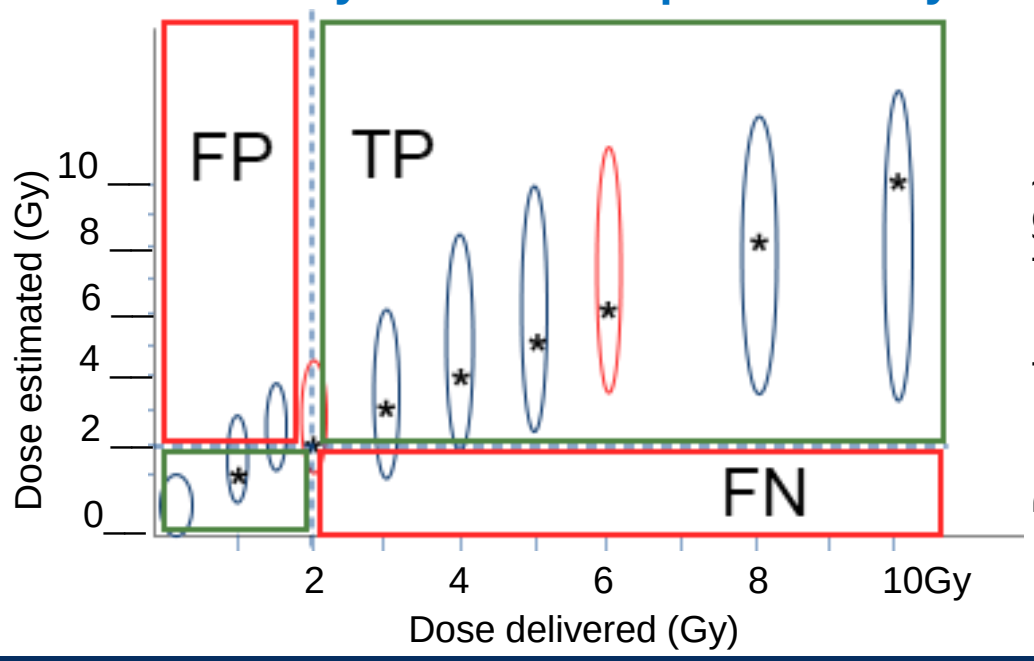
- Utility of biomarkers as a replacement for physical measurement of radiation is limited by inter-individual response variability



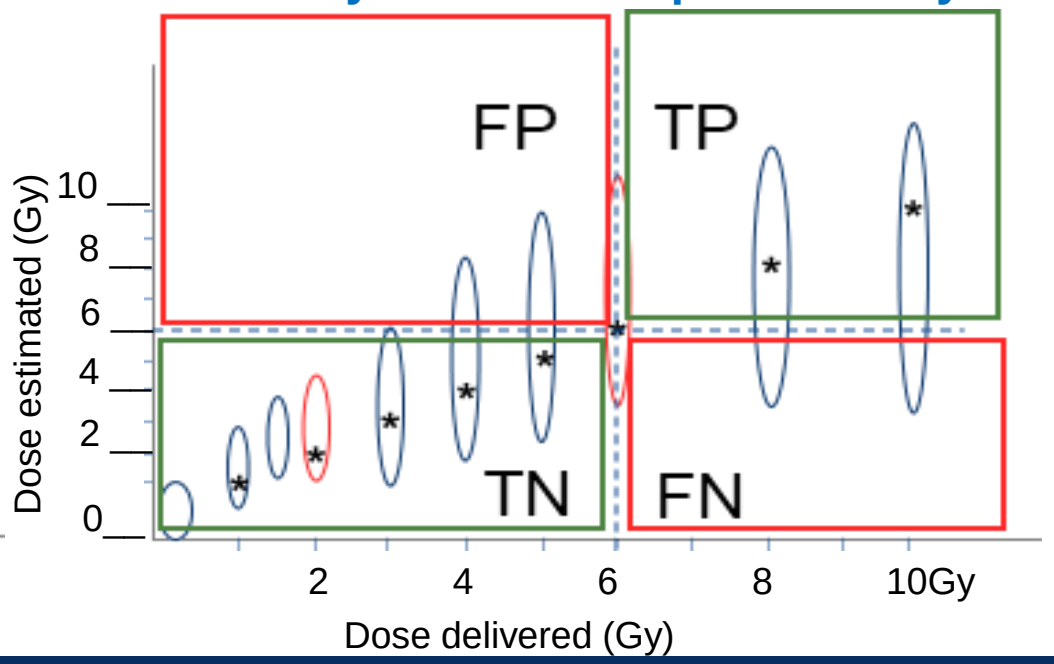
Lessons Learned – Sensitivity and Specificity

- Desired performance goals: 90% sensitivity AND 90% specificity
- Clinical justification of performance, safety and effectiveness - problematic

clinically relevant cut-point: ~ 2 Gy



clinically relevant cut-point: ~ 6 Gy

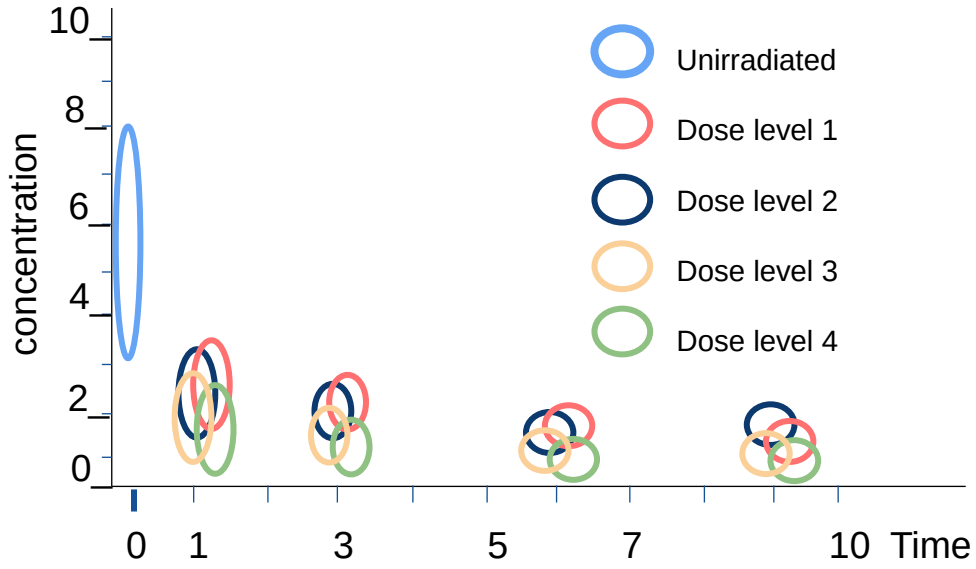


FP False Positive
TP True Positive
FN False Negative
TN False Negative

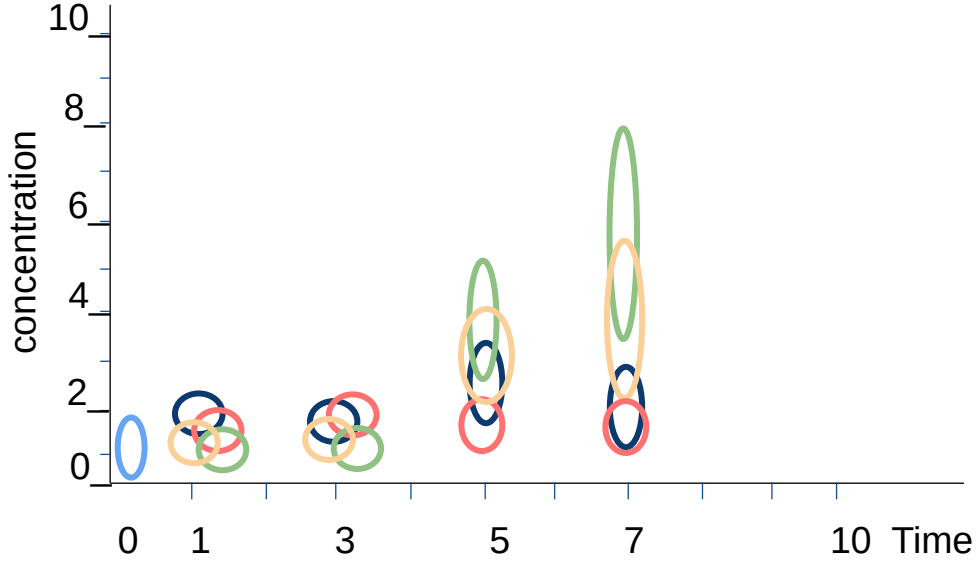
Lessons Learned – Dose and Time Response

- Use of biomarkers as a replacement for physical measurement of radiation is limited by lack of dose and time response

  - Biomarker is radiation sensitive
  - Biomarker is not dose and time responsive

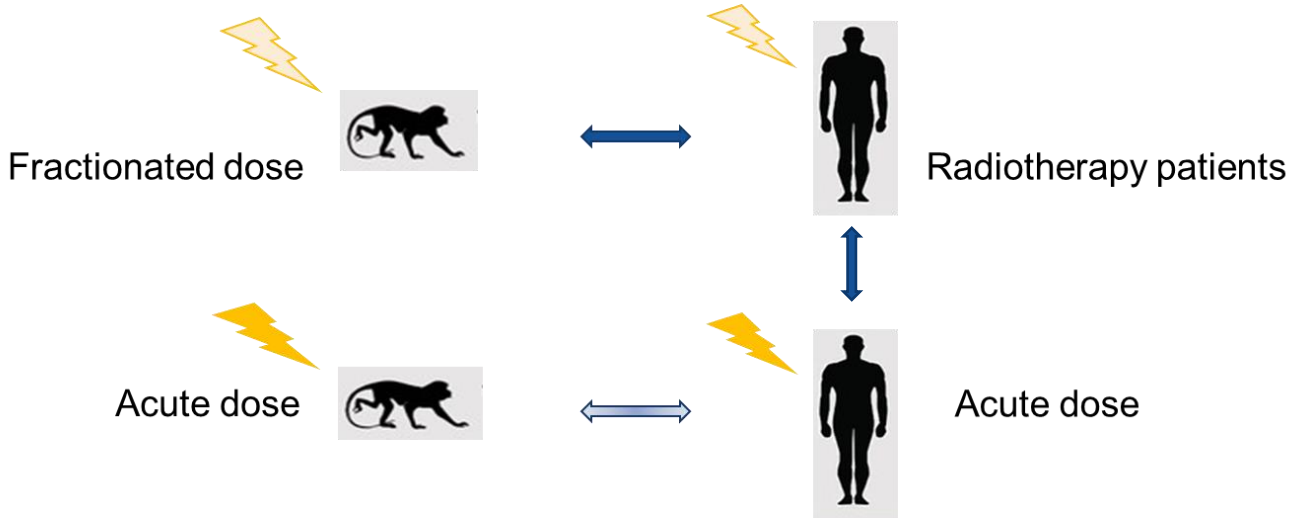


  - Biomarker may be useful, but utility limited to later timepoints, higher doses



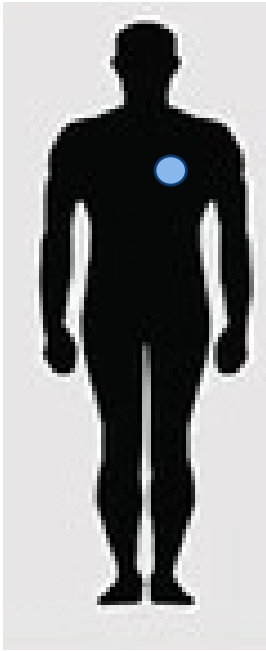
Lessons Learned – Bridging Studies

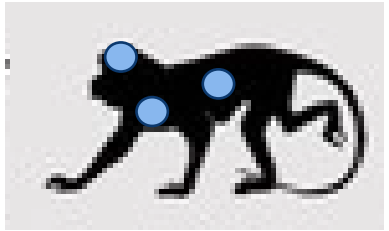
- When human studies are not ethical nor feasible, models are required to demonstrate accuracy and performance
- Bridging studies are necessary to confirm the validity of selected models
  - Animal models must demonstrate adequate similarities to humans in terms of performance (homology, kinetics, and fold-change among others).
  - Radiotherapy (RT) patients as an intermediate step between the intended use population and animals.



Lessons Learned – Bridging Studies (Homology)

- Human
  - Biomarker induced by radiation
  - Specific, dose/time dependent
  - Expressed in a single organ
    - different isoenzymes for different organs



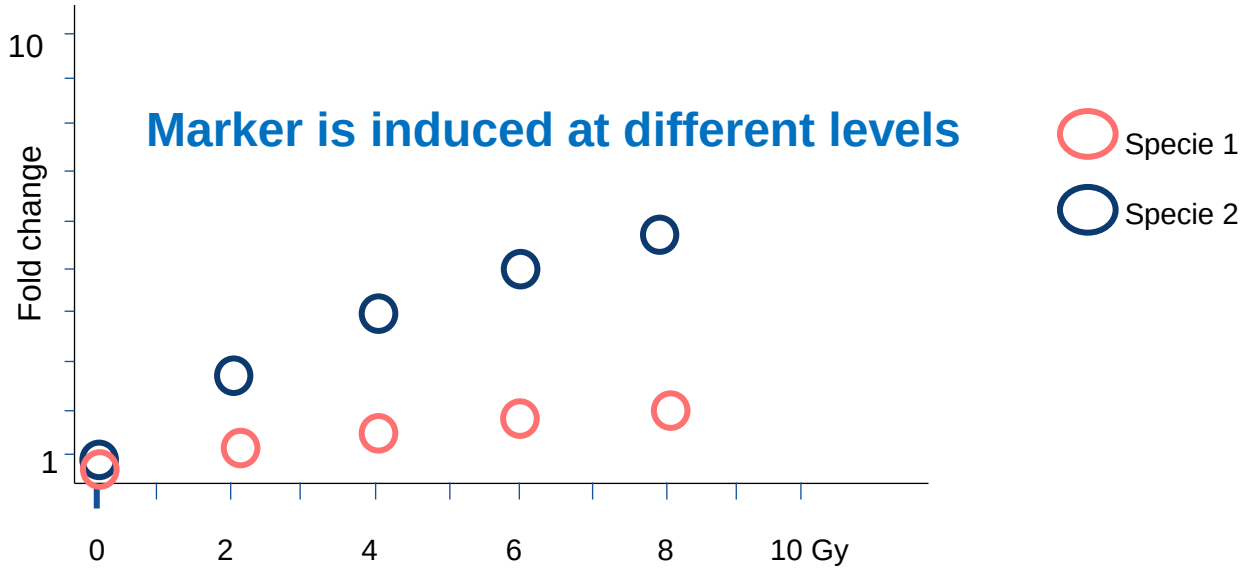


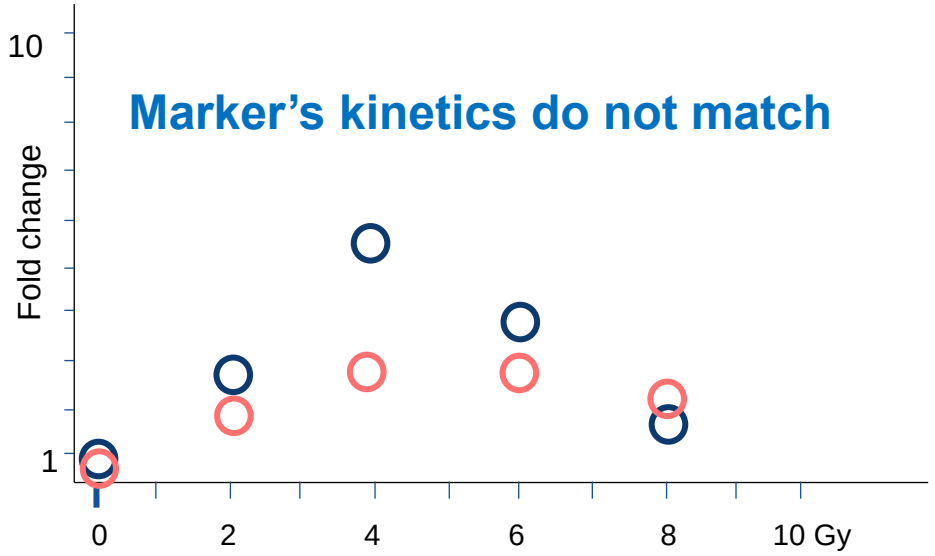
- NHP
  - Biomarker induced by radiation
  - Specific, dose dependent
  - Same isoenzyme expressed in multiple organs

- Model not suitable: lack of homology, assay detects different analytes

Lessons Learned – Bridging Studies (Kinetics and Fold Change)

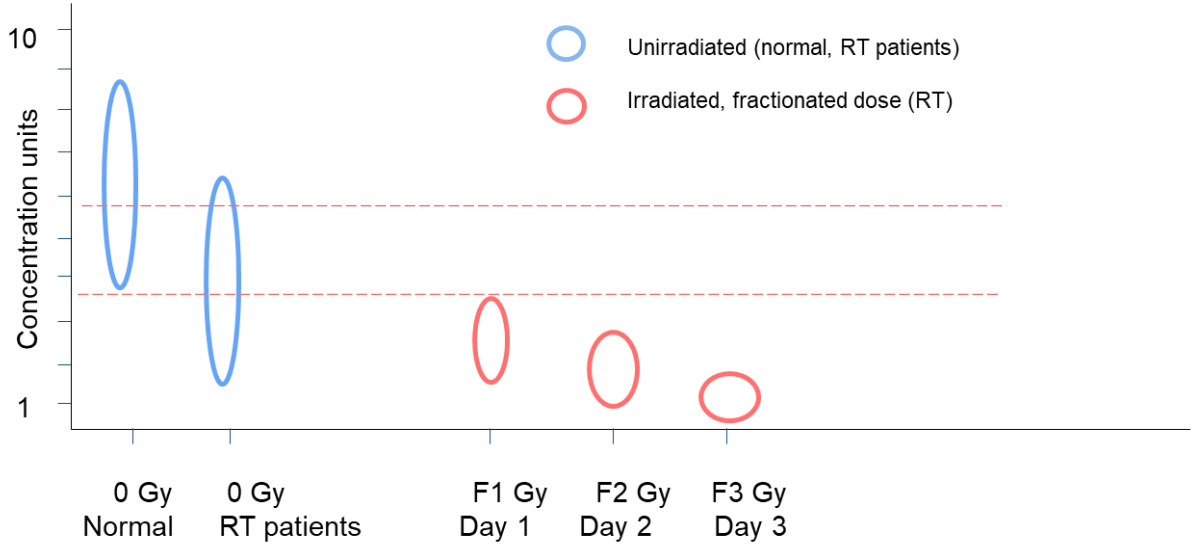
- Biomarker is induced in both species. Time and dose dependent.
  - Fold change is different
  - Kinetics are different
- Model not suitable: inadequate similarities





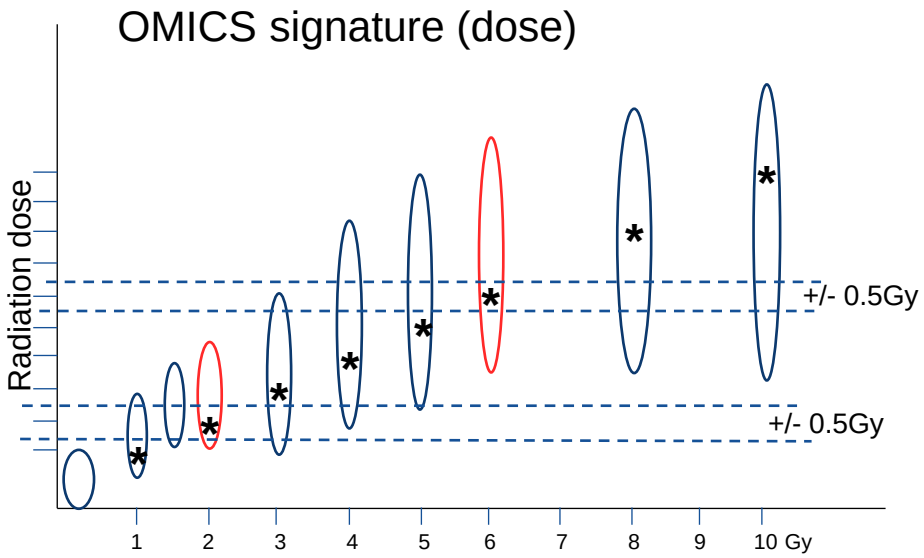
Lessons Learned – Bridging Studies (Controls, Irradiated)

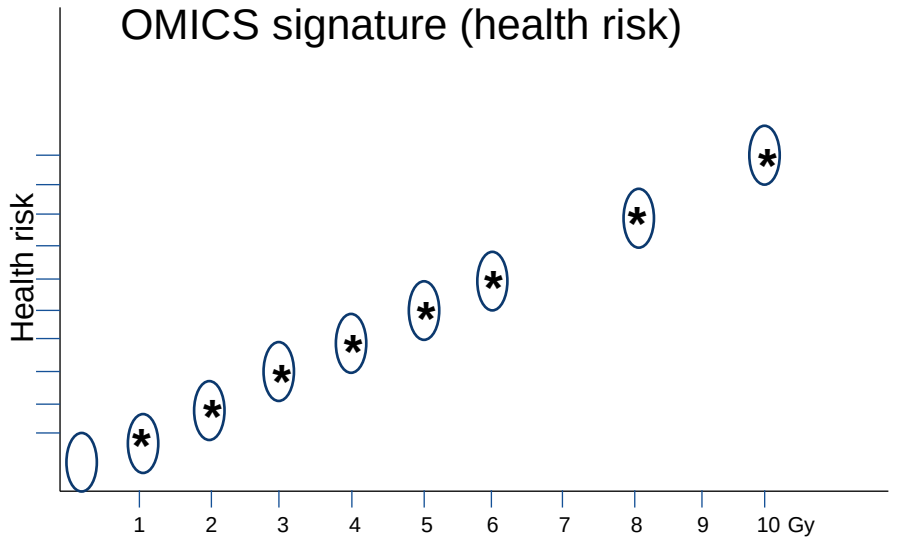
- RT population not representative of normal population
- Limited samples near clinical cut-off, through expected range of exposures and timeframe of intended use.
- Comparison is RT irradiated vs RT unirradiated, not vs normal pop



Biomarkers of Dose versus Biomarkers of Effect

- Biomarkers are used to measure host response
- A biomarker of exposure gives an assessment of absorbed dose
- A biomarker of effect, often referred to as a biomarker, is used in the assessment of health risk





Threat Agnostic Approach for Pathogens

- Identification of novel pathogens is time consuming and delays appropriate medical treatment.

- Detection and response that do not depend on knowing the identity of the threat agent or pathogen but focus on characterizing the agent, host damage, or immune response are being explored for public health preparedness and response.

- Examples of threat agnostic approach:
  - Agnostic diagnostics to identify any pathogen present in a sample — including new pathogens
  - Tissue-agnostic clinical trials for cancer - molecular signatures/biomarkers used to select therapies regardless of the tumor site of origin

Threat Agnostic Approach for Biodosimetry

- Biodosimetry as the study of host response to a threat and its relationship with a biological outcome (not with a radiation dose)

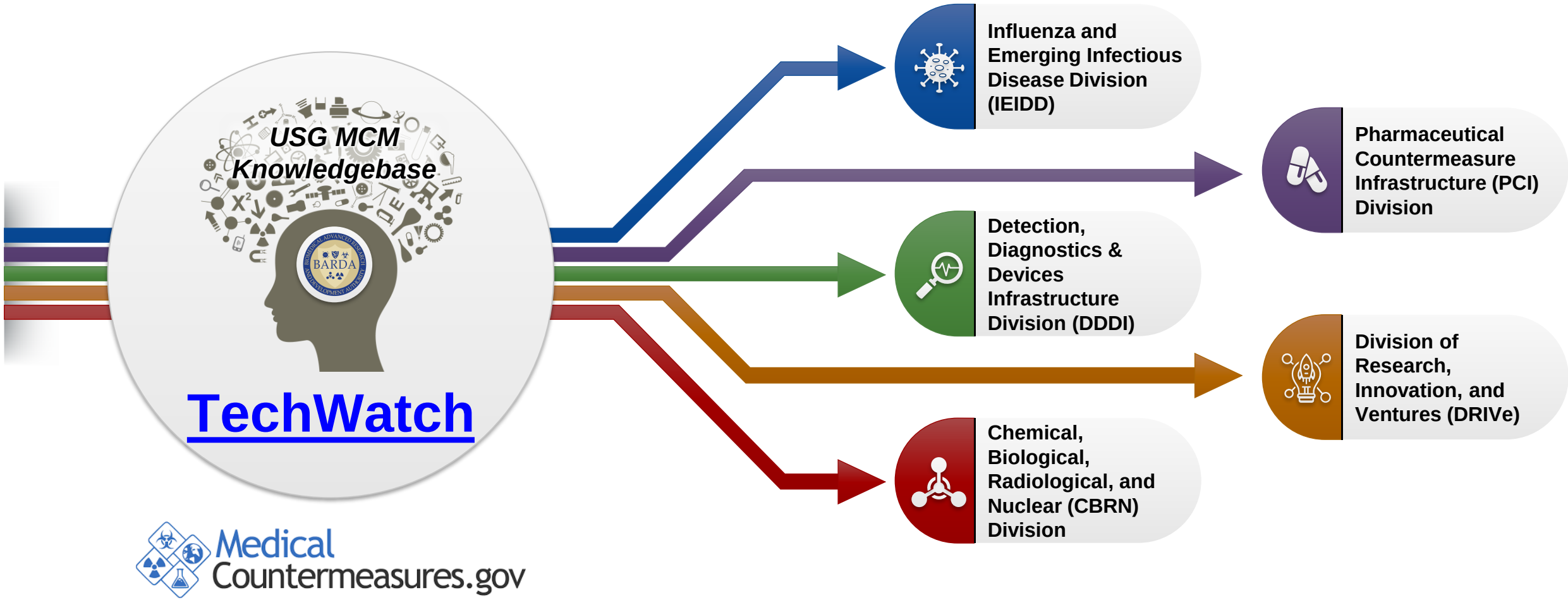
- Nature of threat initially not critical
  - Is it harmful? How harmful is it?
  - Is it common to other threats? What are the commonalities?
  - What are the health consequences? Can we predict them?

- Estimate level of injury instead of the level of dose

Threat Agnostic Approach for Biodosimetry

- Emphasis on commonality of responses with known diseases/conditions, to guide prognosis and medical management
- Artificial intelligence and machine learning to identify common patterns of disease from new and existing multi-omics studies
- Animal models to characterize markers of effect
- Dx repurposing for radiation damage assessment?

TechWatch: Open for Business



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