Qualitative and Quantitative Biodosimetry Diagnostics for Response to a Radiation/Nuclear Event

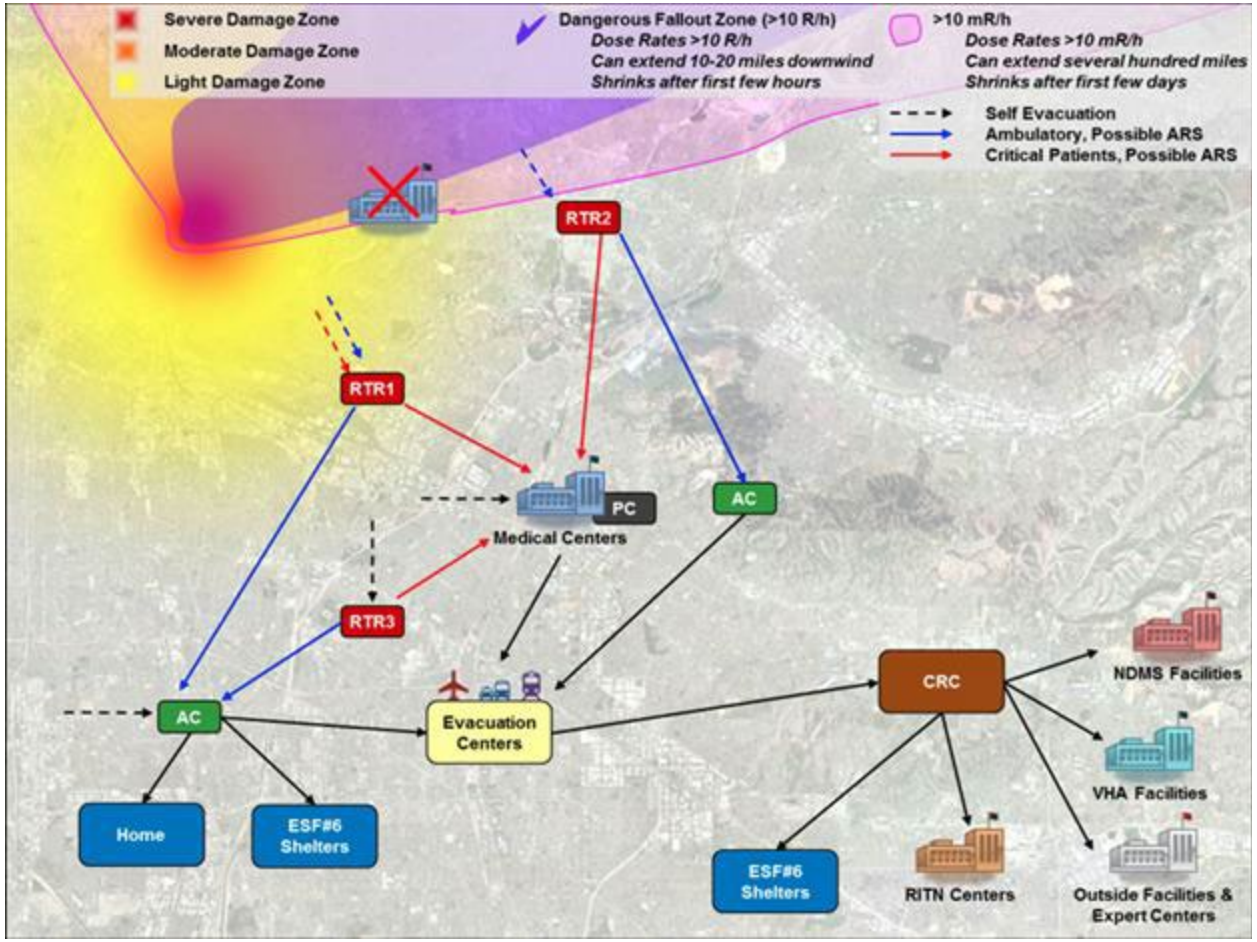
Richard Kowalski, PhD

9 July 2024

Biodosimetry Needs

- FDA authorized biodosimetry tests are needed to support the response to a mass-casualty nuclear incident
- Capable of providing clinically actionable results at scale of 100,000's to 1M+ people
  - Not research tools
- Developed and validated in compliance with medical device regulations (21 CFR 820)
- Pre-deployed to provide rapid response and exercised regularly – ready to go when needed

The RTR Functional Response System (Radiation TRiage, TReatment, and TRansport)[1]



1) Coleman CN, Weinstock DM, Casagrande R, et al. Triage and treatment tools for use in a scarce resources-crisis standards of care setting after a nuclear detonation. Disaster Med Public Health Prep. 2011;5(SUPPL 1). doi:10.1001/DMP.2011.22

Biodosimetry Diagnostics

Screening Tests

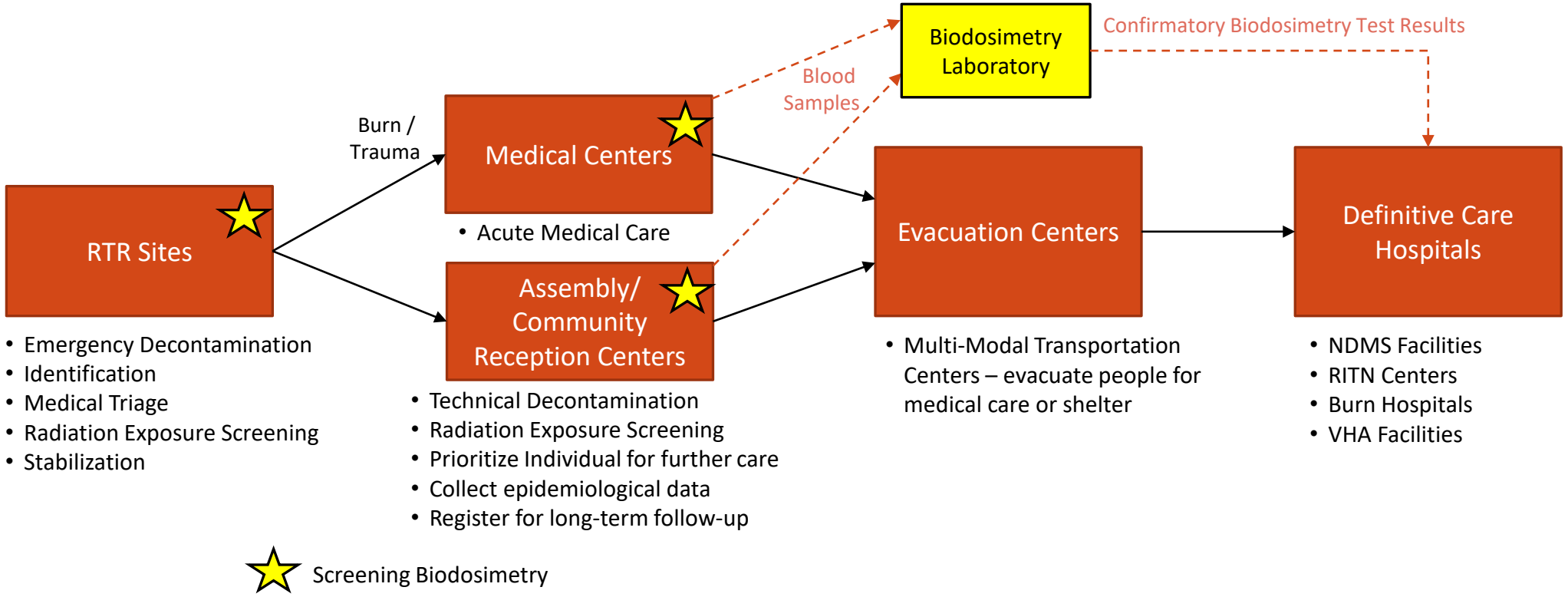
- Qualitative assessment of significant exposure
- Used to help sort population into two groups
  - Those that need immediate medical attention
  - Those that can be treated by non-emergency personnel
- Test characteristics
  - Fast time to result
  - Highly sensitive
  - Accurate from 1 to 7 days post-exposure
  - Widely deployable in a variety of locations/environments – 1M+ results in 7 days
  - Low cost
  - Easy to use – CLIA-waived

Confirmatory Tests

- Quantitative or semi-quantitative measurement of absorbed dose
- Used to inform and refine patient treatment decisions

- Test characteristics
  - Provide estimated dose from 0 to 6 Gy
  - Accurate from 1 to 14 days post-exposure
  - Provide results across majority of population
    - Robust against high prevalence medical conditions and comorbidities (trauma, burns)
  - Leverage existing infrastructure to minimize deployment and sustainment costs

Biodosimetry Testing within RTR Framework



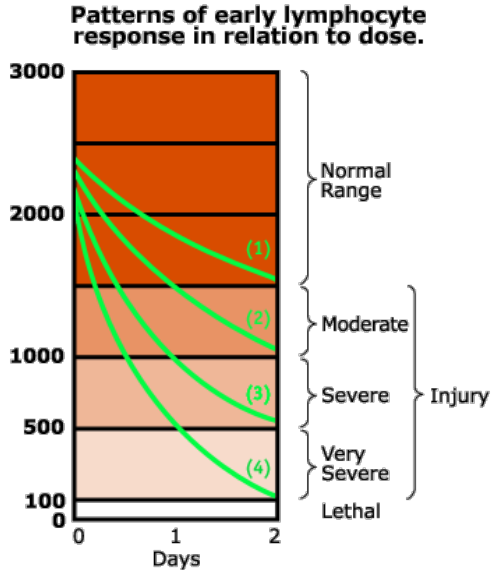
* CONOPs summary based upon Coleman CN, Weinstock DM, Casagrande R, et al. *Triage and treatment tools for use in a scarce resources-crisis standards of care setting after a nuclear detonation*. Disaster Med Public Health Prep. 2011;5(SUPPL 1). doi:10.1001/DMP.2011.22, RITN CONOPS, and other government documents such as ASPR's "*A Decision Makers Guide - Medical Planning and Response for a Nuclear Detonation*"

CellRADx Qualitative Biodosimeter

- CellRADx Software Application can assess ionizing radiation exposure using:
  - A patient's CBC result (at a single timepoint) from existing CBC instruments (lab and point-of-care devices)
  - Time post-exposure, age, select medical conditions
- Benefits:
  - **Operationally Relevant:** Discriminates exposures >2 Gy across 1-7 days post-exposure
  - **Clinically Effective:** 90% sensitivity and 80% specificity across intended use population, including wide variety of demographics, medical conditions, and medications
  - **Easy to Use:** User enters or uploads a CBC result, patient age and other info using simple, CLIA-waived software app
  - **Operational Flexibility:** Compatible with wide variety of CBC instruments; provides triage capabilities in the field, hospitals, and other med facilities w/o added infrastructure or sustainment costs
- Status: Currently under development

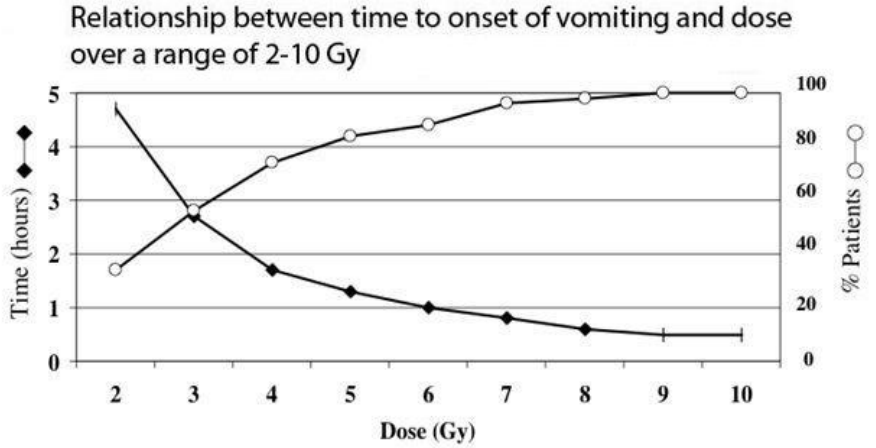
Other Biodosimetry Screening Tools

- Lymphocyte Depletion Kinetics
  - Typically requires two or more measurements – very challenging logistics in chaotic post-disaster environment
  - LDK tool on REMM website
    - Greatly favors specificity when dose estimate is used to bin results into ≤ or > 2 Gy – many false negatives, which could delay treatment for exposed victims
    - Exhibits a high indeterminant rate of 20-30% (no result provided)
- Time to Emesis
  - Reliable method for negative determination (no vomiting = low probability of exposure)
  - Positive determination requires patient to remember when vomiting occurred under high stress situation
  - Also likely confounded by stress-induced vomiting
- CellRADx offers advantages over these other methods
  - Single time point measurement
  - Objective data inputs – does not rely on subjective signs and symptoms
  - Being developed under Design Controls (21 CFR 820.30) to facilitate FDA authorization



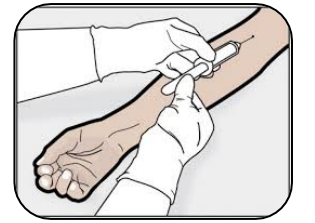
Left: *Lymphocyte depletion curves and accompanying clinical severity range (Goans, 1997).*

Bottom: *Relationship between time to onset of vomiting and dose over a range of 2-10 Gy (Dainiak, 2007).*



CytoRADx™ Quantitative Biodosimeter

- Provides quantitative estimates of absorbed dose to inform patient treatment
  - Customized version of Cytokinesis-Block Micronucleus (CBMN) assay
  - Utilizes MetaSystems' Metafer automated microscopes with existing commercial equipment and infrastructure in CLIA reference labs
    - Fully integrated and automated dose estimation; no manual cell counting
- Benefits:
  - High-throughput – 400k results in 7 days across the network
  - No lab-specific calibration curves – uses standardized cGMP kits, detailed assay protocol, and optimized analysis settings
  - Robust performance across a wide range of demographics, common diseases and likely comorbidities
- Status:
  - Clinical validation studies nearing completion
  - FDA submissions and interactive review in process



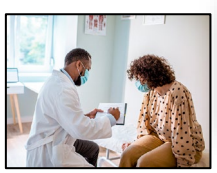
1. Whole blood collected in commercial heparin tubes; shipped to CytoRADx labs

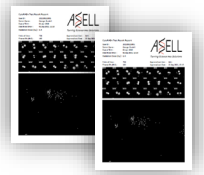
ThermoFisher SCIENTIFIC

2. Samples processed manually using CytoRADx assay, creating slides

3. Slides scanned and analyzed with RADxScan; dose estimates obtained

MetaSystems

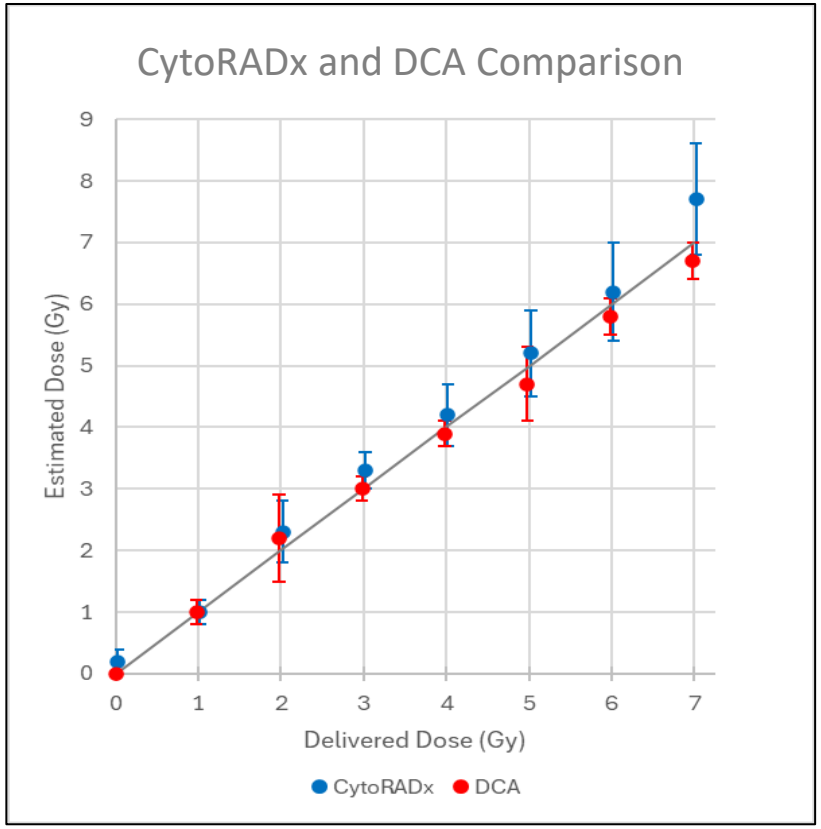


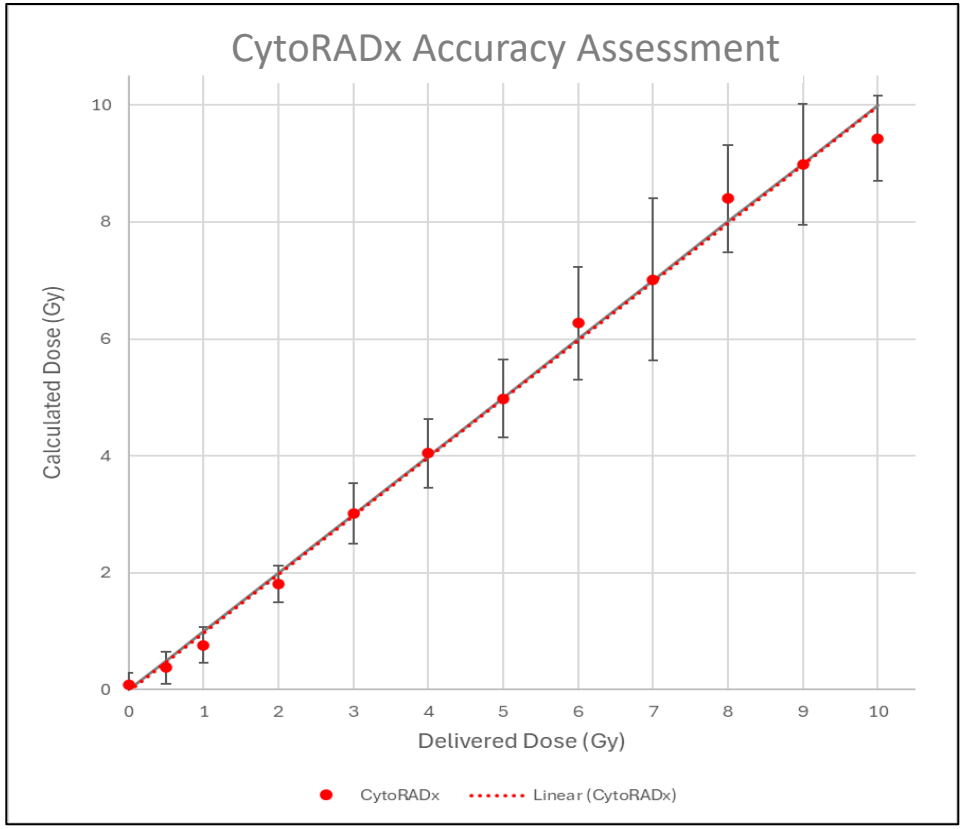


4. Results available to clinicians, informing treatment

CytoRADx Performance & Comparison with DCA

- Extensive collection of validation studies performed in compliance with FDA QSRs
  - Specimens from over 1200 human subjects
  - Demonstrated high accuracy
- Favorable comparison to gold standard DCA
  - No manual scoring
  - >100x greater throughput
  - No calibration curves needed





Left: *CytoRADx vs DCA results from 20 human subjects irradiated ex vivo from 0 to 7 Gy. Results are single culture with up to 7 slides per sample for DCA versus one replicate for CytoRADx. Markers are mean results per dose, error bars are one standard deviation, and the grey line is the one-to-one concordance. DCA testing performed by REAC/TS.* ***Right:*** *CytoRADx accuracy results from at least 49 human subjects irradiated ex vivo at each dose and tested using a single replicate. Markers are mean results per dose; error bars are one standard deviation. The red dashed and solid grey lines are the linear regression and one-to-one concordance lines, respectively.*

Summary

- There is an unmet need for FDA-authorized screening and confirmatory Biodosimetry Diagnostic Devices for use in the aftermath of Rad/Nuc disaster capable of testing hundreds of thousands to millions of people within the first weeks after exposure
- CellRADx is a ***qualitative biodosimetry software application*** that uses a single CBC with differential measurement within 7 days of the event to screen people for significant radiation exposure
- CytoRADx is a ***quantitative biodosimetry system*** that uses a cytogenetic assay and automated imager to calculate an absorbed dose to inform patient treatment
- The use of screening and confirmatory biodosimetry assays will increase the efficiency of emergency medical care through early triage of radiation exposed victims and determination of the amount of radiation absorbed

Acknowledgements

- Armed Forces Radiobiology Research Institute
  - William F. Blakely, PhD.
  - David Bolduc, PhD.
- REAC/TS
- MJW Corporation
  - Ronald Goans, PhD, MD
- MetaSystems

This project has been funded in whole or in part with Federal funds from the Department of Health and Human Services; Administration for Strategic Preparedness and Response; Biomedical Advanced Research and Development Authority, under Contracts HHSO100201000002C, HHSO100201700022C and 75A50122C0050, and by the National Institute of Allergy and Infectious Diseases, under award U01AI148316.

Turning Science Into Solutions