Radiation Biodosimetry Test Development Continues Apace

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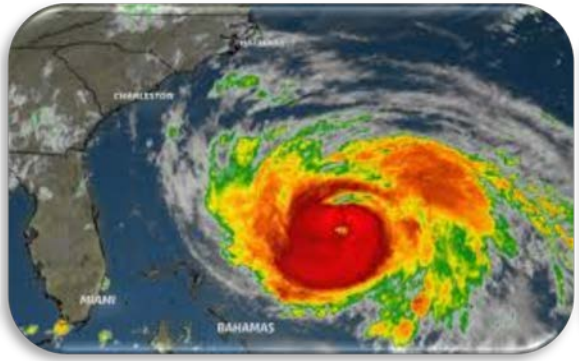
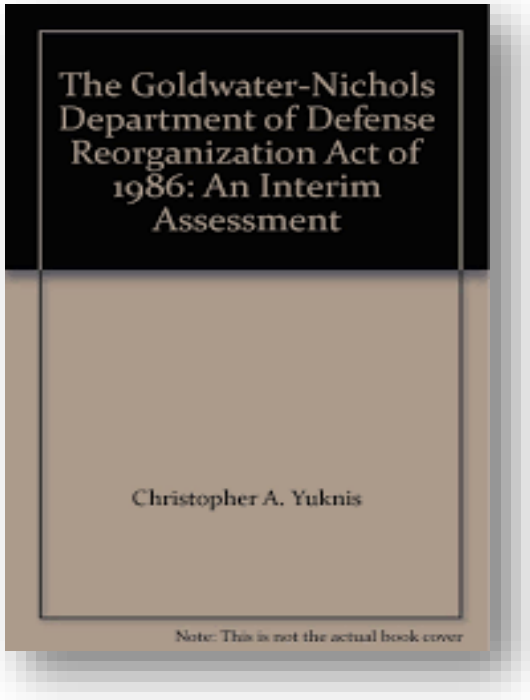
21st Century: An Increasingly Complex & Dangerous World



ASPR's Raison D'etre: "Unity of Command"

Public Law 109-417 Pandemic & All-Hazards Preparedness Act



ASPR Mission

ASPR Priorities for Building Readiness for 21st Century Threats

The BARDA Model

- BARDA develops and makes available medical countermeasures **(MCMs)** by forming unique public-private partnerships with industry partners

Radiation Biodosimetry Program

Objective: Develop rapid, accurate FDA-cleared biodosimetry diagnostic assays/systems to inform patient management, improve health and psychosocial outcomes, and save lives.

Two types of biodosimetry tests are under development:

- **Point of Care Triage Screening Tests** to discern individuals needing medical evaluations from those who can evacuate
- **High Throughput Laboratory Tests** to report the absorbed dose an individual received and inform further care

Biodosimetry Target Product Profiles

	Point of Care Device (POC)	High Throughput Device (HT)
Type of result:	Screening/Qualitative	Quantitative (desired accuracy ± 0.5)
CONOPs:	Initial Triage / Sorting	Injury Assessment / Treatment Tool
Exposure level:	2 Gy - threshold	Range: 0 – 10 Gy
Ease of operation:	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	Labs, hospitals, fixed facilities
# 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 minutes)	Up to 24 hours

Post-irradiation Symptoms And Treatment Strategies

Symptoms and Onset		Mild (1-2 Gy)	Moderate (2-4 Gy)	Severe (4-6 Gy)	Very Severe (6-8 Gy)	Lethal (> 8 Gy)
Vomiting	Onset Incidence	≈ 2 hrs. 10- 50%	≈ 1-2 hrs. 70-90%	≈ 1 hr. 100%	≈ 30 min. 100%	≈ 10 min. 100%
Diarrhea	Onset Incidence	None	None	3-8 hrs. < 10%	1-3 hrs. > 10%	< 1 hr. ≈ 100%
Headache	Onset Incidence	Slight	Mild	4-24 hrs. 50%	3-4hrs. 80%	1-2 hrs. 100%
Consciousn ess	Onset Incidence	Alert	Alert	Alert	Impairment	Lost
Body Temperature	Onset Incidence	Normal	↑ 1-3 hrs. 10- 80%	↑ 1-2 hrs. 80-100%	↑ < 1 hr. 100%	↑ < 1 hr. 100%
Treatment Strategy		Outpatient Observation	General hospital treatment	Specialized hospital treatment	Specialized hospital treatment	Palliative treatment

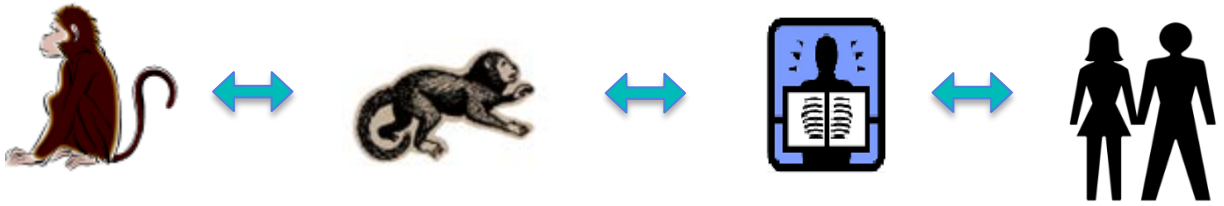
Geographical location at the time of the blast and lymphocyte depletion kinetics will also help determine approximate absorbed dose.

Biodosimetry Pivotal Testing Process

Intense pre-validation of the tests using samples from:

- Normal Humans, ages 2 to 87, with percent ethnicities representative of the US population
- Individuals with potentially confounding conditions such as immunocompromised, pregnant, trauma, burn, diabetes, rheumatoid arthritis, sepsis, and radiotherapy
- Pre-Transplantation patients receiving fractionated irradiation
- Non-human primates (NHP) receiving total body irradiation either in single or fractionated doses
- Humans and NHPs after G-CSF or Leukine administration
- A host of common substances were also spiked into human blood and tested for potential assay interference (such as bilirubin, human serum albumin, human IgG, L-Ascorbic Acid, hemoglobin, acetylcysteine, captopril disulfide, and others depending on the assay chemistry)

Regulatory Strategy



NHP in vivo Single Dose

NHP in vivo Fractionated

Human in vivo Fractionated

Human in vivo Single Dose

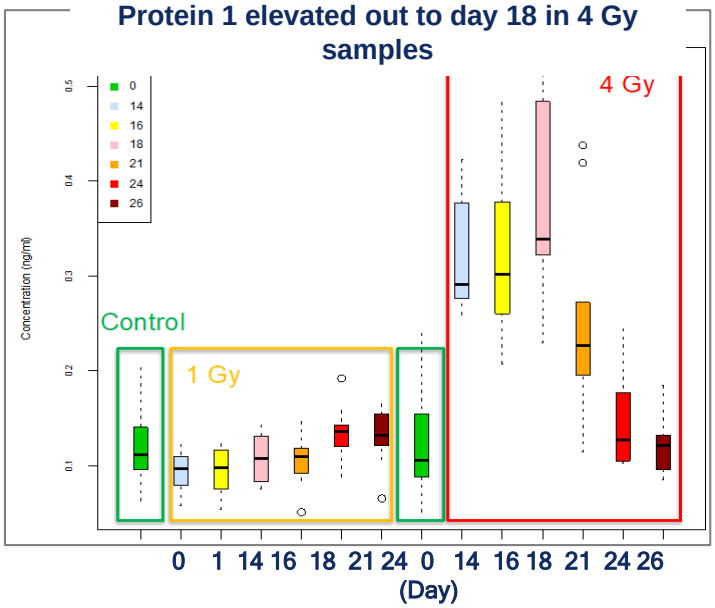
- Demonstrating similarity of gene, protein, or cytological response to single and fractionated dose irradiation across species
- Seeking pre-Emergency Use Authorization status from the United States Food and Drug administration (FDA)
  - One pre-EUA package filed in 2017 and under review
- Pursuing 1st biodosimetry in vitro diagnostics approval from FDA

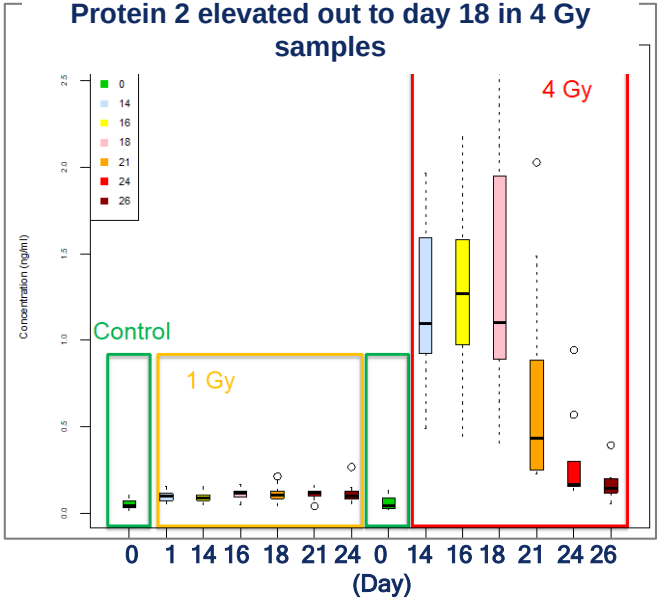
Point of Care Biodosimetry

Developer	Point Of Care Technology	Type	Sample Throughput per Instrument (per hour)
SRI International	Protein Expression Immunoassay	Dual Lateral Flow w/ Reader & Cell Extractor	≈ 24

Completing Verification Phase
Analytical and clinical validation will follow

Biomarker Panel is Predictive Beyond Day 7 in NHPs



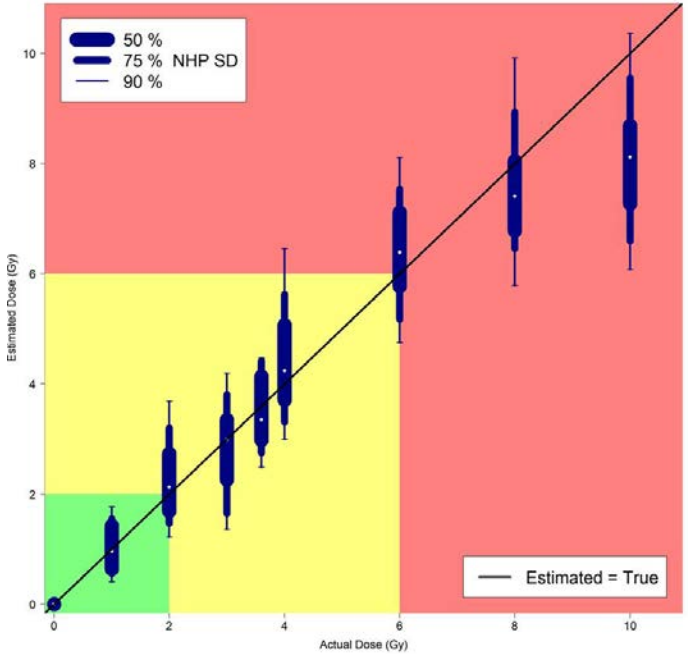


High Throughput Laboratory-based Biodosimetry Projects

Developer	HT Technology	Type
MRI Global/AZ State U/ Thermo Fisher	Gene expression	Semi-automated QuantStudio Dx
ASELL LLC	Cytology - *micronuclei*	Semi-automated including Cytology Microscopes
DxTerity	Gene expression	Semi-automated including ABI 3500 Dx

Completing Verification Phase
Analytical and clinical validation will follow

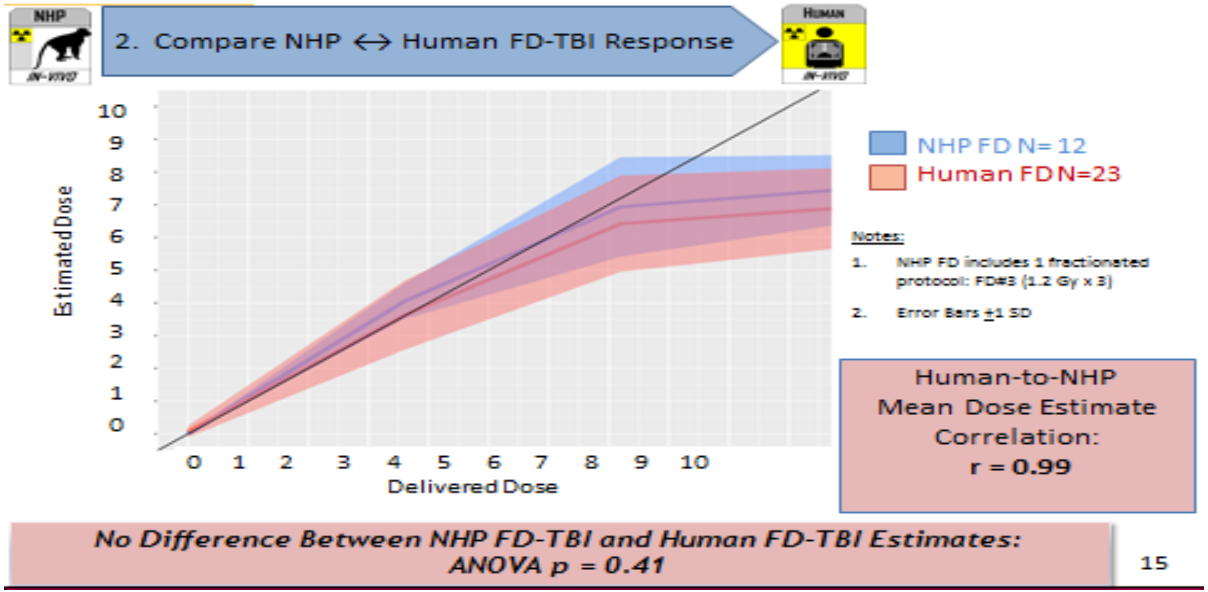
DxTerity Single Dose NHP Data



Confidence Interval Plot of Estimated Dose versus Actual Dose of Cross-validated NHP Single Dose (SD) data (893 samples) for all times post-irradiation combined (1 to 7 Days).

Human to NHP Fractionated Dose Comparison

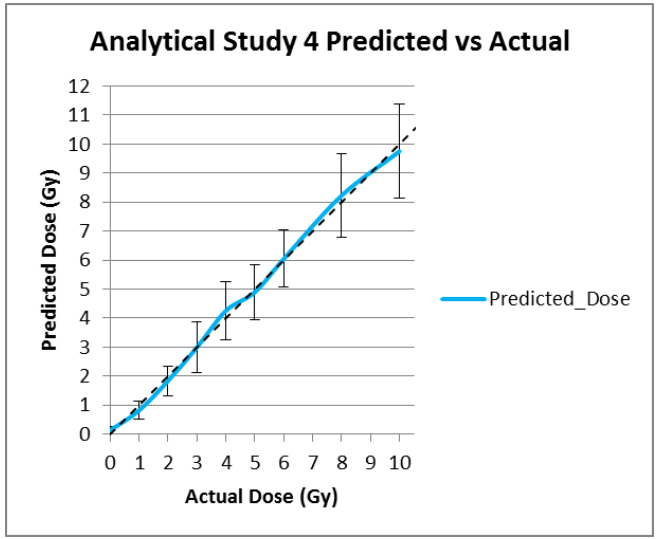
ASU ARAD Biodosimeter (15 biomarkers)



ASELL Human Micronucleus Assay Analytical Performance

Irradiation of human blood samples ex vivo

- Apparently healthy adult human subjects used to establish current analytical performance
- Results demonstrate accuracy with 90% of results within 1.2 Gy of actual dose across 2-6 Gy



Error bars indicate +/-1 SD from the mean at each actual dose level.

Biodosimetry Test Next Steps

Developers are proceeding to:

- Product Validation / Clinical Testing
- Pre-Emergency Use Authorization filing
- FDA clearance
- Acquisition of Initial Test Stockpile
- Maintenance of Stockpile through 2026

Conclusions

BARDA is advancing high-throughput and point of care biodosimetry tests toward:

- Attaining **Pre-Emergency Use** status to continue preparing the nation for a radiological incident
- Seeking **FDA clearance** for at least one high-throughput and one point of care biodosimetry test to enhance our preparedness position
- Developing a **test implementation strategy** with CDC, state and local stakeholders to help inform patient management, improve health and psychosocial outcomes, and save lives