Development of CellRADx as a Tool for Dose Assessment and Triage

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Disclosures

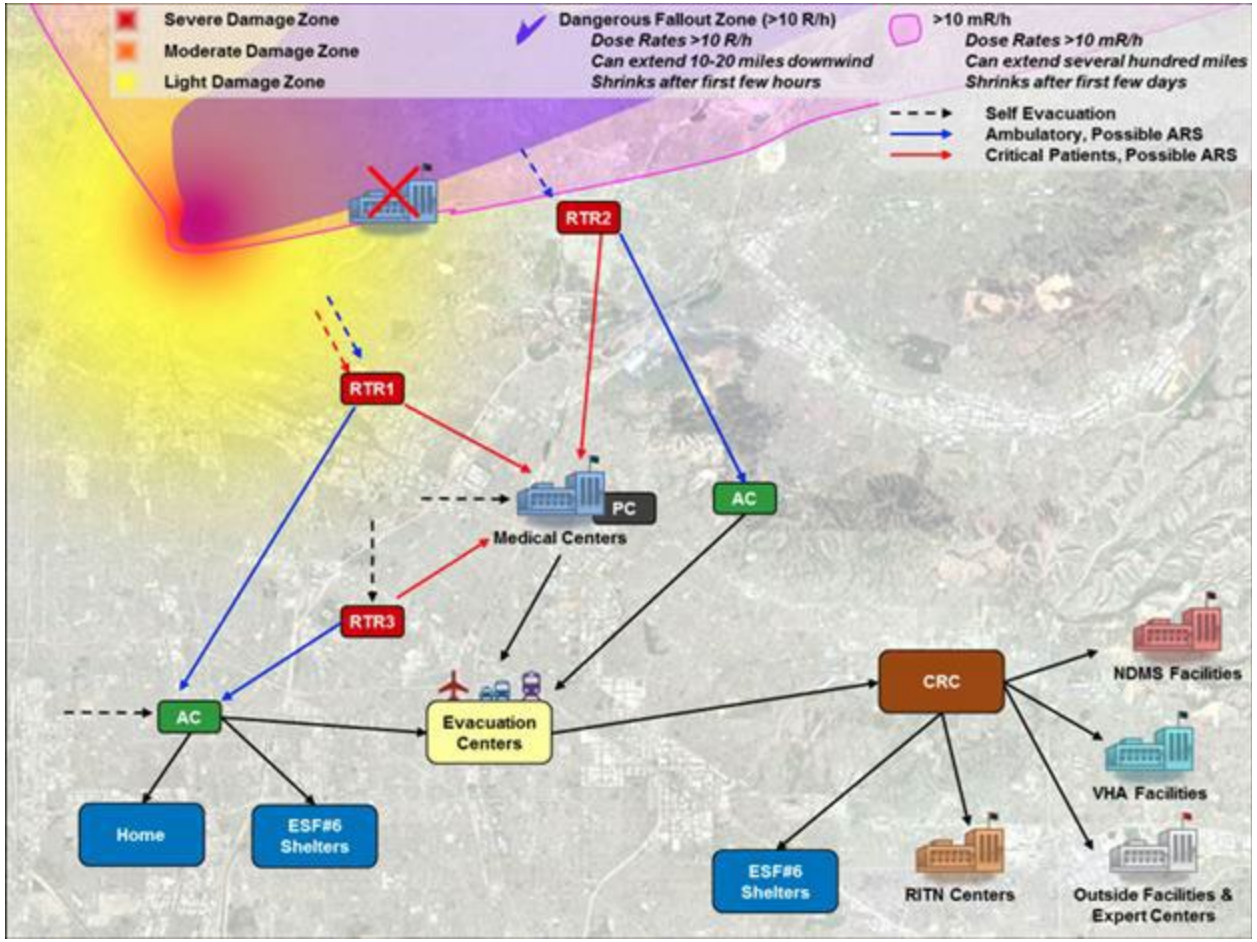
William F. Blakely, PhD.

All relevant financial disclosures have been mitigated.

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
- 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

CellRADx Qualitative Biodosimeter

- CellRADx Software Application designed to identify people with significant ionizing radiation exposure (>2 Gy)
- User Inputs:
  - A patient's CBC result (at a single timepoint) from existing CBC instruments
  - Time post-exposure, age, select medical conditions
- Benefits:
  - **Operationally Relevant:** Discriminates exposures >2 Gy across 1-7 days post-exposure
  - **Clinically Effective:** High sensitivity and 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 software app
  - **Operational Flexibility:** Compatible with wide variety of CBC instruments; provides triage capabilities in field-forward locations and other med facilities w/o added infrastructure or sustainment costs

Triage Sites

Field Hospitals

Treatment Facilities

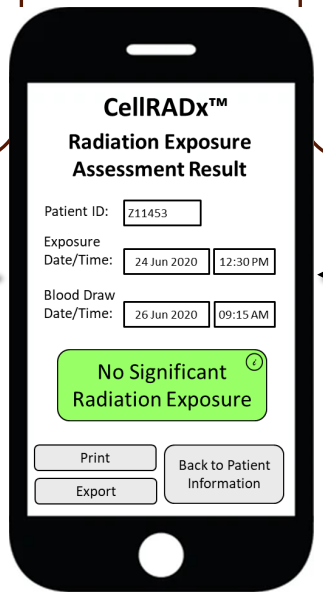
Flexible Architecture

Point of Care CBC Instruments

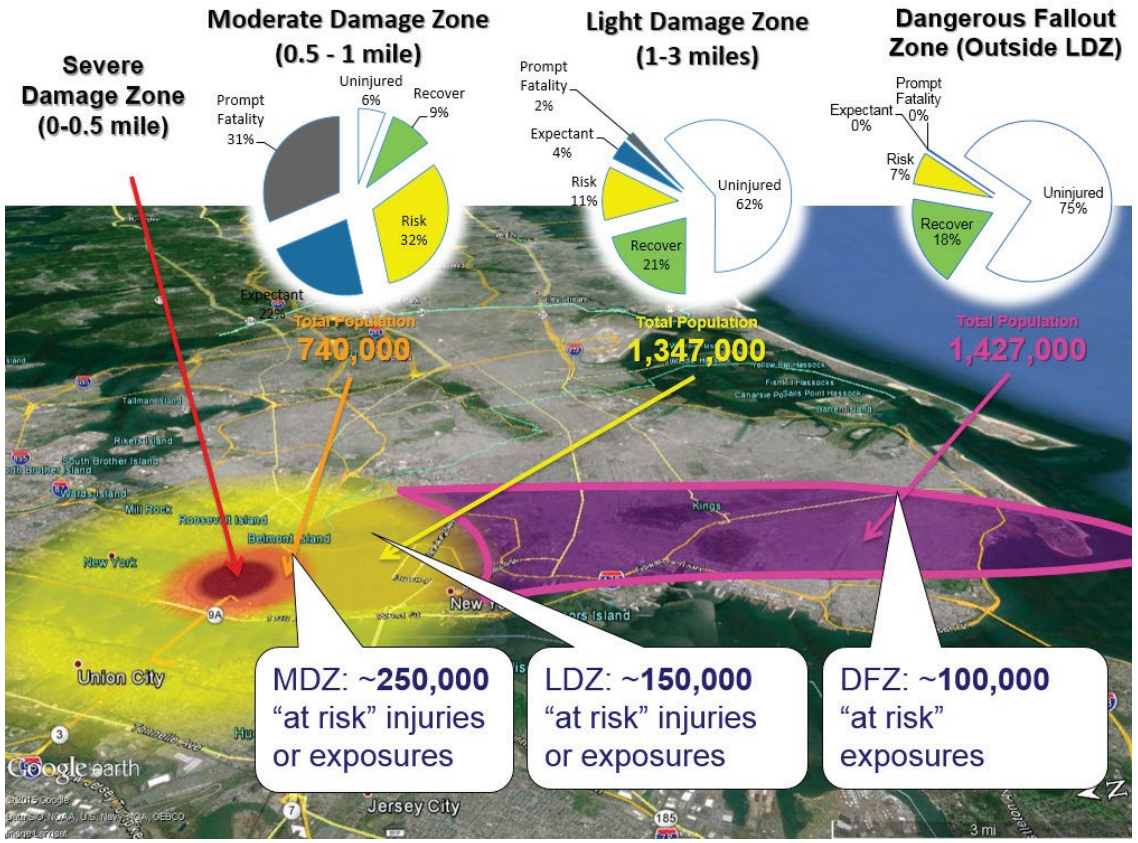
Lab-based High Throughput CBC Instruments

Hematology Data

Hematology Data



Intended Use Population



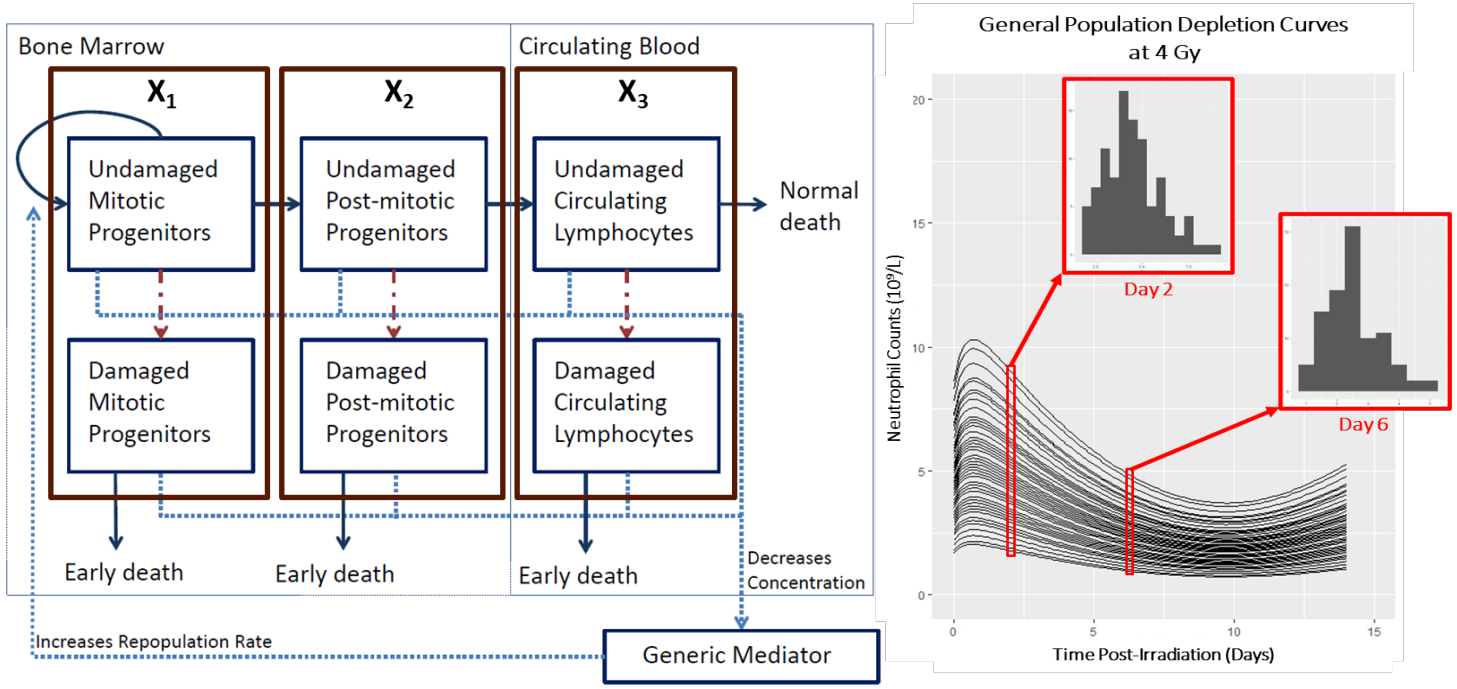
Model of 10kt denotation in NYC. Source: B. Buddemeier presentation[1]

- Evaluating clinical performance requires testing of representative intended use population
  - 'Negative' population – individuals with low or no dose
  - 'Positive' population – individuals with significant dose
- Distribution of absorbed doses in a mass casualty event is uneven. Significantly more low dose exposures (0-2 Gy) than high dose exposures (2+ Gy) are expected.
  - On the order of ~7-10x more 'negative' cases
- Significant prior work in nuclear blast modeling by LLNL (Buddemeier), BARDA (Knebel), and others
  - Many factors can affect absolute casualty numbers
    - Detonation yield, height of burst, population density, building types, weather patterns, etc.
  - However, the relative proportion of the dose distribution across the population is similar

(1) Buddemeier B, *Response Needs After a Nuclear Detonation* presented at "Policies and Regulatory pathways to FDA licensure: Radiation Countermeasures and Biodosimetry devices" workshop hosted by NIH/NIAID/DAIT/RNCP on October 9-10, 2018

In silico Blood Cell Depletion Modeling

- Data from real-world nuclear accidents are limited and prospective studies not possible
- Developed a multi-compartmental hematopoietic model based on prior published studies
  - Based on work by Smirnova, Hu, Blakely, Cucinotta, Wentz, Oldson, and Stricklin
  - Similar models used in clinical trials of MCMs (e.g., dose regimen design for Neulasta and Nplate)
- Model is used to generate simulated data for irradiated population by taking real CBC results from unirradiated subjects and applying cell depletion model
  - Can generate data at any given dose for many days post-exposure
  - Approach can be used to support both development and validation

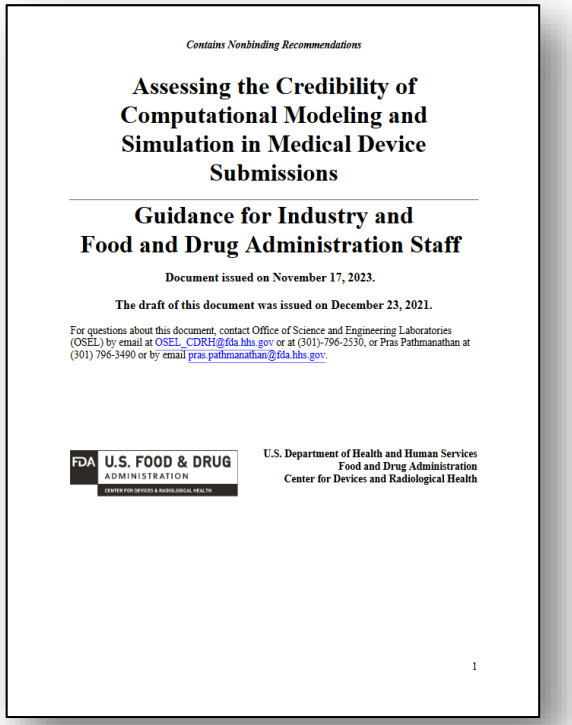


Left: *Graphical representation of depletion model structure (adapted from Wentz, 2014), which simulates the basic functions of the hematopoietic system using a "multi-compartment model" to represent various cell types at a range of maturity levels.* ***Right:*** *Example of modeled data output using 100 subjects randomly selected from general population database simulated with 4 Gy exposure. Each line represents simulated depletion of neutrophils for one person across a given range of time.*

Modeled and Real-World Data

- Modeled cell depletion aligns well with real-world data from accident victims
  - Example neutrophil data shown at right

- FDA published guidance (November 2023) on using computational modelling in Medical Device regulatory submissions



Contains Nonbinding Recommendations

Assessing the Credibility of Computational Modeling and Simulation in Medical Device Submissions

Guidance for Industry and Food and Drug Administration Staff

Document issued on November 17, 2023.

The draft of this document was issued on December 23, 2021.

For questions about this document, contact Office of Science and Engineering Laboratories (OSEL) by email at OSEL_CDRH@fda.hhs.gov or at (301)-796-2530, or Pras Pathmanathan at (301) 796-3490 or by email pras.pathmanathan@fda.hhs.gov.

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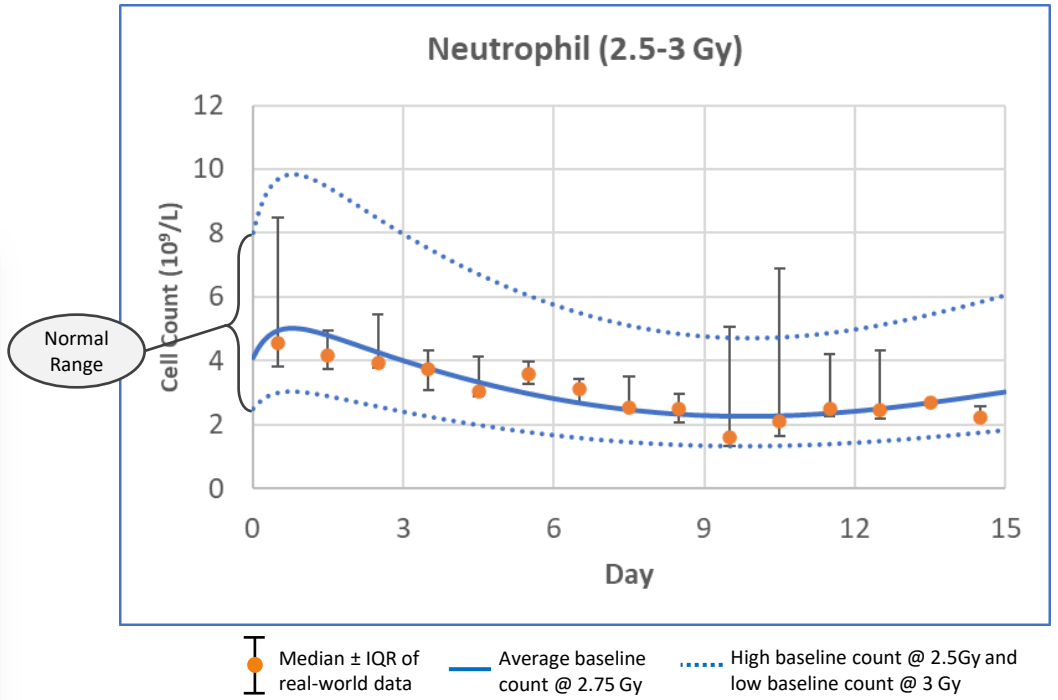
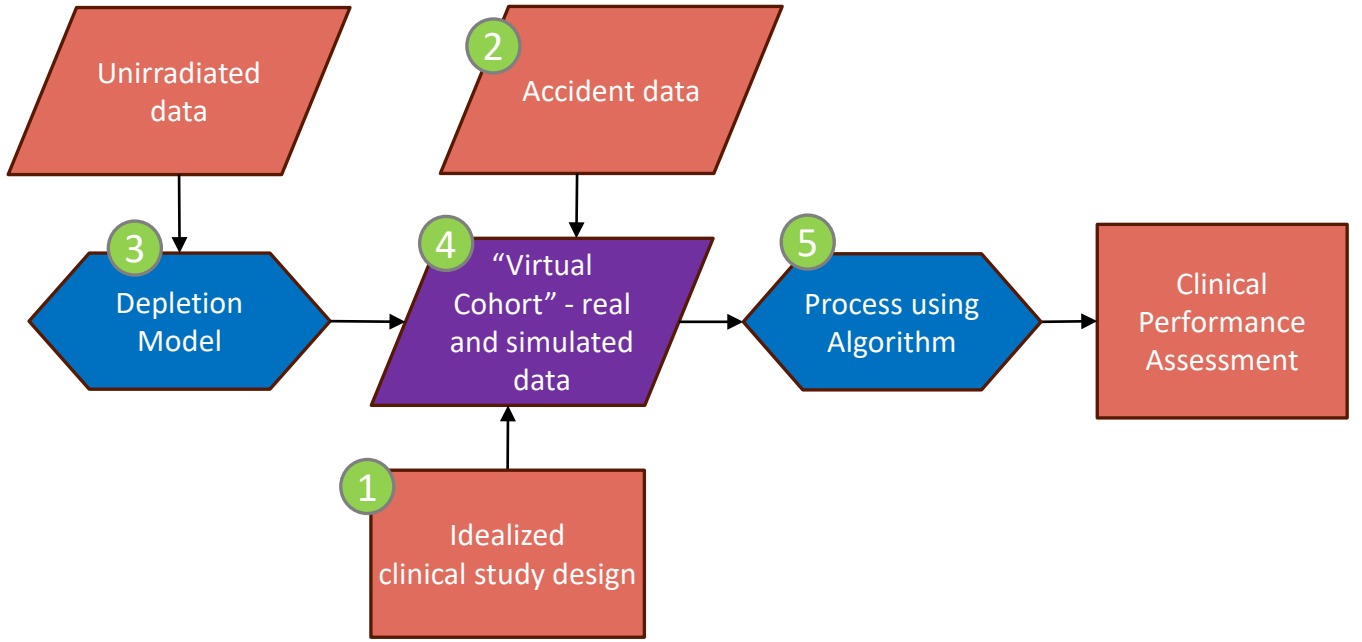


Example range limits for simulated neutrophil counts compared to real-world radiation accident victim data (7 subjects). Simulated data generated using depletion model and initial cell counts (at Day 0) spanning a typical human range.

Clinical Validation Approach

- Clinical validation approach based on conventional study design for qualitative test, but using combination of data sources in place of prospective clinical enrollment

1) Establish how many POS/NEG subjects (total and per dose) are needed based on statistical significance and published disaster models
2) Utilize available real-world accident data (RWD) from Bundeswehr SEARCH database
3) Using cell depletion model and unirradiated human data, generate an array of simulated cell counts as a function of time and dose
4) Supplement available RWD with *in silico* data to create a virtual cohort of subjects for the test population
5) Validate performance of CellRADx across all days and doses using combined dataset

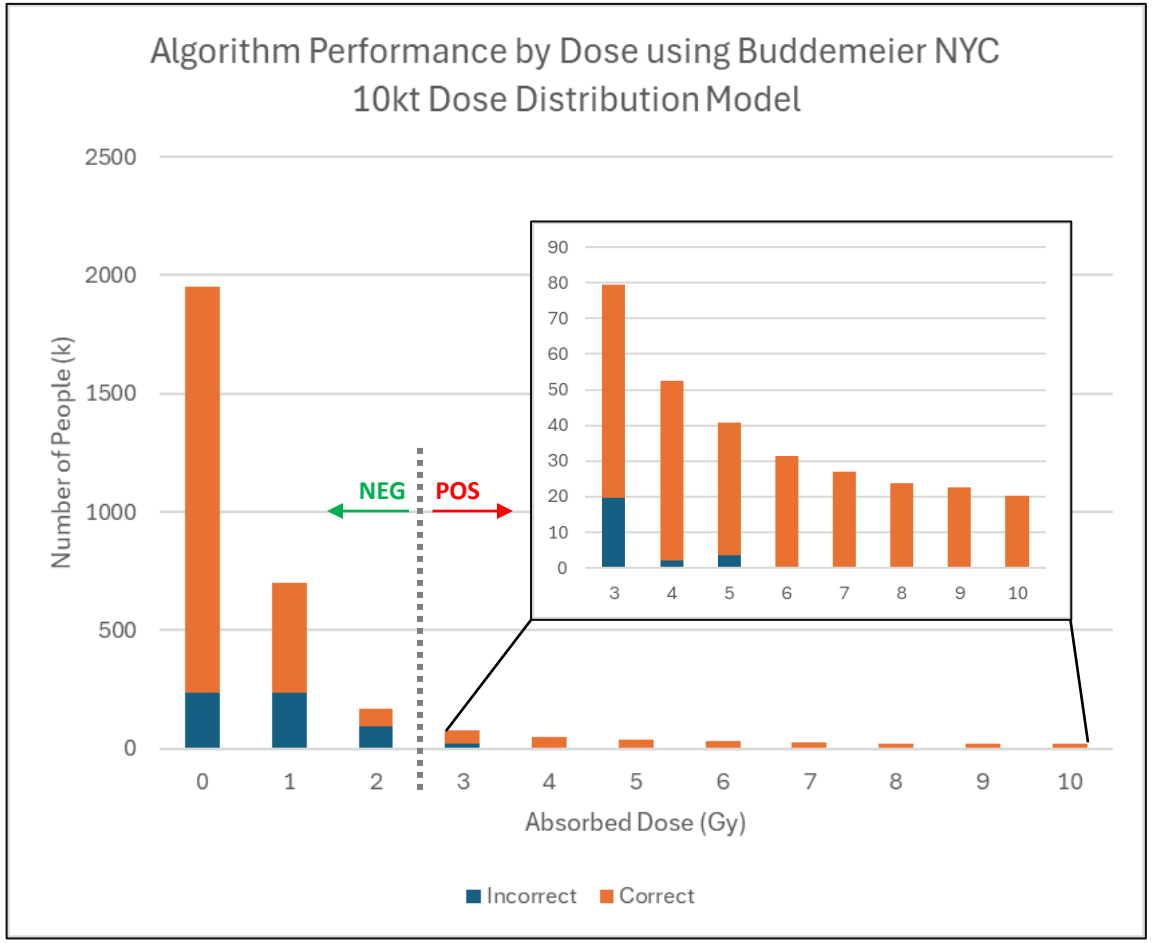


- Other validation studies (repro, usability, flex studies, etc.) in accordance with applicable CLSI and FDA guidance

Assessing Performance

Dry run of validation approach using developmental data

- Assessed performance on general population using intended validation approach
  - Buddemeier-based dose distribution model for 10kt NYC model
  - Radiation accident CBC data from AFRRI, REAC/TS, IAEA and others
  - Unirradiated CBC data from NHANES[1]
- Overall clinical sensitivity of **92%** and specificity of **78%** across general population
  - Assessments with high prevalence demographics (age, sex, race, ethnicity) and comorbidities (burns, trauma, acute infection) show similar performance
- Working to assess performance with other potentially confounding medical conditions with abnormal CBC values



Performance assessment results using combination of real world data from radiation accidents and simulated data based on general population CBC values. Number of subjects per dose matched to relative distribution of doses based on Buddemeier NYC model. Orange bars are correct results, blue bars are incorrect results, based on a 2 Gy POS/NEG threshold.

1) National Health and Nutrition Examination Survey, Centers for Disease Control and Prevention. https://www.cdc.gov/nchs/nhanes/index.htm

Summary

- There is an unmet need for rigorously validated biodosimetry 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
- Use of validated biodosimetry devices will increase the efficiency of emergency medical care through early triage of radiation exposed victims and determination of the amount of radiation absorbed
- Validation of biodosimetry tests is challenging and requires unique approaches to demonstrate safety and effectiveness under FDA regulations
- 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

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Turning Science Into Solutions

Algorithm Performance

Testing with additional subpopulations

- Performance assessed on special populations of significant prevalence (>1%) with abnormal cell counts
  - Used Buddemeier-based dose distribution model (for relative dose proportions within test population) and cell depletion model (to fill gaps in real world data)
- Performance already close to meeting final targets of 90% sensitivity and 80% specificity across wide portion of intended use population
  - Sensitivity (>2-10 Gy) generally above target
  - Specificity (0-2 Gy) meets objective for some subgroups, slightly below target for others
- Further performance improvements expected as part of remaining development efforts

Despite a wide range of cell counts in the IU population, our algorithm overcomes this challenge, with early performance already close to target, even for challenging populations.

Test Population		Prevalence in IU Pop	Sensitivity (Target 90%)	Specificity (Target 80%)
Demographics	Pediatric (age 2-12)	14.5%	89%	90%
	Geriatric (age 65+)	10.8%	94%	74%
	African-American (all age/sex)	13.2%	95%	80%
Pre- and Post-Event Medical Conditions	COPD	3.7%	97%	73%
	Alcohol Abuse Disorder	4.4%	98%	69%
	Obesity	41.9%	97%	77%
	Burn	~15-20%	91%[a]	82%[a]
	Trauma	~20-30%	90%[b]	84%[b]
Common Medications	Amoxicillin (antibiotic)	3.9%	93%	80%
	Ibuprofen (anti-inflammatory)	2.7%	96%	73%
	Omeprazole (proton-pump inhibitor)	4.2%	98%	77%

a. Based on data from 30 subjects ≥10% TBSA. Analysis incorporates platelet counts.
b. Based on data from 30 subjects ISS ≥ 9 Injury Score. Analysis incorporates platelet counts.

Below Target | Target Met