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Making the Case for Absorbed Radiation Response Biodosimetry – Utility of a High-Throughput Biodosimetry System

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There is an unmet need to provide medical personnel with a Food and Drug Administration (FDA)-approved biodosimetry method for quantifying individualized absorbed dose response to inform treatment decisions for a very large patient population potentially exposed to ionizing radiation in the event of a nuclear incident. Validation of biodosimetry devices requires comparison of absorbed dose estimates to delivered dose as an indication of accuracy; however, comparison to delivered dose does not account for biological variability or an individual's radiosensitivity. As there is no FDA-cleared gene-expression-based biodosimetry method for determining biological response to radiation, results from accuracy comparisons to delivered dose yield relatively wide tolerance intervals or uncertainty. The Arizona State University Biodesign Institute is developing a high-throughput, automated real-time polymerase chain reaction (RT-PCR)-based biodosimetry system that provides absorbed dose estimates for patients exposed to 0–10 Gy from blood collected 1–7 days postirradiation. While the absorbed dose estimates result from a calibration against the actual exposed dose, the reported dose estimate is a measure of response to absorbed dose based on the exposure models used in developing the system. A central concern with biodosimetry test evaluation is how variability in the dose estimate results could affect medical decision-making, and if the biodosimetry test system performance is quantitatively sufficient to inform effective treatment. A risk:benefit analysis of the expected system performance in the proposed intended use environment was performed to address the potential medical utility of this biodosimetry system. Uncertainty analysis is based on biomarker variability in non-human primate (NHP) models. Monte Carlo simulation was employed to test multiple groups of biomarkers and their potential variation in response to determine uncertainty associated with dose estimate results. Dose estimate uncertainty ranges from ±1.2–1.7 Gy depending on the exposure dose over a range of 2–10 Gy. The risk:benefit of individualized absorbed dose estimates within the context of medical interventions after a nuclear incident is considered and the application of the biodosimetry system is evaluated in this framework. NHP dose-response relationships, as measured by clinical outcome end points, show expected biological and radiosensitivity responses in the primate populations tested and corroborate the biological variability observed in the reported absorbed dose estimate. Performance is examined in relationship to current clinical management and treatment recommendations, with evaluation of potential patient risk in over- and underestimating absorbed dose.

INTRODUCTION

Physical dosimeters such as radiation monitoring badges, (e.g., the Luxel+; Laudauer, Glenwood, IL), accurately indicate radiation exposure, rather than the amount of radiation absorbed by an individual. Thus, current radiation exposure evaluation methods assume the biological response to exposure to be equivalent in all subjects, and do not account for biological sensitivity/insensitivity of the individual. In contrast, radiation biodosimetry indicates the amount and effect of absorbed radiation on an individual, which is highly variable depending on several factors, including the amount and location of effective radiation shielding, dose rate, radiation type (gamma or neutron), sky- and groundshine, and inherent variability in biological response to radiation due to health, age and immune status, as well as innate radiation sensitivity. Thus, biodosimetry indicates the individual's clinical or biological response to the radiation dose absorbed which, along with other clinical data can be used by physicians to determine appropriate treatment options, benefiting the public health response (*1, 2*). There is currently no FDA-cleared method to quantify absorbed radiation dose, which could be used as an early indicator for acute radiation syndrome (ARS) monitoring, diagnosis and subsystem treatment (hematopoietic, gastrointestinal and cerebrovascular syndromes) (*1, 3*).

The Arizona State University (ASU) Biodesign Institute (Tempe, AZ) is developing a biodosimetry system that will be able to provide patient-specific information to aid clinicians in managing care decisions within the context of a large-scale nuclear incident. The system under

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TABLE 1
Biomarkers Used in ASU Biodosimetry System, Their Response to Radiation and Function

Gene	Response to radiation	Function
ALPK1	Induced	Immune response
CXXC5	Repressed	DNA damage/apoptosis
SPECC1	Repressed	Nuclear structural protein
MYC	Repressed	DNA damage/apoptosis
ALOX5	Induced	Immune response
CAMK4	Repressed	Cell signaling
CDKN1A	Induced	DNA damage/apoptosis
ADGRE5	Induced	Immune response/GPCR receptor
MOB3B	Repressed	Cell signaling
IL27RA	Repressed	Immune response
HBA2	Repressed	Hemoglobin
PNOC	Repressed	Cell signaling
TEX10	Repressed	Cell pluripotency
PPP6R3	Reference gene	Immune tolerance

development is a high-throughput, automated RT-PCR-based test that uses multivariate analysis of the gene expression levels of 13 biomarkers (Table 1) from a whole blood sample to compute an absorbed dose estimate over 0–10 Gy when tested 1–7 days postirradiation. The biomarkers were identified from transcriptomics and RT-PCR analyses of *in vivo* irradiated NHPs, based on comprehensive selection criteria, including dose-response profiles by day, concordance to gene expression patterns in samples from total-body irradiated (TBI) human patients, and modeling-based feature selection (unpublished data). This biodosimetry system measures an individual's response to radiation as ''calibrated'' to the NHP gene expression response after acute exposure over a range of relevant doses. Therefore, the system's measurement is referred to as an estimated absorbed dose of radiation that indicates the level of exposure, although the estimated dose is a measurement of an individual's response to absorbed radiation. More concisely, the ASU biodosimetry system is being developed to measure individualized response to absorbed dose (biodose) of radiation (in Gy). While the relationship between gene expression and dose of exposure is used to calibrate this biodosimetry system, differences between dose of exposure and these individualized responses are expected to result in a comparatively broad tolerance interval or uncertainty. Unfortunately, assessment of biodosimetry accuracy is limited to the non-optimal analysis of delivered dose versus measured absorbed dose because there is no FDA-cleared method for comparing to biological response or biodose to use to determine accuracy.

The ASU biodosimetry system is being developed to provide results that may be used to inform the healthcare professional to help treat a patient in the event of a nuclear incident. The result would not be used by itself, but in combination with physical dose information, if available, clinical symptoms, consideration for combined injuries, and in the context of existing and concurrent medical conditions. We believe this new, high-throughput biodosimetry method may positively influence patient care by providing a quantitative measure of biological response to radiation, while informing long-term clinical management within the constrained health care capabilities and capacities immediately after a large-scale nuclear incident.

OVERVIEW OF POTENTIAL RISKS TO PATIENT HEALTH

The potential risk of biodosimetry tests to patients consists of inaccurate or imprecise test results leading to inappropriate clinical treatment decisions, and misinterpretation of test results, which again could lead to erroneous treatment decisions (*4*). Overestimation of absorbed dose could inappropriately indicate the need for ARS treatment, which could lead to waste of medical countermeasures (MCM) or exposure of the patient to side effects of cytokine MCM treatment, although side effects are not common or deleterious with this treatment (*5*). Overestimation taken to an extreme could lead to incorrect patient classification to the expectant response category, resulting in missed opportunities to provide potentially life-saving treatments in a limited-resource environment. Conversely, underestimation of absorbed dose for higher dose levels (8–10 Gy) could result in failure to administer indicated, possibly life-saving, treatment such as hematopoietic stem cell transplant (HSCT) (*6*), or result in waste of medical resources on a patient that was terminal and required palliative care. At doses $\leq$2 Gy, underestimation of dose by biodosimetry would be less impactful, as lethality due to ARS is 0% (*7*) and lymphocyte depression is not clinically significant (*8*). Underestimation of absorbed dose for the most clinically relevant doses ($>$2–6 Gy), such as those that result in moderate to high ARS lethality, represents the most significant risk to the patient (*4*).

UNMET NEED

Biodosimetry, a test methodology utilizing measurement of specific biomarkers, provides an estimate of absorbed dose of radiation rather than physical dose of exposure. In the case of the ASU biodosimetry system under development, the biomarkers are changes in gene expression for genes involved in a wide range of cellular functions, including response to DNA damage/repair, cell proliferation, receptor signaling and immune responses (Table 1), while the p53 signaling pathway is the top enriched pathway. Cellular processes, immune processes and B-cell-mediated immune cell communication are common biological functions affected by both low dose rate and acute exposure. Mutations in these pathways are already known to increase radiosensitivity in patients with genetic disorders, e.g., ataxia telangiectasia, highlighting how patient response to radiation can be driven by biological predisposition or complement (*9*). It is important to note that the final biomarkers selected in the ASU biodosimetry

system are not represented by one specific biological pathway and respond similarly in both NHPs and humans upon exposure to radiation (Table 1). Different inclusion and exclusion criteria may result in exclusion of some well-known radiation-responsive genes such as FDXR; examples of these criteria are 1. abundance of transcript level; 2. fold change by day and dose after exposure to radiation; 3. performance by different regression models; 4. baseline biological variance (CV); 5. potential confounding by different disease conditions, age and sex; 6. known radiation-related functions; and 7. correlation between NHPs and humans (*10–12*).

There are potentially significant clinical advantages, particularly in the resource-constrained environment of a large nuclear incident, in providing treating physicians with an absorbed dose estimate as opposed to a physical exposure estimate. By analogy, knowing the ingested amount of a potential toxin, such as an opiate, is helpful to caregivers, but it is often not sufficient for patient management. Caregivers prefer to rely on measurements of patient symptoms, including toxin blood levels along with physiological assessment of the patient's response to guide therapy. Biodosimetry measures the biological response to radiation, which by its nature varies across and within biological systems. The latter category includes interpersonal differences in innate radiosensitivity, immune status, patient genetics, nutrition, and confounders such as immunomodulation or administration of cytotoxic or radiomimetic medications. Moreover, in most settings, it will be extremely difficult to estimate an individualized physical exposure, especially with the added complexity of partial shielding leading to partial-body exposure. Clinicians will want to treat the absorbed dose, as this elicits the specific medical syndromes, and not treat the physical dose of exposure (*1, 2*).

Immediately after a large nuclear incident, it will be necessary to manage potentially hundreds of thousands of patients (*1, 13*). Under current scenario guidance from the U.S. Department of Health and Human Services, Office of the Assistant Secretary for Preparedness and Response (ASPR), initial patient triage includes evaluation of clinical signs and symptoms in conjunction with epidemiological information (i.e., location when exposure occurred, additional medical history) (*14–17*). Estimating absorbed dose is essential for patient triage to ensure judicious dissemination of stockpiled MCM, as signs/symptoms, patient location and medical history do not predict absorbed dose accurately (*15, 16, 18*).

Under current guidelines, to facilitate triage, clinicians will sort patients into response categories with corresponding treatment recommendations (*18, 19*). Guidance from the ASPR recommends several factors be evaluated in patient triage: physical trauma/burns or combined injury, dose estimate, and comorbid conditions. This makes dose a significant factor in category assignment (*18*). However, dose estimate alone does not determine the entire course of medical treatment and is used to assist in initial patient assessment and treatment decisions (*2*).

Accurate and timely absorbed dose estimates are essential for treatment, as administration of cytokine MCM to patients with estimated doses of >2 Gy is recommended within the first 24 h (*20–22*); however, there may still be some benefit with later administration (*23*). There are some other biodosimetry methods such as the dicentric chromosome assay (DCA), which has a turn-around time of 2–3 days; however, only a handful of experienced laboratories around the country can routinely run the assay (*24*). With limited throughput (<100 samples per week), the DCA approach will have limited utility during a large-scale nuclear incident (*3, 4, 13*). Timely diagnosis is vital, but review of the average time to diagnosis after radiation exposures from orphaned sources is 22 days (*25*). There is a gap in current capabilities, as there is no specific, accurate and accessible high-throughput biodosimetry assay to handle the massive influx of patients requiring treatment after a major nuclear incident. The ASU biodosimetry system is being developed to address this important gap and provides individualized absorbed dose estimates to guide administration of MCM and other treatments. With limited instruments, during verification, we successfully tested 2,400 samples in 24 h.

ASU BIODOSIMETRY SYSTEM DEVELOPMENTAL PERFORMANCE

Several sources of variability exist that contribute to inaccuracy (compared to dose of exposure or delivered dose) and/or imprecision in biodosimetry assays. Accuracy assessments for biodosimetry utilize comparison to dose of exposure from experimental total-body irradiation models that utilize linear accelerator (LINAC) X-ray machines. The LINAC X-ray machine used to irradiate test subjects, such as those used in the performance testing of biodosimetry systems, have an inherent variability in dose delivery of approximately 3–5% coefficient of variation (CV) relative to intended dose,[2] which can confound delivered dose-versus-absorbed dose analysis. Additionally, normal differences in biological replicates, as well as imprecision in technical replicates, are sources of variability in the data sets used to train the random forest dose estimate algorithm for multivariate analysis in the ASU biodosimetry system. Despite these sources of variability for both the ''actual'' delivered dose and the estimated dose, the repeatability results at ≥ 2 Gy show CVs $\leq 15\%$. Variability can also be introduced in biodosimetry through the intrinsic radiosensitivity of the subject, which can be affected by their general health, medical history, genetics, and history of prior radiation exposure, among others. Table 2 summarizes the developmental performance of the ASU biodosimetry system.

[2] City of Hope, Duarte, CA (personal communication).

TABLE 2
ASU Biodosimetry System Developmental Performance Summary

Parameter	Metric	Performance
Reporting range	Measurement interval	0.5–10 Gy
	NHP calibration (n = 1,362)	95% within 1 Gy
	Human-to-NHP concordance (n = 25 human and 12 NHPs)	Pearson's r = 0.997 (95% CI: 0.966–1.000)
Accuracy (compared to dose of exposure)	False positive (% nonirradiated[a] measure >0.5 Gy)	<3%
	False negative (% irradiated at 1 Gy measure ≤0.5 Gy)	<1%
	MAE for <2 Gy	<0.5 Gy
	MRPE for ≥2 and <6 Gy	≤50%
	MRPE for ≥6 Gy	≤25%
Repeatability (intermediate precision)	SD and percentage CV >2 Gy	SD range 0–1.0 Gy/CV <15%
Reproducibility	SD and percentage CV	(TBD in validation)
Sample throughput	Sample number processed per 24 h continuous operation	Single system: 564 Dual systems: 2,256

Notes. NHP = non-human primate; MAE = mean absolute error; MRPE = mean relative percentage error; SD = standard deviation; CV = coefficient of variation; TBD = to be determined.

[a] Some nonirradiated samples were tested before locking the ASU biodosimetry system workflow. Samples that indicated >0.5 Gy dose estimate were retested using the locked workflow. 125/126 (99%) of a normal, healthy human population measured ≤0.5 Gy. 308/314 (98%) of a special (pre-transplantation, immunosuppressed, trauma) human population measured ≤0.5 Gy. NHP calibration is a measure of the fit of the algorithm training data.

VARIABILITY OF CLINICAL RESPONSE TO RADIATION

The variability of the dose measurements observed in NHP samples could be due to biological differences or radiosensitivity of each primate. To support the radiosensitivity hypothesis, we report data from contemporary dose-response relationships (DRR) determined at various NHP laboratory exposure sites: SNBL (Everett, WA) (*26*), LBERI (Albuquerque, NM) (unpublished data) and Citoxlab (Laval, Canada) (unpublished data). The primary clinical end point, survival at 60 days postirradiation, was used to determine the DRR for TBI in NHP. Table 3 compares the DRR for NHP that received TBI at different NHP laboratory exposure sites and were administered different levels of medical management. First cited is the current literature from the University of Maryland (*27*), followed by DRR information provided by three sites that conduct NHP irradiation testing (Table 3). The mean dose of exposure end points for survival are reported with their 95% confidence intervals (CI). The width of the CI is affected by the confidence level, sample variability and sample size. If the confidence level and sample size are similar between the calculations, the CI can provide a reasonable comparison of biological variability. Figure 1 shows a lethality curve from SNBL to illustrate the width of the CI across doses (*26*).

In the study by Farese *et al*., clinical outcome and variability in survival were attributed to the biological range of radiosensitivity inherent in the test subjects (Table 3) (*27*). These data show excellent agreement in clinical outcome variability between the cited literature and across HP test sites used for the biodosimetry system development. These variability data should be considered best case, as all animals were male adults sourced from a single provider in China. The 95% CI for survival (approximately 0.5–1.5 Gy computed from Table 3) is consistent with the absorbed dose estimates' overall 95% CI of 0.6 Gy obtained with NHP blind experiments (n = 6 per dose) for a dose range of

TABLE 3
Dose-Response Relationship with Confidence Intervals for TBI Non-Human Primates

NHP test site	Farese *et al*. (*27*)	SNBL [Thrall *et al*. (*26*)]	LBERI (unpublished data)	Citoxlab (unpublished data)
NHP type/gender	Chinese rhesus/M	Chinese rhesus/M	Chinese rhesus/M	Chinese rhesus/M
Radiation source	LINAC 6 MV photon	LINAC 6 MV photon	LINAC 6 MV photon	Co-60 1.3 MV gamma
Dose rate	80 cGy/min	80 cGy/min	60–80 cGy/min	60 cGy/min
NHP number	48 (8/dose × 6 doses)	48 (8/dose × 6 doses)	Unknown	110
Supportive care	Full	Full	Minimal	Minimal
LD30/60 (95% CI)	7.06 (5.01, 7.50)	6.88 (5.98, 7.17)	6.4 (5.6, 6.6)	5.69 (5.19, 5.96)
LD50/60 (95% CI)	7.53 (6.50, 7.88)	7.43 (6.92, 7.91)	6.8 (6.3, 7.1)	6.20 (5.92, 6.43)
LD70/60 (95% CI)	7.99 (7.60, 8.65)	7.98 (7.56, 8.81)	NC	6.71 (6.47, 7.07)
LD90/60 (95% CI)	8.66 (8.23,10.73)	8.77 (8.20, 10.39)	7.3 (6.8, 8.0)	7.44 (7.07, 8.20)

Notes. NHP = non-human primate; M = adult males; full = care same as standard care with blood transfusions as indicated; minimal = animals administered analgesics only on a set regimen regardless of indication; LDX/60 = lethal dose for X% of population at 60 days; CI = 95% confidence interval; NC = not computed.

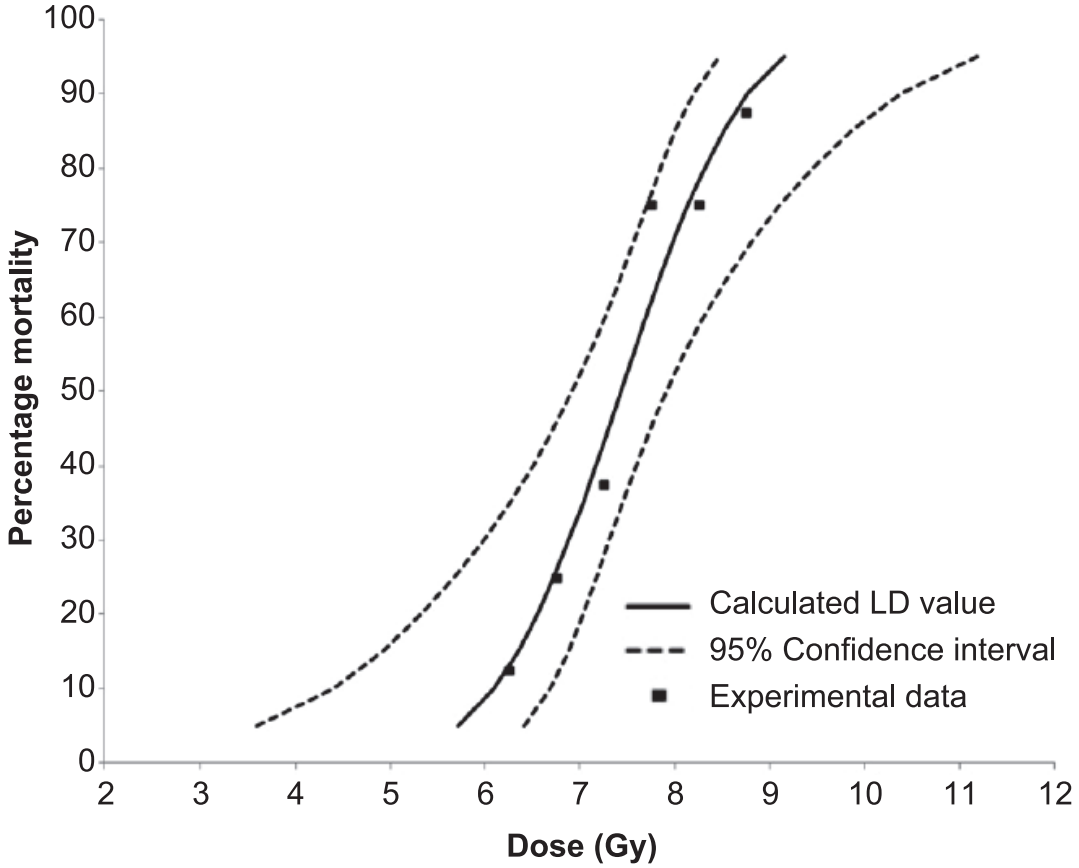

FIG. 1. A lethality curve from Thrall *et al*. (*26*) illustrating the width of the 95% confidence interval with dose. LD = lethal dose. As described by Thrall *et al.,* ''PROBIT plot calculated 60-d lethality of total-body irradiated (TBI) rhesus macaques presented as percent mortality versus TBI dose (Gy). Dashed lines represent that 95% confidence interval and points reflect the actual experimental data. The cohorts were provided supportive medical care, as described by Farese *et al*. 2012. TBI was conducted using 6 MV LINAC-derived photons at a dose rate of approximately 0.8 Gy min^{-1}. The calculated LD50/60 [95% CI] was 7.43 Gy [6.92, 7.91.]'' (Published and modified, with permission, from: Thrall KD, Love R, O'Donnell KC, Farese AM, Manning R, MacVittie TJ. An interlaboratory validation of the radiation dose response relationship (DRR) for H-ARS in the rhesus macaque. Health Phys 2015; 109:502–10.)

2–8 Gy. Comparison of these NHP clinical CI data to the blinded NHP dose estimate CI data suggests that clinical outcome variability is consistent with the variability of individual absorbed dose response as measured using the ASU biodosimetry system. The Table 3 data from Citoxlab indicates less variability but is from a greater sample size than the other comparison studies. These CI comparison data illustrate that biological variability, in this case clinical outcome, is consistent with subject absorbed dose estimate variability (biological response to dose of exposure), as measured using the ASU biodosimetry system.

Use of these biological variability data is not intended to fully address potential inaccuracy of biodosimetry results and the importance of technical variability or imprecision determination is emphasized. In future validation studies, uncertainty of NHP dose estimates provided by the ASU biodosimetry system will also be informed by clinical signs and symptoms of radiation exposure and/or other objective clinical outcomes.

VARIABILITY OF CURRENT CLINICAL PRACTICES IN ESTIMATING DOSE

Utilizing current practices, the Radiation Injury Treatment Network (RITN) holds several exercises a year to prepare participating medical centers for nuclear emergencies. The tabletop exercises in 2017 involved a module where the participating set of RITN centers estimated dose for three hypothetical patients based on a summary that included signs and symptoms, location during blast, time of emesis or nausea (if present), complete blood count (CBC) with differentials and general medical history. The limitations in current methods for estimating dose are exemplified by these data, summarized in Table 4, from the RITN exercises (*28*). As shown in Table 4, the variability in dose estimate, provided by the participating RITN medical centers based on clinical signs and symptoms and CBC, was significant. The dose estimate ranges in Table 4 show the potential for significant over- or underestimation of dose when assigned based on current practices only. Hypothetical patient no. 2

TABLE 4
Summary of Dose Estimate Ranges from Participating Radiation Injury Treatment Network Medical Centers from the 2017 Tabletop Exercises

Tabletop exercise date	Dose estimates (Gy) for hypothetical patients		
	Patient no. 1	Patient no. 2	Patient no. 3
May 30, 2017	4.7–6.0	3.0–4.0	7.0–9.0
June 19, 2017	3.0–4.9	NR	NR
June 28, 2017	3.0–4.7	2.0–6.0	3.0–11.0
July 19, 2017	2.7–7.7	<1.0–3.6	3.6–9.7
August 3, 2017	2.7–6.0	3.0–6.0	7.0–11.0
August 28, 2017	3.0–5.0	3.2–6.0	7.0–11.0
Exercise reported estimated dose based on physical location	3–4	5–6	9–11
REMM LDK dose estimate[a]	4.4	3.1	6.7

Notes. REMM = Radiation Emergency Medical Management website dose estimator; LDK = lymphocyte depletion kinetics; NR = not reported.

[a] Lymphocyte values from exercise materials for the hypothetical patients were used with the online REMM dose estimator. Estimates assume the event occurred at 10:00 and the patient arrived at the hospital and had CBC performed at 15:00, 7 days after the event.

had an estimated dose of 5–6 Gy based on physical location during the blast and 3.1 Gy based on the Radiation Emergency Medical Management (REMM) lymphocyte depletion kinetics (LDK) dose estimate algorithm (*19*).

Therefore, patient no. 2 should receive cytokine MCMs, yet this hypothetical patient was assigned dose estimates by some RITN medical centers as low as <1 Gy, meaning this patient might have missed potentially life-saving treatment. Hypothetical patient no. 3 had an estimated dose based on physical location during the event of 9–11 Gy, and based on the REMM LDK dose estimate algorithm, had an estimated dose of 6.7 Gy. Hypothetical patient no. 3 was assigned a dose estimate by RITN exercise participants of as low as 3 Gy and thus would be administered cytokine treatment but may not have been considered for HSCT or palliative care. It is questionable whether patient no. 3 would have benefited from such cytokine treatment or HSCT, thus leading to waste of medical resources that could benefit other non-expectant patients. Patient no. 1 had a dose estimate of 3–4 Gy based on physical location during the event, and 4.4 Gy based on the REMM LDK dose estimate algorithm. At the high end of the dose estimate range the RITN sites provided for hypothetical patient no. 1, a dose estimate approaching 8 Gy was given, meaning this patient may have been considered for HSCT when it was not perhaps necessary. Given the high resource requirement and patient risk that HSCT presents, this dose estimate uncertainty based on current practices could be significant.

Swartz *et al*. points out that biodosimetry tools should estimate dose within ±0.5–1.0 Gy of the actual exposure dose since known individual variation in radiation response makes more accurate estimations of dose clinically irrelevant (*4*). However, the range in dose based on clinical signs and symptoms exemplified by the RITN exercises far exceeds the individual variability in radiation response. Together, these RITN data highlight the need for objective rather than subjective dose estimation methods, such as that which the biodosimetry systems can provide.

The RITN facilities repeatedly train and prepare for the treatment of bone marrow failure and care for patients suffering from ARS. As the national sites for bone marrow and HSCT transplantation, the RITN practices to respond to nuclear incidents multiple times a year, including how to interpret signs and symptoms to provide a dose estimate. During a large nuclear incident, it is likely that clinicians without such training or expertise will be called upon to make dose estimates and corresponding treatment decisions, thus increasing patient risk of incorrect medical management.

POTENIAL APPLICATION OF A HIGH-THROUGHPUT BIODOSIMETRY SYSTEM IN THE INTENDED USE SCENARIO AND MEDICAL RESPONSE

The potential clinical utility of the high-throughput ASU biodosimetry system is best described in a concept of operations (CONOPS) (Fig. 2) of a hypothetical nuclear detonation event.

Based on the Defense Threat Reduction Agency (DTRA) Hazard Prediction Assessment Capability Program version 3.2.1, assuming a 10-kiloton detonation in a city of 2 million, almost 900,000 people would immediately require some type of medical care or monitoring (*13*).

After decontamination and immediate patient stabilization by first responders, clinical examination would be performed to assess signs and symptoms, and blood would be obtained for a variety of laboratory tests, including lymphocyte counts and absorbed dose estimate from the biodosimetry system. Cytokine MCMs may be administered prior to any such testing or even prior to decontamination in some cases if resources allow. Biodosimetry-based dose estimates would be available to treating clinicians within 24 h of laboratory receipt of the blood samples to help inform or refine treatment decisions.

High-throughput biodosimetry-generated absorbed dose estimates would alleviate the high patient load, an estimated

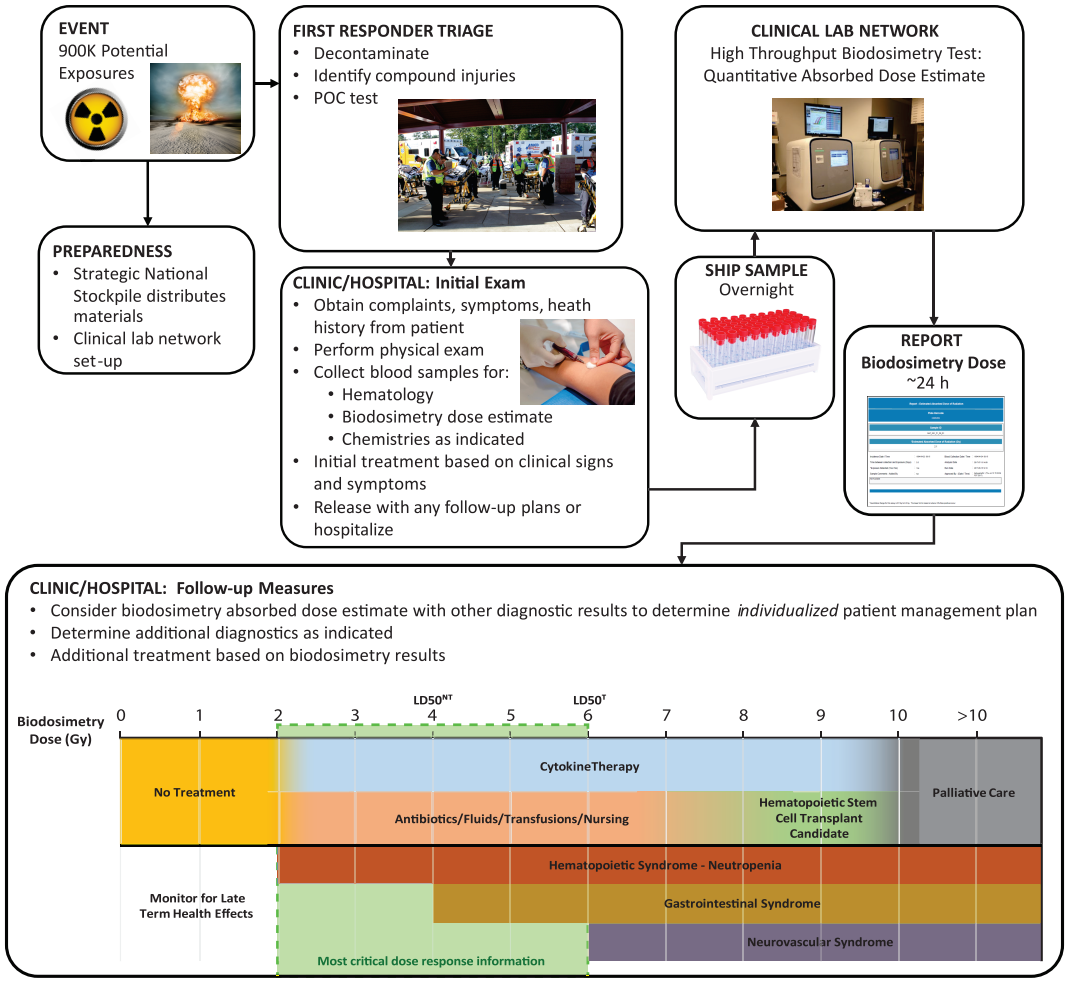

FIG. 2. A concept of operations for a large nuclear detonation scenario presents implementation of the Arizona State University (ASU) high-throughput biodosimetry system currently in development. After a detonation of a 10-kiloton device, approximately 900,000 people would potentially be exposed and seek medical care (*13*). The Strategic National Stockpile would be mobilized to distribute biodosimetry tests and medical countermeasures (MCM) to treating medical facilities. First responders would start treatment with cytokine MCM, if supply allows, perform decontamination, and treat blast-associated injuries (e.g., burns or trauma, among others). If cleared point-of-care (POC) biodosimetry devices are available, they would be used at triage. On initial examination, patient complaints, symptoms and medical history would be obtained. At this stage blood could be collected for lymphocyte counts and/or testing using the ASU biodosimetry system. Whole blood samples would be shipped overnight to the clinical lab network for testing and absorbed dose reports could be available to treating medical personnel as soon as 24 h after sample arrival. Absorbed dose estimates could refine treatment in progress or guide treatment initiation if not already started. The treatment table at the bottom of the figure (*1, 2, 18*) shows guidance for treatment by dose, with the dose that would kill 50% of the population (LD50), indicated as no treatment ($LD50^{NT}$) or with treatment ($LD50^{T}$).

556,000 (*13*) at treating medical facilities in the response area by potentially identifying patients that require no treatment in the 0–1 Gy range at a low false positive rate. While CBCs could help screen this large ''worried well'' population, it is unlikely with this many patients that CBCs, especially serial CBCs, would be a viable test option. The current recommendation for patients with a dose estimate of 0–1 Gy is treatment of physical trauma, if present, and simple monitoring (i.e., watchful waiting). This testing is critical for non-exposed patients who nevertheless exhibit clinical symptoms of radiation exposure due to traumatic stress, such as vomiting and diarrhea, to alleviate any psychological trauma (*13, 19, 25*). The biodosimetry result would give patients the added certainty that their radiation exposure was not threatening in the short or long term.

Patients receiving doses between 2–7 Gy would, in addition to immediate treatment of acute blast injuries, receive antibiotics, fluids and blood transfusions as necessary (Fig. 2, bottom) (*1, 11*). Biodosimetry-based dose estimates in this range would also help to differentiate those patients who may need additional monitoring, diagnostics and/or treatment for radiation-related gastrointestinal sequelae.

Current treatment guidelines recommend administration of cytokine MCMs between 2–9 Gy. Patients with a dose of at least 10 Gy would receive palliative therapy only due to their poor prognosis (Fig. 2, bottom) (*1, 18*). In the DTRA 10-kiloton detonation scenario, the cytokine-treatment patient population would number an estimated 188,000 (*13*). Early administration of cytokines, particularly within 24 h postirradiation, significantly improves prognosis and reduces the severity and duration of the hematopoietic syndrome (*20–22*), although later administration may still be beneficial for gastrointestinal ARS (*23*). Having an absorbed dose estimate would be crucial for patient medical management in this exposure range, as not all patients will present with clear symptoms such as nausea, anorexia and fatigue. Asymptomatic, exposed people will predominate the patient population presenting for care (*25*). Significant percentages of patients will not present with vomiting or diarrhea within the first 2 h postirradiation after exposure to doses up to 4 Gy (*25*). While serial CBCs could help guide treatment decisions, it is unlikely that such testing would be available, given the large number of patients and limited medical resources in such a scenario. Also, the uncertainty for estimating dose based on serial CBC measurements has not been reported; however, from REMM resources it appears that a minimum of three measurements is needed to reduce uncertainty (*19*). Identifying those patients who do not need cytokine treatment ($<$2 Gy), or would not benefit from such treatment ($>$10 Gy), based on biodosimetry absorbed dose, would help conserve precious MCM stockpiles in the resource-constrained disaster setting.

Other clinical signs and symptoms are not necessarily specific to the radiation exposure. Symptoms that mirror clinically significant irradiation, such as vomiting, nausea, dizziness, gastrointestinal distress and fatigue, may present in 30–60% of people experiencing hysteria after an incident or nuclear attack (*29*). Even for patients who have received significant exposure, there is variability in clinical signs and symptoms. Vomiting, for example, is only observed in 10–50% of patients receiving a dose of 1–2 Gy, and in 70–90% of patients receiving doses of 2–4 Gy (*25, 30*). Variability in nausea and vomiting is based on individual sensitivity, a phenomenon that is well known among radiation oncologists (*30*). Time to emesis has a relative error of 200% in dose predication (*31*). LDK is an established tool for very early dose estimation for triage purposes (*32, 33*), but can also present specificity challenges given the wide range of normal levels seen in a healthy population, from 1,000–4,800/ml blood in adults (*34*), and the fact that other medical conditions, medications, or presence of burns and/or trauma can affect LDK accuracy. While signs and symptoms might be helpful for very early triage, biodosimetry systems could provide refinement of the dose estimate before ARS manifests, giving clinicians a head start on treating the coming hematopoietic, gastrointestinal and/or neurovascular syndromes and other radiation-induced organ damage, such as lung and kidney damage.

HSCT may be an effective treatment for those patients receiving a radiation dose of 8–10 Gy, if significant burns are not present (Fig. 2, bottom) (*1, 18*). The HSCT treatment range may vary based on size of the nuclear incident and medical resource availability. This narrow range in dose cannot be quantified by DCA due to significant lymphopenia above 5 Gy (*35*). It is difficult to estimate the number of patients in the DTRA scenario in this HSCT transplant window, but a reasonable estimate might be $\leq$40,000 (*13*). The RITN can currently only support approximately 10,000 HSCT patients (*36*). Given that transplantation is a complex process requiring HLA typing, donor identification, and significant, extended hospital care, identifying patients in this restricted Gy dose window in the resource-limited emergency environment is critical. Given the high resource need to support HSCT and the high number of patients, it is unclear if this treatment would be compatible with a large nuclear incident. The greater the clarity on the absorbed dose a patient has received, the greater the likelihood that patients who could receive benefit can be identified, assuming results of other diagnostic testing in support of HSCT show it as a viable option.

RISK:BENEFIT ANALYSIS

For this risk:benefit analysis (Fig. 3), uncertainty in the ASU biodosimetry measurement is reported as k-factor multiplied by standard deviation (SD), with SD determined by Monte Carlo simulation, which tests the precision of dose estimates when the variability of each biomarker is introduced. The k-factor was set at 95% confidence and 99% coverage for each dose level. This uncertainty based on imprecision is used to test the impact of under- or overestimation of the absorbed dose in the analysis below, rather than uncertainty based on accuracy due to the biological variability of individualized response as discussed earlier. This risk:benefit analysis was performed without consideration for compound injury. The risk was considered according to the following classifications, with influence by risk mitigators that are independent of dose estimate: none (no risk); low; moderate; or unacceptable.

In the case of biodosimetry, the greatest risk to patients is significant underestimation of absorbed dose, yielding a dose estimate under the large Gy ranges over which treatment is prescribed (Fig. 3). Some suggest biodosimetry methods should skew toward overestimation of dose to allow for the most conservative treatment approach (*4*). While this would reduce the MCM resources in the disaster setting, it presents little risk to the patient, whereas underestimation of absorbed dose could result in lack or delay of potentially lifesaving treatment. Responders will want and will tolerate a test that overestimates exposure, with the tolerance level tied to resource supply and not patient risk, due to the much higher patient risk an underestimate would involve (*4*). Physical signs and symptoms of radiation exposure are more apparent with

Risk-Benefit Analysis[a] for Absorbed Dose Estimate Uncertainty for the ASU Biodosimetry System in Development

Dose of exposure (Gy)	ASU biodosimetry system uncertainty range (Gy)[b]	Current treatment[c]	Patient risk if dose underestimated	Patient risk if dose overestimated	Risk mitigators	Biodosimetry benefits
0	≤3% FP	No treatment	None	None	None	Console worried well with greater certainty.
1	≤1% FP			Low		
2	0.8–3.2	Antibiotics/fluids/transfusions/nursing; Cytokine therapy	Low. May miss cytokines but ARS lethality at 1–2 Gy is 0%.[d]	None	Treat considering LDK, emesis, clinical signs and symptoms. No side effects from treatments.	Differentiate low- from high-risk patients with greater certainty.
3	1.7–4.3		None			ID for neutropenia and GI syndrome monitoring.
4	2.6–5.4					
5	3.5–6.5					
6	4.4–7.6				Treat considering hematology. Other diagnostics decide HSCT and monitor for organ damage. HSCT presents its own risks.	ID for neurovascular syndrome; differentiate high- from low-risk patients with greater certainty.
7	5.3–8.7			None. Decision to treat with HSCT not made by dose estimate but determined by hematology		
8	6.3–9.7	HSCT; Cytokine therapy	None. Decision to treat with HSCT not made by dose estimate but determined by hematology.			Potential lifesaving interventions
9	7.2–≥10					
10	8.2–≥10	Palliative care		None	None. Poor prognosis	Confirm palliative care.

FIG. 3. ASU = Arizona State University; ARS = acute radiation syndrome; FN = false negative measured in nonirradiated, normal populations; FP = false positive measured in populations exposed to ≥1 Gy; HSCT = hematopoietic stem cell transplant; GI = gastrointestinal; LDK = lymphocyte depletion kinetics, ID = identify. [a]Analysis performed without consideration for compound injury (trauma, burn, etc.). To consider compound injury, treatment and risk should be evaluated for a dose 2 Gy higher than estimated. [b]Uncertainty ranges are based on k-factor multiplied by standard deviations as computed by Monte Carlo simulation. The k-factor is set to 95% confidence, 99% coverage. [c]Treatment guidance references Garty *et al*. 2017 and Coleman *et al*. 2011 (*1, 18*). [d]International Atomic Energy Agency Report 1998 (*7*).

higher absorbed doses, thus without biodosimetry tests, the classical clinical approach will tend towards underestimation of dose. Biodosimetry testing presents the possibility to detect radiation absorption prior to confirmed ARS symptomology.

To highlight the risk associated with underestimating the absorbed dose estimate, consider the medical decision points at 2 Gy and 6 Gy (Fig. 3). The ASU biodosimetry uncertainty at 2.0 Gy could result in an underestimated dose of 0.8 Gy. Patients receiving such a dose estimate might miss antibiotics, transfusions or fluid treatment, and miss cytokine MCM treatment, although there is not consensus in the literature if cytokine MCM treatment should begin at 2 or 3 Gy (*1, 18*), and the decision to treat with cytokines will be heavily influenced by the resource supply. While cytokine MCM is generally discussed as being initiated at 2 Gy, if the resource supply is high, treatment may be initiated in patients with a dose less than 2 Gy. Conversely, if a significant number of patients present with doses at or above the LD50 without treatment (4 Gy) and resources are limited, cytokine treatment may be reserved for use in these higher-dose patients. ARS at 1–2 Gy is considered mild with only outpatient monitoring required and 0% lethality from ARS (*7*). Considering the 6 Gy point, 4.4 Gy is the low end of the uncertainty range in absorbed dose estimates, yet treatment is the same between 4.4 Gy and 6.0 Gy, resulting in no risk of a missed treatment opportunity.

Looking at patient risk from overestimating dose at medical decision points, the upper end of the uncertainty range at 2.0 Gy is an absorbed dose estimate of 3.2 Gy. Treatment is the same between 2.0 Gy and 3.2 Gy, so there is no risk to the patient. Even if cytokine MCMs were given unnecessarily, this presents little risk to the patient, as side effects are not major and considered uncommon (*5*). At the 6 Gy decision point, with a high-end uncertainty in dose

estimate of 7.6 Gy, treatment is again the same at these two dose levels (Fig. 3).

The most significant risk in underestimating dose occurs around the HSCT treatment decision. Underestimating dose could result in some patients, who could benefit from HSCT, not receiving the procedure; however, the decision to treat with HSCT is not based on dose estimates. Other diagnostics are employed to decide the need for HSCT and are required prior to proceeding with HSCT. Additionally, the benefit from HSCT does not appear to be an absolute. The efficacy in treating radiation exposure with HSCT appears limited from the results of the few patients that received this treatment after nuclear accidents. In fact, HSCT is not recommended if the patient has significant burns or other trauma (*13*), and the majority of patients with doses above 6–8 Gy will have such injuries (*25*). In a 1997 review of 29 patients who received allogeneic stem cell transplant to treat acute bone marrow failure after radiation exposure from nuclear accidents, 26 died within the first year. All patients who suffered burns and received transplants died (*37*). After the 1999 Tokai-mura accident, two patients received allogeneic stem cell transplant, and both later succumbed to radiation-induced injuries to other organ systems or infection within less than a year (*38*). The World Health Organization has only made a weak recommendation for bone marrow transplant for radiation exposure victims with no other organ system failure other than hematopoietic, and then only after failure to improve after 2–3 weeks of cytokine MCM treatment (*39*). It is important to note that medical resource availability would likely be far greater for treatment of victims of a nuclear accident versus a large-scale nuclear detonation.

CLINICAL APPLICATION OF BIODOSIMETRY SYSTEMS

In the event of a nuclear incident, physicians and other suitably trained caregivers will have to make management decisions about the clinical care of the patients exposed or potentially exposed to radiation. As in all medical situations, these decisions need to be informed by multiple lines of evidence. Patient evaluation will typically begin with obtaining a history, including any complaints, a description of the events and any new symptoms, and review of systems and relevant medical history. A physical examination may reveal acute issues and could point to the need for imaging studies. Blood tests may also be indicated to assess hematology and clinical chemistry (*2*). Asymptomatic patients with no or few complaints and patients unable to communicate will present diagnostic challenges, since some portion will indeed have absorbed significant amounts of radiation ($\geq$2 Gy) and would be expected to benefit from interventions designed to reduce injury or improve patient conditions caused by the radiation. Such patients may also need increased vigilance for the onset of new symptoms. Biodosimetry has the potential to provide the healthcare workers with informative data to aid in the effective assessment of a patient's true condition (*2, 8*).

It is likely that clinical care will occur in at least two stages. First, the initial evaluation will enable the treatment of patients for any acute injury, such as burns, trauma, inhalation injury and/or acute radiation injury. At the time of the initial evaluation, the healthcare worker could send blood for a biodosimetry test such as that under development by ASU to obtain a quantitative estimate of the absorbed radiation dose (*40*). This information, along with cell counts, has the potential to help identify radiation injury that is not immediately apparent and will inform the second stage of treatment (Fig. 2, bottom), the use of MCM to treat radiation damage or, if indicated, HSCT (*1, 18*). Estimated absorbed radiation doses, combined with clinical assessment, may help the clinician both effectively manage individual patients and plan the use of limited resources (*2, 8, 18*). Clinicians will recognize that clinical lab tests represent a snapshot in time for a unique individual. There will be a range of values that represent any clinical condition. It is expected that clinicians in this scenario would evaluate the estimated absorbed dose in this context, allowing room for some expected variation, and make clinical decisions that favor a conservative approach as best suits the patient and as resources allow (*18*). The clinician will be guided to interpret the reported absorbed dose estimate as a biological response to radiation, as if the patient had been exposed to an acute total-body dose of the reported Gy level, and to interpret the value with the published uncertainty in the measurement. The availability of a biologically based estimate of the patient's absorbed dose will provide an invaluable foundation upon which to facilitate medical management decision making, particularly because absorbed radiation is often not apparent from current standard methods of clinical evaluation.

CONCLUSION

Preparing for a nuclear incident is unfortunately a challenge of our modern world. The high number of resulting patients would inundate and overwhelm the medical facilities in and around the area. Given the high number of potential casualties and the resource limitations that will be present immediately after such an event, there is a need to provide clinicians and first responders with every available tool to facilitate treatment. The methods currently available to assess dose are lacking and cannot meet the throughput and turn-around required. High-throughput biodosimetry systems such as that being developed by ASU could potentially provide the individualized absorbed dose information physicians will require in a timely manner to effectively manage treatment of the mass casualties in this extremely resource-constrained environment.

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