BIODOSIMETRY: A FUTURE TOOL FOR MEDICAL MANAGEMENT OF RADIOLOGICAL EMERGENCIES

Mary T. Sproull, Kevin A. Camphausen, and Gregory D. Koblentz

With the threat of future radiological or nuclear events, there is a need to model and develop new medical countermeasures for managing large-scale population exposures to radiation. The field of radiation biodosimetry has advanced far beyond its original objectives to identify new methodologies to quantitate unknown levels of radiation exposure that may be applied in a mass screening setting. New research in the areas of genomics, proteomics, metabolomics, transcriptomics, and electron paramagnetic resonance (EPR) applications have identified novel biological indicators of radiation injury from a diverse array of biological sample materials, and studies continue to develop more advanced models of radiation exposure and injury. In this article, we identify the urgent need for new biodosimetry assessment technologies, describe how biodosimetry diagnostics work in the context of a broad range of radiation exposure types and scenarios, review the current state of the science, and assess how well integrated biodosimetry resources are in the national radiological emergency response framework.

Keywords: Biodefense R&D, Countermeasures, Diagnostics, Mass casualty care, Public health preparedness/response, Mass casualty radiation exposure

RADIATION EXPOSURE is a continuing threat to public health security, both from terrorist events involving radiation dispersal devices (RDD), radiation exposure devices (RED), and improvised nuclear devices (IND), and from accidents involving nuclear reactors or lost radioactive sources. Each of these scenarios has the potential to subject large populations to external radionuclide contamination, internal radionuclide incorporation, and external radiation exposure.¹ Radiation exposure differs from radioactive contamination, with the former being the interaction of biological tissue with the ionizing energies from radioactive isotopes or other radiation sources and the latter being the

actual deposition of those isotopes externally on the skin or in internal organs.² A person exposed to radiation is not radioactive, whereas a person contaminated with radionuclides internally or externally may register radioactivity that is detectable with hand-held Geiger counters or whole body scanners.¹ A notable exception to this is the scenario of neutron radiation exposure in which the process of neutron activation can render biological material radioactive.

In the absence of evident contamination, there are 3 options for determining whether or not an individual has been exposed to radiation: physical dose reconstruction, clinical evaluation, and biological dosimetry. Physical dose

Mary T. Sproull is a Biologist, and Kevin A. Camphausen, MD, is Branch Chief, both in the Radiation Oncology Department, National Cancer Institute, National Institutes of Health, Bethesda, MD. Ms. Sproull is also a doctoral candidate, Biodefense Graduate Program, Schar School of Policy and Government, George Mason University, Fairfax, VA. Gregory D. Koblentz, PhD, is an Associate Professor and Director, Biodefense Graduate Program, Schar School of Policy and Government, George Mason University, Fairfax, VA.

reconstruction methodologies involve the use of physical dosimeters, modeling of the estimated position of the person to the radiation source (if known), and dose reconstruction from physical materials present on the exposed person when available. These methods are commonly used for dose estimation in radiation accidents but are difficult to apply for large-scale screening. Medical evaluation of the symptoms of potential victims can be used to determine if they have been exposed to radiation, but the process is imprecise and also ill-suited to mass triage.³ Biological dosimetry is another method of estimating exposure and can be defined as the estimation of received dose from past exposure to an agent through observation of biologic variables or measurements.⁴ Biological dosimetry for radiation exposure has been around for decades with use of the dicentric chromosome assay (DCA), which is still the “gold standard” today. DCA dose prediction is based on ionizing radiation-induced damage to DNA, which results in formation of dicentric chromosomal aberrations. The number of dicentric chromosomes increases with amount of radiation allowing estimation of unknown dose.⁵ DCA is the most universally accepted biodosimetry assay for biological dose assessment and, as such, was the main diagnostic available for use during the Three Mile Island, Chernobyl, and Fukushima radiological events.^{6,7} Though DCA is reliable and accurate, it is also labor- and time-intensive and not currently scalable for mass screening.⁸

Emergency planning and preparedness for a radiological event involves complex crisis management to appropriately triage and treat the exposed population and protect the health of first responders. Based on past experiences with large-scale radiological events and modeling of IND events, a critical component of public health and medical response to a radiological event will be conducting mass screenings of large populations to separate the exposed from the nonexposed.⁸⁻¹⁴

The need for such a capability was vividly demonstrated by the 2011 Fukushima Daiichi nuclear disaster. Following that disaster, the Japanese authorities used hand-held scanners and whole-body counter technologies to screen more than 150,000 people for internal or external contamination, primarily for the isotopes iodine (¹³¹I) and cesium (¹³⁴Cs and ¹³⁷Cs).^{3,15,16} While there is an increasing body of evidence that shows that the levels of radiation exposure received by the local population in the Fukushima Daiichi prefecture from fallout was too low to increase cancer risk, there remains significant psychosocial stress in the exposed population, with more than 350,000 individuals participating in a low-dose radiation lifespan study.¹⁷ Currently, monitoring of the presence of radionuclide contamination in the food supply and environment continues to be used to predict biological exposures in the population.¹⁸⁻²⁰

The medical management of the consequences of the Fukushima disaster, from triage to public health screenings to occupational health of first responders, would have

benefited from an ability to assess and estimate radiation exposure from individual biological indicators. Such an assessment would assure the “worried well” and relieve the psychosocial burden of radiation exposure from the relevant exposed population, provide a personalized dose effect for those with internal contamination to guide clinical treatment, and provide a means to monitor real-time biological effects from contaminated food consumption and other environmental exposures. Consequently, it has been acknowledged that the development of new biomarkers of radiation exposure will have a significant impact on and broad applicability for management of all types of radiological scenarios. In recent years, significant research has been done to develop these new dose prediction models for radiation biodosimetry using a variety of biological markers in the fields of genomics, proteomics, metabolomics, transcriptomics, electron paramagnetic resonance (EPR), cytogenetics, and lymphocyte kinetics.

This article provides an overview of how biodosimetry diagnostics function for different types of radiation exposure settings, the present state of the science, and the current level of development for potential deployment in an actual radiological event setting. We also highlight recent research findings and the latest models developed for radiation exposure. Finally, we identify future challenges and directions for integration of radiation biodosimetry in existing medical management systems for radiological events.

RADIATION TYPE

Radiation biodosimetry technologies are designed to measure the amount of biological effect or damage to biological tissues from ionizing radiation. There are several different types of ionizing radiation, including alpha, beta, gamma, X-ray, and neutrons. X-rays and gamma rays are the primary threat to human health during a radiological event, as these types of ionizing radiation possess sufficient energy to penetrate deep within the human body and damage tissues.²¹ Neutron radiation is of concern primarily for nuclear reactor accidents and IND events. In the case of a nuclear weapon detonation, the prompt radiation (immediate radiation wave) following detonation will include a mixture of radiation types, with the most dangerous being the relatively large amount of X-ray and gamma radiation.²² Alpha and beta radiations possess significantly less penetrating power and, except in the case of beta burns to the skin, are generally only of medical concern as internal contamination. Radioactive isotopes internalized through ingestion or inhalation may cause significant tissue damage, but they are usually not of sufficient quantity to induce acute radiation syndrome (ARS).^{21,23} ARS is a series of predictable stages of biological injury that follow exposure to high doses of radiation. The severity of ARS is determined by the level of dose received, and the subsyndromes are characterized according to the major biological systems

involved and include the cutaneous, hematopoietic, gastrointestinal, and neurovascular syndromes. A comparison of health effects relative to acute high-dose radiation exposure is included in Table 1. Relevant radionuclides of concern for radiological events are shown in Table 2. For the purposes of this article, radiation dose is expressed in Gray (Gy), an SI unit for radiation absorbed dose commonly used in the clinical setting.

Most radiation exposure events are essentially unique, since the biological effects will vary based on the type of radiation, the amount of radiation, the length of time that the biological tissue is exposed, and the frequency of the radiation exposure (single vs serial exposures).³⁸ In an IND event scenario, for example, an individual might be exposed to prompt radiation, where gamma and neutron radiations predominate, and/or to fallout and ground shine (radiation exposure from radionuclides deposited on the ground), which would consist primarily of gamma and beta from fission products produced by the explosion.^{39,40} In an RDD event, the exposure to radiation would be quite different, as it is probable that only a single isotope would be used. In most RDD scenarios, even with the use of a strong gamma-emitting radionuclide, large numbers of significant radiation injuries from onset of ARS would not be expected, as the explosive or dispersive effect of the weapon would scatter the radioactive source to the point where people would be exposed only to small amounts of the isotope. It is possible, however, in certain RDD scenarios to achieve significant radiation injury to a population if very large amounts of a radioactive source are used with advanced engineering designs for dispersal.⁴¹ An RED, such as placement of an unshielded radioactive source in a public place, would also potentially have significant radiation-induced health effects, depending on the time and distance relative to the exposure.⁴²

Biodosimetry diagnostics are useful because they provide patient-specific information regarding the amount of radiation-induced tissue damage, which can then be used to guide medical treatment decisions, including field triage and advanced clinical care. Ideally, a point-of-care (POC) biodosimetry diagnostic will be able to differentiate the exposed from the nonexposed to reduce the burden of the “worried well” on public health resources, in addition to identifying those individuals who have received significant radiation exposures and require medical countermeasure intervention and supportive care. For example, people identified as having received a dose of ≥ 2 Gy should be triaged for medical intervention, and those receiving exposures below that threshold are not of immediate concern.⁴³

The established metrics between specific biological targets (protein expression, DNA signature, etc) and radiation dose will vary in degree of correlation by radiation type; for example, neutron exposure may cause more biological damage than gamma exposure. Yet, biodosimetry assays are not limited in their use by the type of radiation. Essentially, the type and energy pattern of the external radiation

Table 1. Significant Health Effects from Acute Total Body Radiation Exposure During Early Phase Acute Radiation Syndrome

Single Acute Total Body Radiation Exposure	Emesis (time of onset post-event)	Skin Erythema	Lymphocyte/Platelet Depression	Diarrhea	Hematopoietic Syndrome	Gastrointestinal Syndrome	Neurovascular Syndrome	Cutaneous Syndrome
<2 Gy	>2 hrs		^a		^a (>1 Gy)			
2-4 Gy	1-2 hrs	*	*		*			
4-6 Gy	<1 hr	*	*	*	*			
6-8 Gy	10-30 min	*	*	*	*	*		
>8 Gy	<10 min	*	*	*	*	*	* (>12 Gy)	* (>15 Gy)

^aMinimal lymphocyte depression may be seen between 1 and 2 Gy but is generally not clinically significant.

Note: Clinical signs and symptoms presented here are relevant to the early phase (prodromal phase) of ARS. Data presented represent consensus findings from the current literature on medical management of radiological casualties.^{2,12,24,25,26-28}

*Denotes the specific symptom or syndrome correlates to the relevant dose range.

Table 2. Radionuclides of Concern for Radiological Events, Their Probable Sources, and Organs of Interest if Internalized

<i>Radionuclide</i>	<i>Radiation Emitted</i>	<i>Of Primary Concern for Use in an RDD</i>	<i>Of Primary Concern for Use in an RED</i>	<i>Of Primary Concern from a Nuclear Reactor Incident</i>	<i>Of Primary Concern from Use of an IND</i>	<i>Internal Contamination Focal Organ(s)</i>	<i>Potential Source of Radionuclide</i>
²⁴¹ Am	α, γ	*				Bones/liver	Industry
⁶⁰ Co	β, γ	*	*			Liver	Industry, food irradiators, medicine
¹³⁷ Cs	β, γ	*	*	*	*	Muscle/kidney	Industry, food irradiators, medicine
¹³¹ I	β, γ	*		*	*	Thyroid	Medicine, nuclear reactor
¹⁹² Ir	β, γ	*	*			Spleen	Industry, medicine
²³⁸ Pu	α, n	*				Lung/bones/liver	Nuclear weapons program/reactor
²³⁹ Pu	α	*				Lung/bones/liver	Nuclear weapons program/reactor
²²⁶ Ra	α, β, γ	*				Bone	Medicine
⁹⁰ Sr	β	*			*	Bone	Industry
²³⁵ U	α, β, γ	*				Kidney/bone	Nuclear weapons program/reactor
²³⁸ U	α, β, γ	*				Kidney/bone	Nuclear weapons program/reactor

Note: Included radionuclides and associated data represent consensus findings from the DOE/NRC, NCRP and UNSCEAR reports, the CDC and REMM websites, and publications on nuclear terrorism and nuclear weapons fallout.^{10,29-37} Selection of isotopes of primary concern relative to each event scenario was based on half-life, type and strength of the radiation emitted, availability for acquisition, and the relative amount needed to have a significant health impact at the population exposure level. RDD: Radiation Dispersal Device, RED: Radiation Exposure Device, IND: Improvised Nuclear Device

*Denotes the radionuclide is of concern for the specific radiological event type.

exposure is not as relevant for the medical management of ARS as the actual clinical presentation of the patient.²² What is relevant is the amount of biological damage from that ionizing radiation exposure. Radiation biodosimetry diagnostics are not as accurate in quantifying the actual radiation dose received as physical dosimeters would be; instead, they estimate the amount of dose received based on relative biological effect. Biodosimetry assays essentially measure radiation-induced tissue damage and correlate that damage with an approximate received dose. The quantification of damage is either measured directly through methodologies such as EPR or cytogenetics, or indirectly by quantifying the body's response to that damage, such as with analysis of changes to genomic or proteomic signatures.

This aspect of biodosimetry has the added value that it is patient specific. Biological sensitivity to ionizing radiation varies within a population based on an individual's ability to repair radiation-induced damage, so a more radiosensitive individual may show increased tissue damage when exposed to the same dose of radiation as another less sensitive individual because he or she has a weaker ability to repair the injury. Similarly, an individual may be more radiation resistant than the average person and show lower levels of biological damage when exposed to the same amount of radiation because he or she is more efficient at repairing the damage.⁴⁴

Though the research field primarily uses gamma or X-ray sources for development of biodosimetry models, these models are still applicable to radiation exposures of other radiation types, as they approximate the relative amount of tissue damage from ionizing radiation. The type of radiation and identification of the specific isotope is relevant, however, for medical management of internalized radioactive material, where the chemical properties of the radioactive isotope determine how it is metabolized and are key to applying the appropriate decorporation medical countermeasure.^{45,46} There are a number of agents currently available for decorporating treatment (removal/excretion of radionuclides from the body); they are listed in Table 3. Biodosimetry diagnostics are not useful for determining type of radionuclide and will only provide information regarding amount of radiation-induced damage. Identification of external and internal radionuclide contamination must be done using standard radiation detection equipment, and analysis of biological samples sent off-site. Biodosimetry diagnostics are useful, however, for guiding medical treatment decisions by providing clinicians with an approximate dose received, which is useful for predicting which subsyndromes of ARS will manifest in the exposed patient and the subsequent best course of treatment.

Radiation biodosimetry is also sensitive to partial body exposures. For any type of radiological event, the exposure is expected to be heterogeneous. From a practical perspective, uniform total body exposures are only achievable in a clinical therapeutic setting. In an IND event, people may be partially shielded to prompt radiation by the structures surrounding

Table 3. Currently Available Medical Countermeasures for Treatment of Internal Contamination of Radionuclides of Concern

<i>Medical Countermeasure for Internal Contamination</i>	<i>Element</i>	<i>Type of Agent</i>
DTPA (Ca-DTPA/Zn-DTPA)	Pu, Am, Co, Ir	Chelating
Prussian Blue	Cs	Adsorption
KI (Potassium Iodide)	I	Blocking
EDTA	Pu, Ir, Co	Chelating
Deferoxamine	Pu	Chelating
Sodium bicarbonate	U	Mobilizing
Stabile strontium	Sr	Blocking
Aluminum phosphate	Sr	Adsorption
Ammonium chloride	Sr	Mobilizing
Calcium gluconate*	Ra, Sr	Blocking
Calcium carbonate*	Ra, Sr	Blocking
Calcium phosphate	Ra, Sr	Mobilizing
Aluminum hydroxide	Ra, Sr	Adsorption
Sodium alginate	Ra, Sr	Adsorption
Barium sulfate	Ra, Sr	Adsorption

Note: Type of agent refers to the mechanism of action for decorporation including adsorptive agents which reduce gastrointestinal uptake, chelating agents which form water soluble complexes to enhance excretion through the kidney, mobilizing agents which are diuretics, and blocking agents which are stable forms of the element used to saturate the target organ to prevent uptake.

*Calcium carbonate and calcium gluconate are listed here as blocking agents as they compete for bone binding sites. Decorporation countermeasures and associated data represent consensus findings from the current literature on medical management of radiological casualties.^{12,23,26,42,47-49}

them, and exposure to radionuclides from fallout will be non-uniform.²² Similarly, in an RDD event, people will either be exposed to the deposited isotope in their surroundings following the detonation and receive a heterogeneous exposure or will have external contamination from aerosolized radionuclide. This deposition will also not be uniform. Though many of the early radiation dose prediction models were based on uniform total body exposure, new research in the field is directed at developing dose prediction models for partial exposures, in addition to organ-specific markers of radiation damage.^{50,51} These models are expected to be more relevant to radiological event scenarios, and identification of organ-specific markers of radiation damage will enhance medical management of radiation accident victims.

CURRENT STATE OF THE SCIENCE

Biodosimetry techniques currently available for medical management of radiation exposures are limited. The only universally accepted biodosimetry diagnostic is the

cytogenetic assay DCA. It is considered the “gold standard” for biological assessment of received radiation dose, because the biological variable it quantitates, dicentric chromosomal aberrations, have a low naturally occurring background frequency, so detectable changes can be directly attributed to ionizing radiation exposure. It is recommended for use by the International Atomic Energy Agency (IAEA) and International Standards Organization (ISO) and as a reference method for development of new biodosimetry technologies by the FDA.⁴⁴ Though DCA is an established and accurate bioassay for radiation exposure, it is ill-suited for mass screening, as it requires a high level of technical skill, is low throughput, and is restricted to a certain time window for application.⁴² It is also not a point-of-care diagnostic and must be done in an off-site laboratory setting.

Currently, the only point-of-care capabilities for biodosimetry assessment are lymphocyte depletion kinetics and basic clinical exam.⁸ Clinical presentation or evaluation of symptoms associated with prodromal ARS, including nausea, vomiting, diarrhea, and hypertension, can be useful for triage assessment of significant radiation exposures. The amount of time between radiation exposure to onset of emesis (vomiting) has been shown to correlate with dose, but this method has variability of several Gy in dose prediction accuracy.^{24,25} Clinical exams are of limited utility for large-scale screening because of the need for specially trained healthcare workers and low throughput due to the length of time needed to complete a clinical exam. Clinical symptoms such as time to onset of emesis can also be caused by other conditions unrelated to radiation exposure.

Lymphocyte depletion kinetics use the rate of depletion of lymphocytes to estimate received radiation dose and can be measured more quickly than traditional cytogenetic assays such as DCA, using existing high-throughput methodologies.⁵² As measurement of lymphocytes is part of the existing standard of care in the clinical setting, there exist significant laboratory resources that might be used as surge capacity during a radiological event. Yet, radiation dose estimation using lymphocyte depletion kinetics alone is not viable for triage biodosimetry. There are time constraints, as an early lymphocyte count is needed to establish baseline, followed by additional lymphocyte counts that must be taken serially. Such early baseline counts may not be possible during a large-scale event, and serial monitoring is not conducive to mass clinical care.⁵³ There are also confounding effects of inherent population variability and, in the case of an IND event, the complication of combined injury, including trauma and burn injuries, in addition to radiation-induced injuries.⁵⁴

However, a recent NATO exercise and other studies have demonstrated the potential utility of using lymphocyte depletion kinetics for biodosimetry mass screening when early samples are accessible and sufficient resources for processing are available.^{55,56} Several software platforms

have been developed for use in the point-of-care setting that provide a dose estimate using these existing methodologies. The Biodosimetry Assessment Tool (BAT) is a software platform developed by the Armed Forces Radiobiology Research Institute (AFRRI) that allows dose assessment using clinical symptoms and lymphocyte depletion data. The Radiation Event Medical Management (REMM) web portal provides a user-friendly interface and can predict exposures using time to emesis, lymphocyte counts, or DCA data, if available.⁵⁷ HemoDose can be used for dose prediction using blood cell counts alone but requires more detailed hematological input data.⁵⁸

Because of the recognized limitations of the current biodosimetry assessment capability in the United States, the Biomedical Advanced Research and Development Authority (BARDA) in the Department of Health and Human Services (HHS) has supported basic research to identify novel biomarkers of radiation exposure and facilitated late-stage development of biodosimetry devices to quantify received radiation dose.⁵⁹ BARDA has supported many areas of biodosimetry research and continues to fund new studies to develop biodosimetry modeling of radiation exposure and radiation injury.

Currently, development of research models of dose assessment using newly identified radiation biomarkers have been accomplished in the fields of genomics, proteomics, metabolomics, transcriptomics, and novel application of electron paramagnetic resonance (EPR) technology with the goal of development into deployable point-of-care biodosimetry assays. Limited application of some of these novel biomarkers from the fields of proteomics, metabolomics, and EPR have been included in human case studies of accidental radiation exposures. In many of these case studies, new biomarkers were included in the medical management of individuals exposed to unknown amounts of radiation in a complementary approach with lymphocyte depletion analysis and the traditional DCA assay.⁶⁰ For example, following a radiation accident in Dakar in 2006, 63 individuals were screened for dose assessment using a combination of classic cytogenetic biodosimetry, hematological analysis, and measurement of new protein and metabolite biomarkers of radiation exposure.⁶¹⁻⁶³

Many of these new biodosimetry proof-of-concept studies have demonstrated dose correlation between level of the expressed biomarker and received radiation dose in murine and nonhuman primate models. Assessment of these biomarkers in human studies is limited because of a scarcity of human population radiation exposures, though in some cases clinical therapeutic radiation exposures have been used. These new biodosimetry techniques have the potential for high-throughput mass casualty screening and are being developed by BARDA and the Radiation and Nuclear Countermeasure Program of the National Institutes of Allergy and Infectious Diseases (NIAID) at the NIH.⁴³

Table 4 includes a current capability assessment of each area of biodosimetry research, including level of study,

Table 4. Research Areas in the Field of Radiation Biodosimetry Based on Capability, Level of Study, and Development Phase

<i>Phase</i>	<i>Assay Type</i>	<i>Dose Range(Gy)^a</i>	<i>Level of Study</i>	<i>Throughput Capacity</i>	<i>Current Capability or in Development</i>
Investigative phase	Nascent Methodologies	n/a	Proof of concept	n/a	Basic research phase
	Transcriptomics	0.5-12	Murine <i>in vivo</i> study ^b	n/a	Basic research phase
	Genomics	0.1-10	Human clinical study	Automated high throughput	In development
	Proteomics	1-14	Human Accidental Exposure Case Studies	Automated high throughput	In development
Late Development Phase	EPR	1-40	Human Accidental Exposure Case Studies	Surge capacity	In development
	Metabolomics	0.5-10	Human Accidental Exposure Case Studies	Automated high throughput	Current capability ^c
Deployment Phase	Lymphocyte kinetics/clinical exam	1-14	Human Accidental Exposure Case Studies	Automated high throughput	Current capability ^d
	Cytogenetics	0.1-5	FDA Approved	Automated high throughput/ laboratory surge capacity	Current capability/ in development ^e

^aDose ranges are based on dose response relationships reported in research findings not on consensus operational guidelines.

^bPredominant studies in this field use murine models, though at least one study using clinical samples has been reported.

^cMetabolomics current capability is limited to clinical laboratory assessment of plasma citrulline.

^dLymphocyte kinetics is considered a current capability through access of existing clinical laboratory networks and available clinical support.

^eCytogenetic biodosimetry assessment is currently available but not at high-throughput or surge capacity levels.

Note: Rankings are based on complexity of the model studied (in vitro, murine, non-human primate, or human clinical study), their current level of technological deployment capability, and level of advancement in the basic research.

operational throughput capacity, and phase of development. Cytogenetic assessment and lymphocyte kinetics/clinical exam are rated as deployment-ready, though these technologies are not yet available at surge capacity levels. A recent concept of operations assessment of available biodosimetry tools similarly ranked only cytogenetics and lymphocyte depletion kinetics as having immediate capacity for operational use based on scoring by technological readiness level.⁶⁴

The fields of genomics, proteomics, and EPR are rated as late-development phase, as promising biomarker panels in genomics and proteomics have been identified and are now in advanced-development phase with high-throughput automation for genomics and validation studies and field deployable prototypes for proteomic and EPR technologies.^{43,59,65}

In the field of metabolomics, novel metabolite profiles for radiation dose prediction are still in the research phase, but there is current clinical capability for plasma citrulline assessment to evaluate radiation-induced damage to the gastrointestinal system, and studies are ongoing to further characterize this marker for radiation dose prediction.^{66,67}

Transcriptomics offers a novel method of dose assessment using evaluation of miRNA signatures. This new field of biodosimetry is ranked as early development, as it is in the basic research phase. Biodosimetry research has greatly expanded with the support of BARDA and NIAID's Radiation and Nuclear Countermeasure Program, evolving from a relatively limited field of cytogenetic and time to emesis dose assessment to represent a robust multidisciplinary field of radiation biology research using a variety of methodologies that are currently being developed for high-throughput capability.

RADIOLOGICAL EMERGENCY PREPAREDNESS

Federal radiological emergency planning and response guides highlight the importance of radiation dose assessment as a core need for medical management of mass radiation exposures.^{40,68,69} At the same time, radiological emergency preparedness has significant gaps, including the lack of executable interagency procedures for medical triage following a radiological event, adequate biodosimetry laboratory capacity, a strategic plan to activate surge capacity resources for biodosimetry capability, operational guidelines for biodosimetry sample handling and reporting, requirements for short-term and long-term monitoring, and establishment and integration of emerging high-throughput biodosimetry technologies.⁷⁰

The lack of laboratory capacity for biodosimetry assays is a key gap in response capability for radiological event preparedness. The United States currently has only 2 fully operational cytogenetic biodosimetry laboratories: the Department of Energy's (DOE) Radiation Emergency Assistance Center/Training Site (REAC/TS), located in Oak Ridge, TN; and the Department of Defense's (DOD) AFRRI facility, located in Bethesda, MD.^{69,70} Additional

reach-back biodosimetry resources are found at the DOD's Naval Dosimetry Center (NDC) in Bethesda, MD. Deployable response teams for medical management of radiation exposures are also limited to AFRRI's Medical Radiobiology Advisory Team (MRAT) and REAC/TS's emergency response teams, though deployable subject matter expert teams are also available through HHS and the Department of Veteran's Affairs Medical Emergency Radiological Response Team (MERRT).^{69,71}

To remediate the current shortcomings in cytogenetic laboratory capacity, the Assistant Secretary of Preparedness and Response (ASPR) in HHS has proposed establishing a national cytogenetic biodosimetry network that would leverage approximately 150 existing clinical cytogenetics laboratories that routinely perform cytogenetic assays for detection of cancer and birth defects and existing clinical laboratories currently providing hematological assessments as reach back biodosimetry resources. Ideally, this Integrated Clinical Diagnostics System (ICDS) would increase the nation's biological dose assessment capability and would include use of DCA and lymphocyte depletion kinetics to support triage during a radiological event. Such laboratory capability is urgently needed, as there exist substantial laboratory resources for chemical and biological events in the CDC's Laboratory Response Network (LRN), but not for radiological events.⁷² Specialized training is required, however, to educate existing cytogeneticists on performing DCA for radiation dose assessment, and interlaboratory standardization and proficiency evaluation will be required.⁷³ Automated platforms for cytogenetic biodosimetry are also in development to adapt DCA and other cytogenetic assays for mass casualty screening, such as the Columbia Center for High-Throughput Minimally Invasive Biodosimetry's Rapid Automated Biodosimetry Tool (RA-BiT).⁷⁴

Preliminary work has been done to develop operational biodosimetry concepts of operations at the triage level, including proposed integration of existing biodosimetry techniques into medical management of large-scale radiological events and risk assessment modeling to identify dose ranges where biodosimetry evaluation would be most effective in improving medical management outcomes.^{8,14,22,54,64,75} Several software platforms have been developed for triage management using existing biodosimetry techniques, such as time to emesis, lymphocyte kinetics, and DCA, and include AFRRI's (BAT) and the HHS-managed Radiation Event Medical Management (REMM) web portal.⁵⁷ Yet, there are currently no stockpiled or deployable point-of-care biodosimetry diagnostics, and consensus concepts of operations for deployment of biodosimetry diagnostics in a civilian mass care setting have not been fully developed. Though great strides have been made toward implementation of emergency response biodosimetry capability, more work needs to be done before this methodology can be useful in a mass casualty radiation event.

PROSPECTS FOR ADVANCED BIODOSIMETRY

Future priorities for biodosimetry include research to develop and validate new dosimetry technologies, development of point-of-care and/or field-deployable laboratory capabilities using these new technologies, and improved planning to integrate these technologies into radiological emergency medical response. Future directions in the field of radiation biodosimetry research include application of these emergent technologies to models that more closely simulate actual field exposures, including exposure to mixed field radiation (simultaneous exposure with multiple radiation types including neutron), internal exposures from inhalation or ingestion of radionuclides, accumulated serial exposures, and combined injury. This is very relevant as many experimental models used to evaluate novel markers of radiation exposure use acute, whole-body exposures to X-ray or gamma sources that do not reflect a triage scenario, which would include predominantly partial body mixed field exposures with or without concomitant internal contamination or traumatic injury. Though existing biodosimetry models using X-ray or gamma can be applied regardless of the radiation source, their dose predictions may not be as accurate as desired. The type of triage scenario also varies with the type of radiological event. An IND event would represent the most complex scenario, with acute partial and whole-body exposures with mixed field radiation, possible internal contamination, serial exposures from fallout, and combined injury. An RDD event is unlikely to present combined injury, but internal contamination would be a factor. With an RED, internal contamination and combined injury are not factors, but in this scenario, there is a higher possibility of acute exposures resulting in onset of ARS.

New biodosimetry research should focus on models using mixed field radiation, partial body exposures, and internal contamination. Dose estimates using combined injury modeling are also relevant, as concurrent inflammatory processes from traumatic injury may mask biomarker expression for radiation dose assessment, but combined injury effects are predominantly associated with an IND event, the least likely of the radiological events to occur. Internal contamination models and partial body exposure models should be given greater priority, as RDD and RED events have a greater probability of occurrence. Studies are needed to apply existing biomarker panels developed for whole body exposures to partial body models, and organ-specific biomarkers of radiation damage are needed to enhance medical management of ARS.⁵⁰ As biodosimetry diagnostics reflect a received “dose,” which is used as a surrogate for received “damage,” advanced biodosimetry technologies should seek to include an output for “radiation injury” concurrent with dose to aid with medical triage. New models also need to be developed to test existing biomarkers of radiation exposure in the context of common preexisting disease states, such as cardiovascular disease and diabetes, as well as in special populations, such as pediatric and elderly populations.

As no single biodosimetry technique is likely to be sufficient for dose prediction at all doses, timepoints, and exposure conditions, multivariate approaches using integration of multiple techniques will be necessary. Emerging proteomic and EPR dose assessment techniques have recently been incorporated with existing cytogenetic and lymphocyte kinetics assays in human case studies of accidental radiation exposures, and proteomic biodosimetry has recently been added to the DOD doctrine for medical management of radiological casualties.^{61,71,76} Though in several recent case reports from accidental exposures new biodosimetry techniques have been included in the medical management of those exposed, these new assays remain unvalidated, and there exist neither consensus guidelines for application nor FDA approval. As appropriate human models of radiation exposure do not exist for use in validation of new biodosimetry techniques, it is imperative that greater collaboration occur between basic research laboratories and clinical management of accidental human exposure cases. Banking of samples from these incidences would advance biodosimetry research and validation efforts and complement biodosimetry licensing applications using the Animal Rule.⁷⁷

In the United States, there is a diverse array of technical resources available across the federal agency landscape with either deployment capability or technical reach back support for radiological event scenarios. The DHS's Nuclear/Radiological Incident Annex elaborates the complexity of the interagency response to a radiological event and how that command structure is affected by the type of radiological event scenario. Federal deployable medical response teams possess practical experience with medical management of accidental radiation exposures and should be the lead resource for deployment of biodosimetry diagnostics. In a mass casualty event, they should have point-of-care capability to assist state and local initial emergency response. Radiation injuries are never medical emergencies unto themselves. Internal radioisotope contamination can be considered an “urgent” medical situation, as decorporation countermeasures need to be administered within a few hours to be effective. Yet, for external radiation exposures, biological injury takes days to manifest, so point-of-care capability is necessary but not sufficient to manage the medical consequences of a radiological event. However, a point-of-care diagnostic would relieve the “worried well” and provide a vital ability to reduce the strain on medical resources by identifying those exposed from those who have received no radiation exposure. Point-of-care technology also alleviates the need for complex sample labeling and tracking systems required for automated off-site processing. Additional reach back dose assessment capability should complement primary triage, as these automated and laboratory processing resources require additional time but will enhance medical management of those known to need more advanced medical intervention.

Though substantial collaborative efforts have been made in the federal community to develop conceptual emergency response plans for radiological events, greater work remains

for establishing consensus approaches for medical management and triage of events where scarce resources, such as decontaminating agents, are expected.¹⁴ Currently, training for medical management of radiation injuries is also not integrated into the primary or continuing education of physicians and first responders.⁷⁸ This training is essential so that primary medical caregivers have a working knowledge of biodosimetry diagnostic applications. Formation of an ICDS cytogenetic radiation biodosimetry network could also serve as a surge capacity resource for radiological events.

Finally, operational point-of-care response plans need to be formalized for medical management of mass casualty radiological events with integration of biodosimetry diagnostics into the triage management work flow. Tabletop and live exercises including integration of existing available deployment-ready medical response teams for radiation exposure and subject matter experts in radiation exposures at the administrative level will help to ensure that the complexity of the interagency response during a radiological or nuclear event does not hinder the medical management of mass screening efforts. There is a rapidly accumulating body of biodosimetry research knowledge, and several novel dose assessment diagnostics using genomics, proteomics, and EPR approaches are in late phase development. With validation of these technologies through field testing and formalization of reach back diagnostic laboratory networks, the United States will have a greater level of radiological emergency preparedness.

ACKNOWLEDGMENTS

This research was supported in part by funding from the Radiation and Nuclear Countermeasures Program, #Y2-OD-0332-01 NIAID, and by the Intramural Research Program of the National Institutes of Health, National Cancer Institute. The authors would like to thank Robert Miller, PhD, acting chief of Radiation Physics and Dosimetry in the Radiation Oncology Branch of the NCI, for his health physics support.

REFERENCES

1. Bui E, Joseph B, Rhee P, Diven C, Pandit V, Brown CV. Contemporary management of radiation exposure and injury. *J Trauma Acute Care Surg* 2014;77(3):495-500.
2. Jarrett DG, Sedlak RG, Dickerson WE, Reeves GI. Medical treatment of radiation injuries—current US status. *Radiat Meas* 2007;42(6-7):1063-1074.
3. Miyazaki M, Ohtsuru A, Ishikawa T. An overview of internal dose estimation using whole-body counters in Fukushima Prefecture. *Fukushima J Med Sci* 2014;60(1):95-100.
4. Mendelsohn ML. An introduction to biological dosimetry. In: Gledhill BL, Mauro F, eds. *New Horizons in Biological Dosimetry*. New York: Wiley-Liss Inc.; 1991:1-10.
5. Wong KF, Siu LL, Ainsbury E, Moquet J. Cytogenetic biodosimetry: what it is and how we do it. *Hong Kong Med J* 2013;19(2):168-173.
6. International Atomic Energy Agency. *The Fukushima Daiichi Accident: Technical Volume 4/5. Radiological Consequences*. Vienna: IAEA; 2015. <http://www-pub.iaea.org/MTCD/Publications/PDF/AdditionalVolumes/P1710/Pub1710-TV4-Web.pdf>. Accessed November 2, 2017.
7. Wald N. Biomedical rationale for cytogenetic dosimetry. *J Radiat Res* 1992;33(Suppl):31-43.
8. Sullivan JM, Prasanna PG, Grace MB, et al. Assessment of biodosimetry methods for a mass-casualty radiological incident: medical response and management considerations. *Health Phys* 2013;105(6):540-554.
9. Flood AB, Nicolalde RJ, Demidenko E, et al. A framework for comparative evaluation of dosimetric methods to triage a large population following a radiological event. *Radiat Meas* 2011;46(9):916-922.
10. Flynn DF, Goans RE. Nuclear terrorism: triage and medical management of radiation and combined-injury casualties. *Surg Clin North Am* 2006;86(3):601-636.
11. Buddemeier B, ed. *Medical Needs in the Aftermath of Nuclear Terrorism*. Weston, FL: Radiation Research Society; Lawrence Livermore National Laboratory; 2015.
12. Goans RE. *Medical Management of Radiological Casualties*. Bethesda, MD: Armed Forces Radiobiology Research Institute; July 2013.
13. Sixt KM, Smith FR, Kim D, Curling CA. *Research and Development Strategies for the Current and Future Medical Treatment of Radiation Casualties*. Alexandria, VA: Institute for Defense Analysis; September 2014.
14. Coleman CN, Parker GW. Radiation terrorism: what society needs from the radiobiology-radiation protection and radiation oncology communities. *J Radiol Prot* 2009;29(2a):A159-A169.
15. Matsuda N, Kumagai A, Ohtsuru A, et al. Assessment of internal exposure doses in Fukushima by a whole body counter within one month after the nuclear power plant accident. *Radiat Res* 2013;179(6):663-668.
16. Hayano RS, Tsubokura M, Miyazaki M, et al. Internal radiocesium contamination of adults and children in Fukushima 7 to 20 months after the Fukushima NPP accident as measured by extensive whole-body-counter surveys. *Proc Jpn Acad Ser B Phys Biol Sci* 2013;89(4):157-163.
17. Clancey G, Chhem R. Hiroshima, Nagasaki, and Fukushima. *Lancet* 2015;386(9992):405-406.
18. Yajima K, Kurihara O, Ohmachi Y, et al. Estimating annual individual doses for evacuees returning home to areas affected by the Fukushima nuclear accident. *Health Phys* 2015;109(2):122-133.
19. Kim E, Tani K, Kunishima N, Kurihara O, Sakai K, Akashi M. Estimation of early internal doses to Fukushima residents after the nuclear disaster based on the atmospheric dispersion simulation. *Radiat Prot Dosimetry* 2016;171(3):398-404.
20. Imoto T, Nunokawa J, Fujii H, et al. Collaboration of local government and experts responding to increase in environmental radiation level due to the nuclear disaster: focusing on their activities and latest radiological discussion. *Radiat Prot Dosimetry* 2015;167(1-3):358-364.
21. Gusev IA, Guskova AK, Mettler FA, eds. *Medical Management of Radiation Accidents*. 2d ed. Boca Raton, FL: CRC Press; 2001.

22. Coleman CN, Koerner JF. Biodosimetry: medicine, science, and systems to support the medical decision-maker following a large scale nuclear or radiation incident. *Radiat Prot Dosimetry* 2016;172(1-3):38-46.
23. Rump A, Stricklin D, Lamkowski A, Eder S, Abend M, Port M. Reconsidering current decorporation strategies after incorporation of radionuclides. *Health Phys* 2016;111(2):204-211.
24. Demidenko E, Williams BB, Swartz HM. Radiation dose prediction using data on time to emesis in the case of nuclear terrorism. *Radiat Res* 2009;171(3):310-319.
25. Koenig KL, Goans RE, Hatchett RJ, et al. Medical treatment of radiological casualties: current concepts. *Ann Emerg Med* 2005;45(6):643-652.
26. Bushberg JT, Kroger LA, Hartman MB, et al. Nuclear/radiological terrorism: emergency department management of radiation casualties. *J Emerg Med* 2007;32(1):71-85.
27. Blakely WF, Salter CA, Prasanna PG. Early-response biological dosimetry—recommended countermeasure enhancements for mass-casualty radiological incidents and terrorism. *Health Phys* 2005;89(5):494-504.
28. Fliedner TM, Friesecke I, Beyrer K, eds. *Medical Management of Radiation Accidents—Manual on the Acute Radiation Syndrome*. Plymouth, UK: British Institute of Radiology; 2001.
29. DOE/NRC Interagency Working Group on Radiological Dispersal Devices. *Radiological Dispersal Devices: An Initial Study to Identify Radioactive Materials of Greatest Concern and Approaches to Their Tracking, Tagging, and Disposition*. Report to the Nuclear Regulatory Commission and the Secretary of Energy. May 2003. <https://energy.gov/sites/prod/files/edg/media/RDDRPTF14MAYa.pdf>. Accessed November 3, 2017.
30. U.S. Department of Health and Human Services: Radiation Emergency Medical Management (REMM). Isotopes of interest: properties, treatment and fact sheets. <https://www.remm.nlm.gov/rdd.htm#isotopes>. Accessed November 3, 2017.
31. Centers for Disease Control and Prevention. Emergency Preparedness and Response: radioactive isotopes. CDC website. Updated October 16, 2014. <https://emergency.cdc.gov/radiation/isotopes/>. Accessed November 3, 2017.
32. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). *Sources, Effects and Risks of Ionizing Radiation*. UNSCEAR 2013 Report to the General Assembly, Volume 1, Scientific Annex A. http://www.unscear.org/unscear/en/publications/2013_1.html. Accessed November 3, 2017.
33. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). *Sources and Effects of Ionizing Radiation*. UNSCEAR 2008 Report to the General Assembly, Volume II, Scientific Annex D. http://www.unscear.org/unscear/en/publications/2008_2.html. Accessed November 3, 2017.
34. National Council on Radiation Protection and Measurements. *Population Monitoring and Radionuclide Decorporation Following a Radiological or Nuclear Incident*. NCRP Report No. 166. Bethesda, MD: NCRP; April 2010. <https://www.ncrp.com/publications.org/Reports/166>. Accessed November 3, 2017.
35. National Research Council; Division on Earth and Life Studies; Board on Radiation Effects Research; Committee to Review the CDC-NCI Feasibility Study of the Health Consequences from Nuclear Weapons Tests. *Exposure of the American Population to Radioactive Fallout from Nuclear Weapons Tests: A Review of the CDC-NCI Draft Report on a Feasibility Study of the Health Consequences to the American Population from Nuclear Weapons Tests Conducted by the United States and Other Nations*. Washington, DC: National Academies Press; 2003.
36. Beck HL, Bouville A, Moroz BE, Simon SL. Fallout deposition in the Marshall Islands from Bikini and Enewetak nuclear weapons tests. *Health Phys* 2010;99(2):124-142.
37. Ferlic KP, McManaman VL. Nuclear weapons fallout. In: Conklin JJ, Walker RI, eds. *Military Radiobiology*. Orlando, FL: Academic Press; 1987:25-54.
38. Bertho J. The use of biological indicators in the evaluation of radiation injury in selected cases: the Dakar (Senegal) and Fleurus (Belgium) radiation accidents. In: Christensen DM, Sugarman SL, O'Hara FM, eds. *The Medical Basis for Radiation-Accident Preparedness*. Oak Ridge, TN: Oak Ridge Associated Universities; 2013:249-260.
39. Buddemeier B. Reducing the consequences of a nuclear detonation: recent research. *The Bridge* 2010;40(2):28-38.
40. Homeland Security Council: Interagency Policy Coordination Subcommittee for Preparedness & Response to Radiological and Nuclear Threats. *Planning Guidance for Response to a Nuclear Detonation*. 2009.
41. Harper FT, Musolino SV, Wentz WB. Realistic radiological dispersal device hazard boundaries and ramifications for early consequence management decisions. *Health Phys* 2007;93(1):1-16.
42. Pandey BN, Kumar A, Tiwari P, Mishra KP. Radiobiological basis in management of accidental radiation exposure. *Int J Radiat Biol* 2010;86(8):613-635.
43. Homer MJ, Raulli R, DiCarlo-Cohen AL, et al. United States Department of Health and Human Services biodosimetry and radiological/nuclear medical countermeasures programs. *Radiat Prot Dosimetry* 2016;171(1):85-98.
44. US Department of Health and Human Services; Food and Drug Administration; Center for Devices and Radiological Health. *Radiation Biodosimetry Medical Countermeasure Devices. Guidance for Industry and Food and Drug Administration Staff* 2016. <https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM427866.pdf>. Accessed November 3, 2017.
45. Leiterer A, Bardot I, Ménétrier F, et al. Medical countermeasures after a radiological event: an update from the CATO project. *Int J Radiat Biol* 2014;90(11):1043-1047.
46. Wiley AL. Some lessons learned from the analysis of severe internal-contamination accidents (with suggestions on new methods for risk evaluation, mitigation and prevention of lethal radiotoxicity). In: Christensen DM, Sugaman SL, O'Hara FM, eds. *The Medical Basis for Radiation-Accident Preparedness*. Oak Ridge, TN: Oak Ridge Associated Universities; 2011:211-219.
47. US Department of Health and Human Services; Radiation Emergency Medical Management (REMM). Managing internal contamination. Isotopes of interest: properties, treatment and fact sheets. https://www.remm.nlm.gov/int_contamination.htm#blockingagents_1. Accessed November 3, 2017.
48. Domínguez-Gadea L, Cerezo L. Decontamination of radioisotopes. *Rep Pract Oncol Radiother* 2011;16(4):147-152.
49. U.S. Department of Health and Human Services; Food and Drug Administration; Center for Drug Evaluation and Research. *Guidance for Industry: Internal Radioactive Contamination—Development of Decorporation Agents*. Rockville, MD: FDA; March 2006. <https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071944.pdf>. Accessed November 6, 2017.

50. Sproull M, Kramp T, Tandle A, Shankavaram U, Camphausen K. Multivariate analysis of radiation responsive proteins to predict radiation exposure in total-body irradiation and partial-body irradiation models. *Radiat Res* 2017;187(2):251-258.
51. Blakely WF, Sandgren DJ, Nagy V, Kim SY, Sigal GB, Ossetrova NI. Further biodosimetry investigations using murine partial-body irradiation model. *Radiat Prot Dosimetry* 2014;159(1-4):46-51.
52. Blakely WF, Ossetrova NI, Whitnall MH, et al. Multiple parameter radiation injury assessment using a nonhuman primate radiation model-biodosimetry applications. *Health Phys* 2010;98(2):153-159.
53. Ainsbury EA, Bakhanova E, Barquinero JF, et al. Review of retrospective dosimetry techniques for external ionising radiation exposures. *Radiat Prot Dosimetry* 2011;147(4):573-592.
54. Berger ME, Leonard RB, Ricks RC. *Hospital Triage in the First 24 Hours After a Nuclear or Radiological Disaster*. Oak Ridge Institute for Science and Education (ORISE); 2010.
55. Dörr H, Abend M, Blakely WF, et al. Using clinical signs and symptoms for medical management of radiation casualties—2015 NATO exercise. *Radiat Res* 2017;187(3):273-286.
56. Port M, Pieper B, Knie T, et al. Rapid prediction of hematologic acute radiation syndrome in radiation injury patients using peripheral blood cell counts. *Radiat Res* 2017;188(2):156-168.
57. Waller E, Millage K, Blakely WF, et al. Overview of hazard assessment and emergency planning software of use to RN first responders. *Health Phys* 2009;97(2):145-156.
58. Hu S, Blakely WF, Cucinotta FA. HEMODOSE: a biodosimetry tool based on multi-type blood cell counts. *Health Phys* 2015;109(1):54-68.
59. Larsen JC, Disbrow GL. Project BioShield and the Biomedical Advanced Research Development Authority: a ten year progress report on meeting U.S. preparedness objectives for threat agents. *Clin Infect Dis* 2017. doi: 10.1093/cid/cix097.
60. Sproull M, Camphausen K. State-of-the-art advances in radiation biodosimetry for mass casualty events involving radiation exposure. *Radiat Res* 2016;186(5):423-435.
61. Bertho JM, Roy L. A rapid multiparametric method for victim triage in cases of accidental protracted irradiation or delayed analysis. *Br J Radiol* 2009;82(981):764-770.
62. Bertho JM, Roy L, Souidi M, et al. New biological indicators to evaluate and monitor radiation-induced damage: an accident case report. *Radiat Res* 2008;169(5):543-550.
63. Bertho JM, Roy L, Souidi M, et al. Initial evaluation and follow-up of acute radiation syndrome in two patients from the Dakar accident. *Biomarkers* 2009;14(2):94-102.
64. Milner EE, Daxon EG, Anastasio MT, Nesler JT, Miller RL, Blakely WF. Concepts of operations (CONOPS) for biodosimetry tools employed in operational environments. *Health Phys* 2016;110(4):370-379.
65. Williams BB, Dong R, Flood AB, et al. A deployable in vivo EPR tooth dosimeter for triage after a radiation event involving large populations. *Radiat Meas* 2011;46(9):772-777.
66. Onal C, Kotek A, Unal B, et al. Plasma citrulline levels predict intestinal toxicity in patients treated with pelvic radiotherapy. *Acta Oncol* 2011;50(8):1167-1174.
67. Singh VK, Newman VL, Romaine PL, Hauer-Jensen M, Pollard HB. Use of biomarkers for assessing radiation injury and efficacy of countermeasures. *Expert Rev Mol Diagn* 2016;16(1):65-81.
68. National Security Staff Interagency Policy Coordination Subcommittee for Preparedness & Response to Radiological and Nuclear Threats. *Health and Safety Planning Guide for Protecting First Responders Following a Nuclear Detonation*. December 2016. <https://www.dhs.gov/sites/default/files/publications/IND%20Health%20Safety%20Planners%20Guide%20Final.pdf>. Accessed November 6, 2017.
69. U.S. Department of Homeland Security. *Nuclear/Radiological Incident Annex to the Response and Recovery Federal Interagency Operational Plans*. October 2016. https://www.fema.gov/media-library-data/1478636264406-cd6307630737c2e3b8f4e0352476c1e0/NRIA_FINAL_110216.pdf. Accessed November 6, 2017.
70. U.S. Department of Homeland Security. *DHS Strategy for Improving the National Response and Recovery from an IND Attack*. March 2010. <https://info.publicintelligence.net/DHS-INDResponse.pdf>. Accessed November 6, 2017.
71. Blakely WF, Romanyukha A, Hayes SM, et al. U.S. Department of Defense multiple-parameter biodosimetry network. *Radiat Prot Dosimetry* 2016;172(1-3):58-71.
72. US Centers for Disease Control and Prevention. Emergency preparedness and response: the Laboratory Response Network partners in preparedness. CDC website. Updated September 30, 2014. <https://emergency.cdc.gov/lrn/>. Accessed November 6, 2017.
73. Blumenthal DJ, Sugarman SL, Christensen DM, et al. Role of dicentric analysis in an overarching biodosimetry strategy for use following a nuclear detonation in an urban environment. *Health Phys* 2014;106(4):516-522.
74. Garty G, Bigelow AW, Repin M, et al. An automated imaging system for radiation biodosimetry. *Microsc Res Tech* 2015;78(7):587-598.
75. Swartz HM, Flood AB, Williams BB, Meineke V, Dörr H. Comparison of the needs for biodosimetry for large-scale radiation events for military versus civilian populations. *Health Phys* 2014;106(6):755-763.
76. Prasanna PG, Blakely WF, Bertho JM, et al. Synopsis of partial-body radiation diagnostic biomarkers and medical management of radiation injury workshop. *Radiat Res* 2010;173(2):245-253.
77. U.S. Department of Health and Human Services; Food and Drug Administration. *Product Development Under the Animal Rule: Guidance for Industry*. October 2015. <https://www.fda.gov/downloads/drugs/guidances/ucm399217.pdf>. Accessed November 6, 2017.
78. Hauer JM. Preparing the country for nuclear terrorism. *Bull At Sci* 7 October 2016.

Manuscript received June 22, 2017;
 revision returned August 21, 2017;
 accepted for publication August 22, 2017.

Address correspondence to:

Mary T. Sproull
 National Institutes of Health/National Cancer Institute
 Radiation Oncology Branch
 9000 Rockville Pike, 10 B3B100
 Bethesda, MD 20892

Email: sproullm@mail.nih.gov