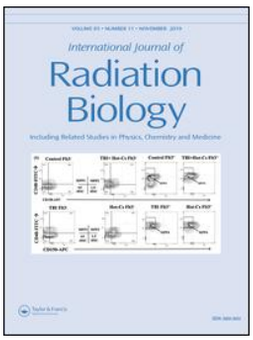

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MINI-REVIEW

Using biodosimetry to enhance the public health response to a nuclear incident*

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ABSTRACT

Radiation Biodosimetry is a continually developing clinical diagnostic field, which focuses on biological markers that proportionally change in relationship to the amount of ionizing radiation absorbed. Examples of host marker response include changes in white cell count, specific proteins in circulation, RNAs in white blood cells, or chromosome fidelity in affected lymphocytes. Measurements of radiation biomarkers correlate with the approximate radiation dose absorbed and indirectly provide an assessment of the likelihood of developing acute radiation syndrome. The aim of this review is to summarize four biodosimetry programs that are in advanced development, later pipeline stages with funding from the Biomedical Advanced Research and Development Authority (BARDA), an agency under the Assistant Secretary for Preparedness and Response (ASPR) in the U.S. Department of Health and Human Services (HHS). With BARDA financial support, biodosimetry diagnostic assays in development will inform patient management, improve health and psychosocial outcomes, and save lives after a nuclear disaster. These tests include an SRI International developed rapid on-site screening test requiring only a finger stick of blood to triage those who have received little or no radiation from those who have received clinically significant levels of radiation and need further immediate patient management. In addition, multiple laboratory-based, high-throughput quantitative tests, currently under development by MRIGlobal, DxTerity, and ASELL, will more accurately define dose levels and possibly predict cellular and organ-damage and other longer-term effects of radiation. In the future, when clinical and analytical validation of these assays is complete, the data is reviewed by the FDA, and agency use status is obtained, rapid triage and laboratory-based biodosimetry test results will enable emergency medical teams to do the most good for the largest number of people after a nuclear blast.

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Introduction

A large nuclear disaster will necessitate evaluation and clinical management of potentially hundreds of thousands to millions of individuals (Waselenko et al. 2004; Buddemeier and Dillon 2009; FDA 2016; Assistant Secretary for Preparedness and Response (ASPR) 2017; Garty et al. 2017). Initial triage of individuals includes evaluation of approximate exposure location, preexisting medical health (Coleman et al. 2011; ASPR 2017), and basic clinical assessment of vomiting, diarrhea, headache, consciousness, and body temperature (Koenig et al. 2005). Biodosimetry, the measurement of the biological response to an absorbed dose of ionizing radiation, offers an added clinical benefit to patient observation for post-irradiation symptoms by estimating qualitative and quantitative absorbed ionizing radiation dose. A point-of-care (POC), rapid qualitative test can deliver dose prediction to triage low- and no-absorption victims from all others. A quantitative dose absorption test can inform physicians in advance of the onset of acute radiation syndrome (ARS) and neutropenia. Further, it can better inform therapeutic management, with consequently better allocation of scarce medical countermeasure resources.

Discussion

In contrast to physical dosimetry, which measures external or environmental exposure, radiation biodosimetry indicates the amount of absorbed radiation and reflects radiation-induced tissue/organ damage, which medical staff can use to more accurately assign individuals in need of increased levels of clinical evaluation, determine appropriate treatment options, or release them to evacuate the area. Because of the likelihood of scarce resources and high patient numbers, it

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is crucial that the available medications and staff efforts be directed to those individuals most able to benefit. In addition, biodosimetry test results could be used as early indicators of impending radiation-induced immunosuppression and resulting increased susceptibility to infection (Waselenko et al. 2004; Coleman and Koerner 2016; Dainiak 2018). This approach can complement the public health response by informing patient management, improving health and psychosocial outcomes, and saving far more lives (Coleman and Koerner 2016; Garty et al. 2017). However, there are currently no FDA cleared tests to measure absorbed radiation (Sullivan et al. 2013; Coleman and Koerner 2016).

Qualitative and quantitative biodosimetry tests, are currently under development with support from the United States Department of Health and Human Services (HHS). Early dose estimates are critical to determine medical urgency and the need to initiate myeloid cytokines. The cut points are likely to be in the range of 2 Gy to initiate cytokine therapy, 6 Gy to consider transport to a transplantation center, and 8 Gy to be considered expectant. There are four biodosimetry tests in late development within BARDA. One of these tests under development by SRI is designed to be a triage, patient-side qualitative assay providing a quick assessment of individuals who have an absorbed dose of 2 Gray (Gy) or greater. The SRI Biodosimetry Diagnostic is a lateral flow immunoassay run on nitrocellulose strips impregnated with antibodies to three proteins released into plasma after initial absorbance of radiation, Salivary Alpha Amylase (AMY1A), Fms-related tyrosine kinase 3 ligand (FLT3L), and Monocyte Chemotactic Protein 1 (MCP1). The concentrations of these proteins are radiation-responsive in a dose-dependent fashion from 0 to 10 Gy, beginning at 24 hours and continuing to at least 14 days post-irradiation, and can be detected from a finger-stick of blood (Balog et al. 2018). The qualitative readout in <35 minutes accurately distinguishes radiation absorption below 2 Gy from ≥2 Gy. Based on a population exposure model and interpolated data from human and non-human primate studies, in a preliminary testing format of an ELISA assay, SRI calculates the performance data from the existing datasets to be a specificity of 90% and a sensitivity of 94.3%. This qualitative biodosimetry test has a target product profile (TPP) that would specify a clinically relevant absorbed dose threshold. Attributes of the test include ease of use, require minimal training, uses a small specimen volume, is operable in temporary shelters, and has a simple output report.

After an initial triage assessment, individuals likely to have received an absorbed dose ≥2 Gy will be sent for further medical evaluation which would include a multiparametric approach for individualized treatment based on approximate geographical location, clinical signs and symptoms, hematology, physical dosimetry, and organ-based radiotoxicity. To facilitate a more comprehensive assessment of radiation absorption, specific quantitative biodosimetry could enable the medical staff to target appropriate individualized therapy. To be clinically useful, a laboratory-based quantitative biodosimetry test must report an accurate absorbed dose over a range of 0–8 Gy, be performed under CLIA certification, run on a highly automated device, be incorporated in a network of specifically trained facilities, and deliver a total output of up to 400,000 results within a few days of the incident.

There are at least three such tests supported by HHS funding that are currently completing the device verification phase with the intent to seek full FDA clearance to market. Two of these exploit changes in mRNA levels of radiation-responsive genes. Both use mRNA expression levels calibrated to the non-human primate radiation response patterns following an acute dose . The ARad test from Arizona State Univeristy and MRIGlobal uses quantitative reverse transcription PCR (qRT-PCR) to measure changes in 14 different mRNAs, 13 of which are radiosensitive, and one is a radioinsensitive control. The second test, REDI-Dx from DxTerity, uses a similar number of radiosensitive and insensitive mRNAs (15 and 3 respectively). Only two of the RNA species are in common with the panel from the ARad test. The amplification strategy with the REDI-Dx test differs from that of the ARad test in that the targeted RNAs are converted to specific amplifiable DNA fragments not by reverse transcription but by chemical ligation of two contiguous, hybridizing DNA fragments that are then amplified by qPCR and distinguished by size using capillary electrophoresis. Although they share only two out of the 32 mRNA species, both tests measure dose-dependent radiation response in Gy from a post-exposure venous blood specimen. The test times are comparable at 6–8 hrs per run and comparable in daily output using multiple instruments to process more than 1000 patient results per 24-hour day. The REDI-Dx test demonstrated a 98.5% sensitivity and 90% specificity at 2 Gy and a 92% sensitivity and 84% specificity for 6 Gy in verification testing (Jacobs et al. 2020). Recent data from the Arad test has shown a mean dose correlation between total body fractionated dose irradiated human and non-human primate data ($r = 0.99$) up to a dose of about 8 Gy. Thus far, early testing of the devices, algorithms, and operator use of the assays are promising.

The third high-throughput quantitative test is the CytoRADx test, a highly advanced cytokinesis-block micronucleus (CBMN) assay, a mature version of the early CBMN assays (Vral et al. 2011) developed by ASELL. This is a more direct measure of radiation injury because it is based on the abundance of micronuclei (MN) generated from radiation-induced breakage of DNA in quiescent lymphocytes. Studies have shown that the number of radiation-induced MN strongly correlates with dose and quality of radiation (Fenech and Morley 1986; Balajee et al. 2014; Bertucci et al. 2016). The CBMN assay involves overnight cell culture, resulting in a longer time-to-result than the gene expression assays. Using less than 1 mL of blood exposed *ex vivo* with a commercial blood irradiator, the CytoRADx system has demonstrated accurate and precise measurement of radiation exposures from 0 to 8 Gy (>90% of results within 1.2 Gy of delivered dose) which encompass the critical medical decision levels of 2 and 6 Gy. In vivo testing is underway with

both human pre-transplantation and non-human primate studies.

Initial assessments of test accuracy and positive/negative predictive values over a range of 0–8 or 0–10 Gy (depending on assay) are underway using extensive clinical and non-clinical advanced development testing. These studies include testing thousands of human and non-human primate samples acquired from Institutional Review Board (IRB) and Institutional Animal Care and Use Committee (IACUC) approved protocols. The human studies involve healthy adults, pediatric, adolescent, and geriatric samples. In addition, human specimens from potentially confounding populations such as burn, trauma, infection/sepsis, HIV, inflammatory bowel disease, rheumatoid arthritis, pregnant, and diabetic individuals are tested to evaluate the impact of these conditions on assay results. Samples from patients undergoing pre-transplantation irradiation and non-human primates given single dose or fractionated irradiation are used to correlate test results across species. Clinical Laboratory and Standards Institute (CLSI) guideline-driven testing is used to evaluate the analytical characteristics of each test.

A major concern in managing the medical aftermath of a nuclear blast is the rationing of available medical countermeasures (MCMs) due to the limited stockpiles of IV fluids, cytokines, antibiotics, and other medical supplies. Patient location and medical history are not accurate predictors of absorbed dose (Densow et al. 1997; Coleman et al. 2011; Garty et al. 2017). However, recent animal data has shown that gene expression changes (Ostheim et al. 2019) and plasmatic biomarkers coupled with hematological parameters (Valente et al. 2015) may be useful in distinguishing exposure patterns and improve the prediction of patient clinical outcomes. Following initial triage using qualitative biodosimetry, there can be several days until the most severe hematological affects manifest. Therefore, follow-on evaluation using quantitative, laboratory-based biodosimetry tests would significantly facilitate the prudent dissemination of stockpiled MCMs. For example, administration of a cytokine MCM to patients with estimated absorbed doses of two to six Gy are most effective when administered within the first few days post-irradiation (Chen et al. 2010; Farese et al. 2013; Hankey et al. 2015).

In a mass-casualty event, clinicians typically rely on various pieces of information for the management of patients. Estimates of absorbed dose can be made by various methods that may include external dosimetry that links location of a victim with levels of radiation in his or her immediate environment or biological dosimetry that uses laboratory results and clinical signs and symptoms for evaluations. A panel of global experts recommends that clinicians use as many methods of dose and predicting severity of ARS as they have to design treatment strategies (Dainiak et al. 2011). If one or more of the biodosimetry tests currently under investigation reach a high level of clinical maturity, perhaps the medical community will have additional individualized patient data to consider in a radiation response effort. Hopefully, in the future even newer strategies will be implemented that move beyond absorbed dose to more sophisticated predictive approaches to clinical outcomes (Port et al. 2019; Abend and Port 2018) and more innovative biodosimetry tools.

Conclusions

Recognizing the gaps in our current preparedness and technologies is crucial to develop well-laid plans, mitigate potential casualties, and be as prepared as possible for an inherently unpredictable disaster such as a radiological incident. A nuclear detonation would result in hundreds of thousands of irradiated individuals in need of medical intervention, but also result in millions of concerned, highly anxious individuals who have not had clinically significant radiation exposure. Their numbers would overwhelm medical systems lacking sufficient means to triage and develop treatment plans for victims. There is a need to provide clinicians and first responders every available tool to facilitate treatment in austere settings. Near-victim triage tests and laboratory-based high throughput biodosimetry tests can provide individualized absorbed dose information physicians will require in a timely manner to effectively manage treatment in this extremely resource-constrained environment. The four most mature biodosimetry tests funded by BARDA have undergone extensive verification testing and will continue to undergo pre-validation testing to ensure accurate, specific, and rugged tests are carried forward into the next stage of development. Current work with federal and industry partners will enable the development, regulatory review, and potential acquisition of radiation biodosimeters within the next few years. The availability of biodosimetry testing will greatly enhance the ability of the federal government to assist the state, nations, and local authority response to a large-scale nuclear incident.

Disclosure statement

The authors have no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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