1 Program Summary

The goal of the Targeted Evaluation of Ionizing Radiation Exposure (TEI-REX) program is to establish novel biodosimetry approaches enabling improved quantification of low-dose ionizing radiation exposures (<0.75 Gray)[1] from minimally and non-invasive samples, while also expanding quantitative and qualitative knowledge of the exposure environment. To accomplish this, the TEI-REX program will discover, characterize, and model biomarkers associated with a variety of ionizing radiation events, especially low-dose exposures, from minimally- or non-invasive samples, which can be collected unobtrusively (hereafter known as 'TEI-REX samples'). The new capabilities developed under TEI-REX align with the United States Government's mission objectives ranging from investigation of exposure events to ensuring compliance with established dosimetry protocols.

Current biodosimetry approaches, including the gold standard dicentric chromosome assay (DCA), are effective for determining a high-dose radiation exposure, but suffer from multiple limitations. These constraints include: the need for invasively collected sample(s), such as blood; requiring multiple collections of the sample; a limited period for which a first sample must be collected post-exposure for an accurate prediction of dose exposure; a dependence on transient markers to calculate exposure dose, resulting in a limited period the test is effective following an exposure; and wide standard deviations of dose calculations at low-dose exposures. The TEI-REX program aims to establish and characterize novel biomarkers, which can overcome many of the limitations that current biodosimetry approaches do not address.

Recently published research has demonstrated that biomarkers associated with ionizing radiation exposure can be detected across numerous biological targets including proteins, peptides, metabolites, and lipids[2]. While recent research has focused on basic targets in simple models, they showcase the potential for expanding biodosimetry techniques to novel tissue and sample types, while overcoming limitations associated with current biodosimetry techniques. As these earlier efforts focused on high dose exposures and/or high dose rates *ex vivo*, TEI-REX is advancing this research by focusing on more complex sample targets in more complex (e.g., *in vitro* and *in vivo*) environments at lower dose exposures, with the hypothesis that irradiation of proteins and other biological targets will demonstrate a minimal- or no-threshold, non-linear sensitivity response to the exposure. This hypothesis should be considered distinct, but potentially overlapping, from the linear, no-threshold model used by the EPA to assess the clinical risk associated with low-dose radiation exposure[3].

2 Scientific Premise for the Program

The concept of the TEI-REX program relies upon the law for the conservation of energy. Ionizing radiation contains energy, which is transferred to the organic and non-organic elements with which it interacts. In biological systems, as cells and intercellular spaces are predominately comprised of water, much of this linear energy transfer (LET) results in the generation of reactive species (e.g., reactive oxygen species (ROS) and reactive nitrogen species (RNS)), but some energy may directly

[1] One Gray (Gy) is **the international system of units (SI) equivalent of 100 rads**, which is equal to an absorbed dose of 1 Joule/kilogram.

[2] (Benjamin B Minkoff, 2019; Jelena Tamuliene, 2020; Merriline M. Satyamitra, 2020; Elisabeth Vicente, 2020; William Blakely, 2010; Younghyun Lee, 2018; Changran Geng, 2020)

[3] (United States Environmental Protection Agency, 2021)

transfer to biological materials, such as: DNA, proteins, metabolites or lipids (Figure 1). LET or reactive species may cause changes, often in the form of damage, to various components of the cell[4]. Most biodosimetry approaches rely upon calculating damage done to DNA or the downstream effects of irradiative damage. TEI-REX is researching the effects done to the other biological components, specifically those which are long lasting and directly attributable to the initial ionizing insult.

Lower doses of ionizing radiation will result in fewer molecular changes compared to high-dose exposures, making detection even more difficult as low-dose exposures approach ambient background, but the changes will still be present. Researchers recently demonstrated, when using free amino acids and 3-residue peptides, a consistent order of reactivities exists across amino acids when exposed to higher doses of radiation[5]. Other researchers have also shown that glutamine, for example, has unique electron impact fragmentation patterns based upon variable and high dose exposures[6]. Finally, additional researchers are in the early stages of characterizing irradiated proteins to demonstrate the potential for a biologically informed dosimeter[7].

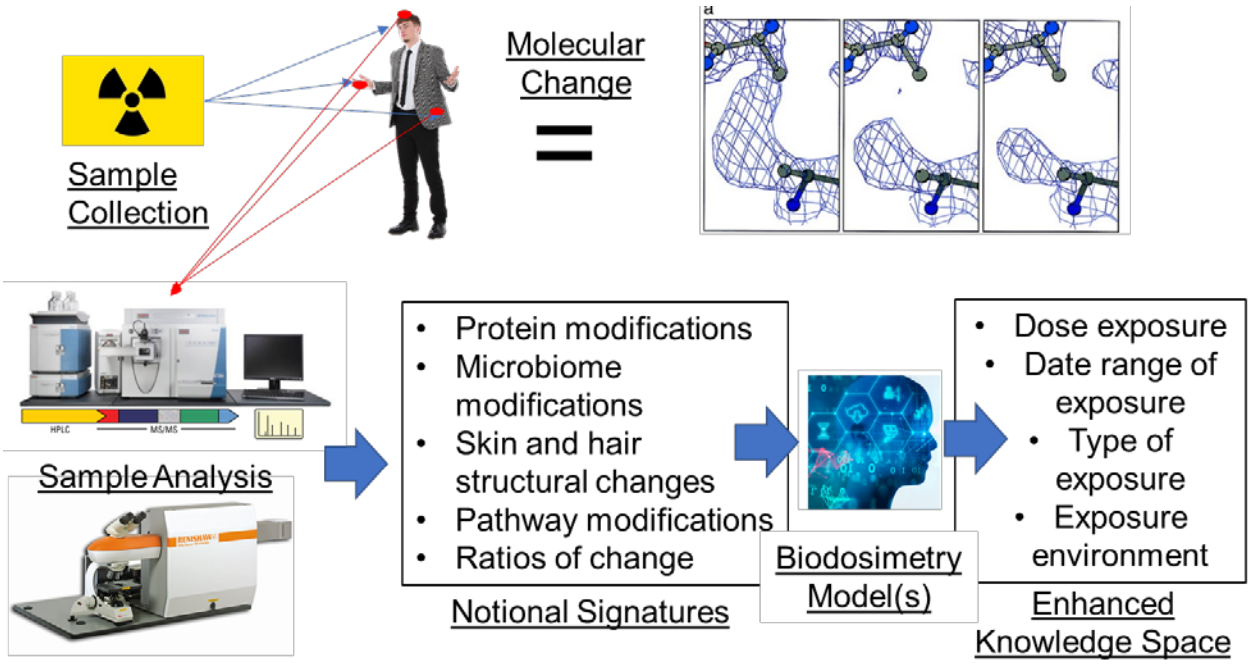

Figure 1: Overarching TEI-REX concept with notional signatures and detection methods.

3 New Methods for Evaluating Low-Dose Ionizing Radiation Exposure

The TEI-REX program seeks proposals for new methods of quantifying low-dose (<0.75 Gray) ionizing radiation exposure to an organism, shifting away from methods which are dependent upon

[4] (Keisz, Bansal, Qian, Zhao, & Furdui, 2014)
[5] (Benjamin B Minkoff, 2019)
[6] (Jelena Tamuliene, 2020)
[7] (Changran Geng, 2020)

invasive sampling and more traditional DNA, RNA, and expression-based signatures. The objectives are to discover robust biomarkers associated with samples of interest, develop methods for enabling the detection of these signatures, and develop models to interpret these signatures in relation to the exposure event. Ideally, these biomarkers will be conserved across organisms and/or sample types enabling improved extensibility. Realistically, the program recognizes the significant challenge this research objective represents and that initial steps likely will focus on a limited number of optimal model organisms and sample targets. Offerors are encouraged to describe how extensible their biomarker may be to other targets or organisms but must focus on how they will apply their proposed research against the primary objectives of this program instead of theorizing towards an ideal objective.

4 Program Structure

The TEI-REX program is anticipated to be a 3.5-year (42 months) effort, comprised of three (3) Phases. All three (3) Phases are being solicited under this BAA. Phase One (1) will be 18 months in duration, Phase Two (2) will be 12 months, and Phase Three (3) will be 12 months. Each phase will encompass two (2) main technical Focus Areas:

- Focus Area 1 (FA1): Signatures and detection methodologies for characterizing ionizing radiation exposures within 25 days of an exposure event, from TEI-REX samples.
- Focus Area 2 (FA2): Signatures and detection methodologies for characterizing ionizing radiation exposures 90 days or greater from an exposure event, from TEI-REX samples.

Offerors shall propose to all three (3) Phases and both Focus Areas of the Program under this BAA. Proposals that submit to only 1 Focus Area or less than 3 Phases per Focus Area may be considered non-compliant. Awardees may be selected for a single Focus Area following review of their entire proposed approach.

The goal of Phase 1 is the successful prediction of higher-dose, 1 to 4 Gray, exposure and the timeline of exposure, days to months, from at least one TEI-REX sample. Performers are expected to make these predictions by evaluating unique biomarkers associated with TEI-REX samples and using them to develop an effective biodosimetry model. These dose ranges were selected as the most likely to enable discovery of radiation induced biomarkers, without being suppressed by the noise associated with severe cellular damage and/or cell apoptosis. To accomplish this, performers are expected to establish a research pipeline for the discovery, characterization, and modeling of robust biomarker signatures, induced by ionizing radiation exposure. **Offerors must propose research approaches that enable evaluation**, aligning to TEI-REX metrics (Table 3) and the Test and Evaluation (T&E) approach, **of radiation dose exposures and the timeline of exposure** through discovery of relevant biomarkers found in or on **skin, hair, or other accessible sample types** (e.g., sweat, sebum, dermal interstitial fluid, hair follicles, etc.). Offerors must propose well-reasoned and supported research approaches for successfully identifying biomarkers from these high-dose exposures in addition to modeling approaches that will meet Phase 1 metrics and T&E approaches.

The goal of Phase 2 is the successful prediction of: low-dose exposure, defined as ambient background[8] to 0.75 Gray; the timeline of exposure, from days to months; the type of radiation (particulate, electromagnetic, and/or mixed), and; the dose rate of exposure (mGray/min) from at least two TEI-REX samples. Performers are expected to leverage and optimize their efforts from Phase 1 to demonstrate successful analysis of samples at lower dose exposures, a greater variety of exposure time points, and a wider variety of samples/organisms while also improving upon overall confidence and accuracy of these predictions (Table 3). Offerors must propose improvements and optimizations for their research approach and describe why the approach has a high likelihood of success against the lower dose exposures and expanded Phase 2 metrics and T&E approaches.

Across both Phase 1 and 2 offerors may **propose models distinct from those described under the T&E process**. Any proposed approach must demonstrate technical strength and high likelihood of extensibility to T&E sample types. Blinded T&E activities should not be expected to conform to specific performer unique model systems nor approaches, although adaptation to specific sample types may be feasible. The baseline for reference samples developed and provide by the program will be hair and skin from human-associated or mouse models.

The goal of Phase 3 is the successful evaluation of a range of realistic exposure scenarios across a range of doses, timelines, and organism types. Performers will be expected to integrate and expand the model systems developed under Phase 1 and 2 and apply their research efforts towards identifying the limits of the newly developed TEI-REX capabilities. This Phase will rely upon even more challenging metrics from Phase 2 (Table 3). Offerors will be expected to integrate, improve, and adapt their discovery, detection, modeling, and deductive approaches to evaluate at least 3 sample types. The most likely models and sample types will be discussed throughout Phase 2 and decisions will be released at the Phase 3 kickoff, offerors should plan for sample counts and testing timelines aligning with what is described further below.

5 Research Focus Areas by Phase

Phase 1: Research the discovery, detection, and modeling of signatures associated with higher dose ionizing radiation exposures from minimally or non-invasive samples.

Offerors are expected to describe how they will establish the exposure environment and the research efforts that support the discovery and characterization of biomarkers associated with higher dose exposures. Offerors must describe how their research approach aligns with TEI-REX objectives, to include planned radiation exposure environment, model system(s), sample type(s), analytical biomarker discovery and detection pipeline, and the biodosimetry modeling approach with strong and supported scientific reasoning. Offerors should account for the T&E approach d and adapt their research plan appropriately so they can evaluate samples or models distinct from the models and sample types used for internal research activities. Offerors must ensure their discovery and detection research proposal aligns with all program metrics in Table 3. Leveraging these systems to generate and discover appropriate biomarkers, offerors will be expected to model

[8] The natural radiation that is always present in the environment. It includes cosmic radiation which comes from the sun and stars, terrestrial radiation which comes from the Earth, and internal radiation which exists in all living things. The typical average individual exposure in the United States from natural background sources is about 300 millirems per year (https://www.nrc.gov/reading-rm/basic-ref/glossary/background-radiation.html).

the biomarkers and associated data, enabling evaluation across a range of ionizing radiation doses for a given exposure timeline for each FA:

> Phase 1/FA1: Research the discovery, detection, and modeling of signatures associated with **higher dose, 1-4 Gray,** ionizing radiation exposures within **25 days** of an exposure event from TEI-REX samples.
>
> Phase 1/FA2: Signatures and detection methods for characterizing **higher dose, 1-4 Gray,** ionizing radiation exposures, greater than **90 days** from an exposure event, from TEI-REX samples.

For both FA1 and FA2 in Phase 1, offerors will be responsible for describing their proposed model system(s), their research plan to include irradiation of the models(s) and evaluating appropriate samples, with the expectation to include biomarker research from **at least one sample type of either skin or hair**. Offerors will develop their own protocols and systems for irradiation of models and samples. Offerors must describe their approach for ensuring low-dose exposures across multiple radiation types in a highly consistent and quantitative manner; collection of samples, analysis of samples, discovery of biomarkers, and development of models from biomarkers enabling accurate prediction of exposure dose and dose timeline are all, at least, expected to be described in approach. Offerors will be expected to generate approximately 100 irradiated samples associated with their selected model system(s) and sample types to provide to T&E teams. Offerors will be expected to evaluate T&E blinded samples, to include at least hair or skin samples, using the models developed throughout their research efforts (Figure 2). Offerors shall consider as deliverables their: protocols, selected biomarker panels, irradiated samples, details on model systems, raw analytical data, and final outputs which includes reporting of alignment to program metrics (Table 3).

Phase 2: Research signatures and detection methods for characterizing lower dose ionizing radiation exposures from minimally and non-invasive samples.

Offerors are expected to leverage the methods, models, platforms, and overall capabilities developed under Phase 1 to investigate biomarkers associated with low-dose exposures. Offerors will be expected to improve upon metrics associated with biodosimetry modeling and biomarker detection as detailed under Table 3. Additionally, offerors are expected to research methods for applying biomarker analysis, from a single sample or multiple samples collected from a single model individual, towards assessing the type of radiation exposure (particulate, electromagnetic, or mixed) and the exposure dose-rate. The approaches for detecting biomarkers will be evaluated based upon the same metrics as the blinded T&E activities.

For both FA1 and FA2 in Phase 2, offerors will be responsible for optimizing their proposed model system(s), completing irradiation of the models(s), and evaluating appropriate samples from at least one additional model from Phase 1, with the expectation to include biomarker research from **at least one sample type of either skin or hair**. Submitted approaches that provide strong technical support for extensibility of biodosimetry capabilities aligning to program objectives and to additional models or sample types will be viewed favorably in review. Approaches which propose unsupported or technical unsound support for greater extensibility may be reviewed

unfavorably. Offerors will develop their own protocols for irradiation of models to include: collection of samples, analysis of samples and discovery of biomarkers, and development of models from biomarkers enabling accurate prediction of exposure dose and dose timeline. Offerors will also generate approximately 100 irradiated samples associated with their selected model system(s) and sample types to provide to T&E teams. Offerors will be expected to evaluate T&E blinded samples, to include at least hair or skin samples, using the models developed throughout their research efforts. Offerors shall consider as deliverables their: protocols, selected biomarker panels, irradiated samples, details on model systems, raw analytical data, and final outputs which includes reporting of alignment to program metrics (Table 3). The lower dose exposure timeline for each Phase 2 FA is defined as follows:

> Phase 2/FA1: Signatures and detection methods for characterizing **lower dose, background to 0.75 Gray,** ionizing radiation exposures within **25 days** of the last exposure event from minimally and non-invasive samples.
>
> Phase 2/FA2: Signatures and detection methodologies for characterizing **lower dose, background to 0.75 Gray,** ionizing radiation exposures **90 days or greater** post-exposure event from minimally and non-invasive samples.

Phase 3: Research with application of biomarker detection against samples generated to mirror realistic scenarios.

For both FA1 and FA2 in Phase 3, offerors are expected to optimize the capabilities developed under Phases 1 and 2, and integrate their protocols, biomarkers, and models, against a series of realistic and challenging model types, sample types, and/or confounders selected with direct input from program transition partners. Offerors should expect to test the viability and robustness of their biodosimetry pipeline against new model systems, to include the potential for larger mammals, insects, and plants. Additionally, a range of confounders, to include age, gender, UV exposure, chemical exposure, and the presence of natural antioxidants may be tested. Offerors must describe how their platform will adapt to these challenging sample types, and propose how these factors may impact previously identified biomarkers. Evaluation of these samples will provide empirical evidence towards overall capability and extensibility, while also pushing offerors to research methods for challenging and niche use cases.

6 Recommended Team Expertise

The research associated with the TEI-REX program is expected to incorporate a collection of diverse technical fields. Offerors are strongly encouraged to ensure all capabilities below are clearly identified with demonstrated expertise within their team. Expertise associated with an ideal TEI-REX program, not ordered by criticality, should include, but are not limited to:

1. Radiation biology
2. *In vitro* and *in vivo* models associated with radiation exposure
3. Analytical biochemistry
4. Biomarker discovery
5. Biodosimetry
6. Machine learning and Artificial Intelligence
7. Radiation dosimetry/health physics

8. Statistics
9. Program management

7 Program Scope and Limitations

Proposals shall explicitly address all four of the following:

I. Underlying theory: Proposals shall summarize their proposed models, samples, and methods for likelihood of robust biomarker detection. Detailed support reinforcing the technical approach should be included as referenced papers.

II. Research activities: Proposals shall describe the technical approach(es) being pursued to meet TEI-REX metrics and milestones for all three phases.

III. Technical risks: Proposals shall identify technical risks and proposed mitigation strategies for each.

IV. Software development: Proposals shall describe the approach for developing software that enables effective and interpretable biodosimetry-based assessment of samples.

The following sample types, biomarkers, and confounders **are out of scope** for this program:

I. Any samples which cannot be collected through minimally- or non-invasive means, unobtrusively. Samples which do not fit this category can still be utilized for initial research efforts, but final capabilities and associated biomarkers must align with these minimally- or non-invasive sample types in an offeror's proposal. Types of collected samples that fall outside of scope are:

   a. Drawn blood from vein or finger prick (comparable to blood glucose tests)

   b. Cheek or other mucosal cells collected directly from source by swab

   c. Tooth enamel

The TEI-REX program is not focused on detection of radionuclides absorbed, ingested, or injected into an organism.

The below categories of biomarkers are **out of scope**:

I. DNA damage to include single or double stranded breaks or associated repair signatures

II. Transcriptional effects, including RNA, mRNA, and miRNA

III. Biomarkers that require multiple collections from the same biological target (including baselines)

Radiation types **out of scope**:

I. Cosmic or heavy ions radiation

Final activities **out of scope**:

I. Manufacture of new equipment for analytical biomarker analysis.

II. Improvements on throughput, scalability, and multiplexing of existing biodosimetry approaches.

8 Program Test and Evaluation

The Government will use the Program Goal , Metrics (Table 3), and Significant Milestones and Deliverables (Table 4) to evaluate the effectiveness of proposed solutions in achieving the stated program objectives, and as a partial means to determine whether satisfactory progress is being made to warrant continued funding for the program. TEI-REX will utilize independent T&E teams to assist in evaluating progress and success of TEI-REX approaches. Progress towards these milestones and metrics are a portion of how program success will be monitored and assessed. They are intended to focus the TEI-REX program, while permitting flexibility, creativity, and innovation in the proposed solutions to meet the TEI-REX program goals.

In addition to describing how proposed approaches address government-specific metrics, offerors should provide a detailed description of additional metrics or milestones relevant to their unique technical approaches. IARPA withholds the right to modify, remove, or add new milestones or metrics as the program progresses to ensure the research activities can be appropriately and effectively monitored and evaluated. Expected final Phase 1 metrics (Table 3) will be provided by the Government during the Phase 1 Kickoff Meeting. Any additional changes to milestones or metrics after program kickoff may be provided by the Government following discussions with program stakeholders.

The test and evaluation process includes three primary activities: 1) evaluation of self-reported scoring, against program metrics, by performer teams using their own samples throughout each Phase with progress reported through monthly deliverables; 2) evaluation of performer protocols, identified biomarker panels, and models by the T&E teams to substantiate self-reported scoring; and 3) evaluation of performer biodosimetry and biomarker data outputs by T&E teams when evaluating blinded samples provided to performers by T&E. Dose exposure, timeline, and dose-rate associated with each blinded T&E sample will not be provided (refer to Table 2), performers will be evaluated based upon how well their models and predictions meet program metrics when the ground truth of the blinded samples is released.

T&E is **limited in the number of models and samples it can generate** and offerors are encouraged to consider this when proposing an appropriate model system in their research pursuit of robust biomarkers. Proposed approaches which demonstrate very strong technical likelihood to meet the objective of TEI-REX while also falling outside of the model systems described will be considered but offerors must propose viable approaches for third-party test and evaluation approaches, enabling evaluation against program metrics, to account for the deviation.

TEI-REX T&E in Phases 1 and 2 will predominately leverage samples derived from *in vivo* mouse systems and full-thickness 3-D (mouse/human) constructs primarily derived from commercial sources. The Government, through the T&E Team(s), will provide up to 500 samples per T&E event. Events include Phase 1 Round 1 and Phase 1 Round 2, and Phase 2 Round 3 (refer to Table 1 and Figure 2 for specific timing on T&E events) with note that sample numbers are inclusive of experimental and biological replicates, controls, and standards to each team for each Focus Area. T&E will include up to 25 unexposed negative controls per sample/model type per FA and up to

50 exposed samples with details of exposure prior to each T&E evaluation event (Table 1 and Figure 2) for performer self-assessment and development guide. Many of these samples will likely be either skin, skin-like, or hair samples. If an offeror's research focuses on additional sample types of interest that can be easily collected from either of these model types, the T&E team will attempt to provide a sufficient number of supporting, blinded samples to enable testing and evaluation, but this is not assured. If these alternative samples cannot be provided by T&E, performers will still be expected to meet program metrics by evaluating the samples provided.

Offerors should plan to receive two (2) sets of predominately blinded T&E samples in Phase 1. The first set of samples, Phase 1 Round 1, will be used to establish a baseline capability of each performer's approach against program metrics, while Phase 1 Round 2 will demonstrate how the teams have progressed across the Phase and their capability to achieve program metrics. Both sets of blinded samples will include at least one (1) sample type from one (1) model type. Each Focus Area will have its own set of samples. Offerors will be given 60 days to analyze all provided samples and submit their raw data and computational outputs from their models following guidelines provided by the Government prior to receipt of T&E samples. In Phase 1, performers are expected to determine, at least, the exposure dose and exposure timeline, to include error. Biodosimetry model outputs must include error and interpretable association back to the biomarkers which informed towards the biodosimetry predictions. Biomarker detection metrics will align with true positive rate (TRP), false positive rate (FPR), and precision as statistical measurements as well as meeting sample mass/volume and extensibility requirements. Offerors are also expected to identify appropriate industry accepted quality score metrics or propose reasonable scoring approaches, based upon their analytical approach, which can be used to demonstrate successful biomarker detection from the matrix.

Offerors should plan that blinded Phase 2 T&E samples will include additional model types, determined by program progress and performer successes in Phase 1, while still leveraging mouse and full-thickness 3-D constructs. Offerors will receive one (1) batch of predominately blinded samples, up to 500 samples, inclusive of blinded experimental and biological replicates, unblinded controls, and unblinded standards to each team for each Focus Area. These samples will include at least two (2) sample types across two (2) model systems. Offerors will be given 60 days to analyze all samples provided and submit their raw data and outputs from their computational models. In Phase 2, metrics will expand from only scoring the prediction of dose exposure and exposure timeline to also evaluating the prediction of radiation exposure type and dose rate. Biodosimetry model outputs must include error and be interpretable that is providing association to the biomarkers from which biodosimetry predictions were informed. Biomarker Detection metrics will align with true positive rate (TRP), false positive rate (FPR), and precision as statistical measurements as well as meeting sample mass/volume and extensibility requirements. Offerors are also expected to identify appropriate industry accepted quality score metrics or propose reasonable scoring approaches, based upon their analytical approach, which can be used to demonstrate successful biomarker detection from the matrix.

Offerors should plan to receive multiple sets of a limited number of blinded samples across Phase 3, under 100 samples per Round. Phase 3 is aimed at researching and adapting the functional capabilities developed under Phases 1 and 2 to realistic samples. These samples will be directly informed through IARPA engagement with TEI-REX transition partners. The samples will often

be limited in number and provide only empirical evidence of capability without strong statistical confidence, but performers will be expected to meet or exceed the sample metrics as required in Phase 2. These samples may include a wider range of model types, to potentially include samples from the Göttingen minipig, insects, human, and plants. These samples may include a range of confounders including: variations in age, gender, UV exposure, dose rate, and common chemicals typically used on hair or skin. Throughout Phase 3, performers are expected to adapt and optimize their models appropriately throughout the three rounds of the Phase while continuing to improve their platform and achieve Phase 3 metrics (Table 3).

Offerors should be prepared to use a reporting template, provided at the beginning of T&E activities in each Phase, in which to submit their results. This template will be developed by the T&E team(s) in coordination with each team. All supporting raw data derived during performer analysis after each T&E event will also be submitted for T&E review.

Biodosimetry models developed by performers will be evaluated by T&E based upon selected metric outputs, interpretability of model outputs, and likelihood to meet overall TEI-REX objectives computed based on nonparametric statistical power studies to predict future model performance as a function of the number of available training samples.

Phase 1	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18
T&E provide baseline samples for comparison			■															
T&E provide unblinded samples for training							■											
T&E provide blinded samples for testing									■						■			
T&E deliver controls and standards to support testing									■						■			
Performers send samples and protocols for 3rd party testing												■						

Phase 2	M19	M20	M21	M22	M23	M24	M25	M26	M27	M28	M29	M30
T&E provide baseline samples for comparison		■										
T&E provide unblinded samples for training						■						
T&E provide blinded samples for testing										■		
T&E deliver controls and standards to support testing										■		
Performers send samples and protocols for 3rd party testing								■				

Phase 3	M31	M32	M33	M34	M35	M36	M37	M38	M39	M40	M41	M42
T&E provide blinded samples for testing	■				■				■			
T&E deliver controls and standards to support testing	■				■				■			

Figure 2: Timeline for T&E sample activities across all three Phases

9 Government Provided Equipment and Samples

To support the research and T&E processes, the T&E teams will provide multiple sets of government derived samples, to include unblinded negative control samples which are not irradiated and unblinded positive control standards that have been irradiated with a stepwise increase in dosage, within the relevant dose ranges, to support performer adaptation to T&E samples. Table 1, below, lists and describes these samples along with the expected metadata to be delivered with each sample set.

Table 1: Table of TEI-REX Provided Samples

Sample Name	Phase/Activity	Sample Description	Sample Metadata
Baseline (reference) samples	P1/M3 and P2/M20	Unexposed samples aligning with the T&E model systems and sample types to be tested in the respective phase and Focus Area. Up to 25 samples.	• Model (age/gender/strain) • Sample origin (hair/skin) • Sample mass/volume
Unblinded training samples	P1/M7 and P2/M24	Irradiated samples aligning with T&E model systems and sample types provided prior to active T&E to enabled performers to test their biodosimetry approach in advance using 3rd party samples. Up to 50 samples.	• Dose information (exposure/rate/timeline/ environment) • Model (age/gender/strain) • Sample origin (hair/skin) • Sample mass/volume
Blinded T&E samples	P1/M9, P1/M15, and P2/M28	Irradiated samples, primarily aligning with skin and/or hair, from T&E models. Blinded regarding all exposure information. Up to 500 samples.	• Model (age/gender/strain) • Sample origin (hair/skin/etc.) • Sample mass/volume • Spike-in concentrations • Spike-in digestion profiles
T&E controls and standards	P1/M9, P1/M15, and P2/M28	• Irradiated controls with known doses to create a positive control calibration curve. • Process control and platform performance standards spiked into or onto blinded samples to enable evaluation of sample prep by performers.	• Dose information (exposure/rate/timeline/ environment) • Model (age/gender/strain) • Sample origin (hair/skin) • Sample mass/volume • Spike-in concentrations • Spike-in digestion profiles
Blinded realistic samples	P3/M31,35,39	Blinded irradiated samples derived from a variety of model systems aligning with exposure environments informed by transition partners. Up to 100 samples per round.	• Sample origin (hair/skin/etc.) • Model system

10 Models, Software, and Application of Machine Learning/Artificial Intelligences Towards Biodosimetry

Offerors will be required to provide the algorithms, models, code, and/or software deliverables via a hosting environment established by the T&E team in a manner that conforms to industrial best practices, including containerized code to automate deployment. Offerors should describe how models will be developed, language(s) used, and expectations of command line or user interface development. Biodosimetry models will not be evaluated by hardware requirements but must be deployable on a cloud environment and packaged in a Docker or Singularity package with pre-identified dependencies. TEI-REX will not be providing an environment to train model systems and software.

The specifics of model and data delivery to the T&E environment will be provided at TEI-REX program Kickoff. Offerors should expect to utilize standardized reporting templates, likely in JSON or similar, with consistent and pre-identified terminology for labeling metadata tags. Biodosimetry models are expected to incorporate both big data training from TEI-REX biomarkers and implicitly programmed elements focusing on known biodosimetry evaluation techniques, radiation physics, and biology. Predictions from the biodosimetry models must be interpretable, enabling review of the specific biomarkers leading towards the output results (Table 3). Biodosimetry models must adhere with industry accepted coding standards and conventions and that all models developed using machine learning/deep learning (ML/DL) can be retrained by end-users.

T&E will leverage software deliverables to evaluate the functionality of the TEI-REX technologies, assess the extensibility of the technologies on different biomarker targets, sample types, and model types, and potentially ensemble multiple the approaches and/or training databases developed under TEI-REX. This evaluation will be accomplished by T&E analyzing individual performer model outputs using raw biomarker data inputs generated across the program. Results of T&E verification should align with self-reported data from the performer teams and program metrics, any significant deviations will require further review of technologies by T&E with support from performer teams.

11 Program Waypoints, Milestones, and Metrics

The Government will use Milestones and Metrics to quantitatively track program progress, which for the purposes of this concept are defined as:

- Waypoint (Table 2): An intermediate performance target, tied to a specific time in the program execution, established by the performer but linked to a Milestone or Metric.
- Milestone (Table 4; Figure 3): A specific Government-provided performance target, tied to a specific time in the program execution (e.g., establishment of irradiation testbed by Month 3). All milestones are required.
- Metric (Table 3): A quantitative or qualitative measure of program performance (e.g., prediction of exposure dose).

A Waypoint is a performer-specific performance target, tied to a specific time in the Program's Execution (each performer will supply their own system- and approach-specific Waypoints).

Waypoints provide evidence that the technical and programmatic risks associated with the proposed approach are being addressed. Waypoints must be clear, well-defined, quantitative, and logically connected to offeror and/or Government decisions. Offerors must include Waypoints in their proposal and provide, as a deliverable, updates to the Program Waypoints at the start of each Phase. Performance against these waypoints will be reviewed throughout the Program to assess whether course corrections are needed to ensure Program success.

Program Milestones and Metrics define the scope and goals of the effort. The Government shall use the Program Milestones and Metrics, summarized in Tables 2 and 3, to evaluate the effectiveness of proposed solutions in achieving the stated program objectives, and in part to determine whether satisfactory progress is being made to warrant continued funding of the program. The offeror may also propose appropriate additional Milestones and Metrics to improve evaluation of progress. Additional Program Milestones should be proposed to provide evidence that the technical and programmatic risks associated with the proposed approach are being addressed. Any such Milestones and Metrics shall be clear and well-defined, with a logical connection to enabling offeror decisions and/or Government decisions.

The Metrics in Table 3 and overall constraints are intended to bound the scope of the effort, while affording maximum flexibility, creativity, and innovation in proposing solutions to the stated research problem. The TEI-REX program metrics are broken into three types: 1) Primary capability metrics associated with evaluation of effectiveness of biodosimetry models to predict exposure data; 2) interpretability metrics that are critical for ensuring the robustness of the biomarkers and their associated interpretability in relation to the biodosimetry outputs; and 3) progress and foundational science metrics associated with the discovery of the biomarkers across sample and dose types. These metrics may change as the Program progresses to ensure mission objectives are maintained while also continuing to drive innovation and growth within the Program. Most changes to metrics will occur following discussions between the TEI-REX IARPA team, ARO, TEI-REX transition partners, TEI-REX T&E team(s), and the performer(s) impacted by the change.

All Biodosimetry Model metrics are associated with the computational model developed by performers and its predictions, extensibility, and interpretability when evaluating TEI-REX and performer developed samples. All metrics should provide data associated with samples, based on the variable being tested, and all samples evaluated as a whole, as appropriate per model and sample type. Accuracy targets are defined as aggregated statistical measures for a given phases' model predictions across dose, timeline, dose-rate, and ionizing radiation type. Median Absolute Error (MAE) is a statistical measure aimed to describe model prediction error. Precision is the statistical measure for measuring repeatability of model predictions across samples. Extensibility is a binary call of yes or no, defined by how well the biodosimetry model is able to predict the variable exposure factors when analyzing a new model type(s) with greater than 50% confidence across all samples. Interpretability is a retrospective correlative requiring the biodosimetry model to correlate predictions back to the biomarkers enabling the prediction to be made.

All Biomarker Detection metrics are associated with the analytical detection of biomarkers following irradiation exposure. True positive rate (TPR) is the statistical measure used, as an aggregate across all possible biomarkers being targeted, with the goal of maximizing true

detections. False positive rate (FPR) is the statistical measure used, as an aggregate across all possible biomarkers being targeted, with the goal of minimizing false detections. Precision is the statistical measure for measuring repeatability of biomarker detection, in aggregate. Extensibility is a binary call of yes or no, evaluated as achieving at least one (1) appropriate biomarker, used by the biodosimetry model to make predictions, in at least 50% of the new model systems.

Waypoints and Milestones, developed by offerors and submitted with the proposal, shall include appropriate corresponding Metrics, should be captured in a single table or timeline, similar to the structure found in Table 2, below.

Table 2: Template for Milestones and Waypoints, to be Completed by Offeror.

Phase	Month(s)	Event (Milestone or Waypoint)	Description	Comment	Associated Deliverable or Metric

Table 3: Program Metrics Across All Phases and Focus Areas

	Metric (FA1 and 2)	Phase 1	Phase 2	Phase 3
Biodosimetry Model	**Prediction of Absorbed Dose***			
	Accuracy	70%	80%	90%
	MAE	30%	15%	10%
	Precision	60%	70%	80%
	Predicted Timing of Exposure (in days)*			
	Accuracy	70%	80%	90%
	MAE	30%	15%	10%
	Precision	60%	70%	80%
	Prediction of dose-rate (mGray/min)*			
	Accuracy	N/A	60%	70%
	MAE	N/A	30%	20%
	Precision	N/A	70%	80%
	Prediction of Ionizing Radiation Type (Particulate and/or Electromagnetic: α / β / γ or x-ray / γ + neutron)*			
	Accuracy	N/A	60%	80%
	Precision	N/A	70%	80%
	Extensibility: Absorbed Dose Predicted in at Least X Sample Type(s) from X Model(s)	1 Sample / 1 Model	1 Sample / 2 Models	1 Sample / 3 Models
	Model Interpretability: Model identifies X percent of composite biomarkers informing towards predictions	70%	80%	90%
Biomarker Detection	TPR	70%	80%	90%
	FPR	30%	15%	10%

	Precision	60%	70%	80%
	Sample mass/volume	< 50mg/50µL	< 5mg/5µL	< 5mg/5µL
	Extensibility: Biomarker(s) Detected in at Least X Sample Type(s) from X Model(s)	1 Sample / 1 Model	1 Sample / 2 Models	1 Sample / 3 Models

*must be evaluated at the grouped level of sample evaluation (target variable is held constant) as well across the entire collection of samples evaluated

12 Program Period of Performance, Timeline, and Deliverables

IARPA will use the timelines as described in Figure 3 and Table 4 to monitor, evaluate, and maintain overall Program progress and its 42-month Program Schedule. Offerors should plan for a 42-month effort for the Period of Performance over three phases: Phase 1 of TEI-REX shall last 18 months; Phase 2 shall last 12 months, and Phase 3 shall last 12 months. Only successful offerors will move on from Phase one to the other phases. Refer to Figure 3 for a more complete capture of Program timeline and activities. Table 3 includes a schedule for the key deliverables the offerors shall provide. In addition to technical oversight of progress, technical reviews will assess programmatic progress against proposed work plans. Offerors may add additional deliverables as needed to the minimum set listed in Table 3.

Table 4: Significant Milestones and Deliverables Associated with TEI-REX

Phase/Month	Milestone/Deliverable
P1/M1, P2/M19, P3/M31	Program/Phase kickoff meetings, likely in Washington DC Metropolitan area. Drafts of presentation material are due 5 workdays prior to kickoff. Final materials due 15 calendar days following meeting date.
P1/M1, P2/M19, P3/M31	Processed approvals, as appropriate for Phase 1 activities, to include IRB and IACUC review. These approvals shall be updated annually or as appropriate.
P1/M1	Updated Phase 1 research plan to include waypoints and relevant non-Program Metrics/Milestones.
P1/M3	Comprehensive irradiation testbed design and biomarker discovery research plan
P1/M3	T&E provides limited number of unexposed samples to performers.
P1/M3 (and roughly every 6 months following)	Site visits, refer to program timeline for projected events. Performers shall participate and provide final meeting documents, to include captured action items, within 15 calendar days following the meeting. Draft materials, for any presentations, are due 5 workdays prior to the meeting.
P1/M7	T&E provide limited number of irradiated samples, to include standards, to performers.
P1/M8	Finalized template for T&E reporting (developed in coordination with T&E teams)
P1/M8	Summary of discovered biomarkers, to include self-reporting scores aligning to Program Metrics, protocols used for discovery and detection, and requested deviations or unique needs associated with upcoming T&E blinded samples. Raw analytical data to be included as well.
P1/M9	T&E provide blinded samples to performers for Round 1 T&E

Phase/Month	Milestone/Deliverable
P1/M10	Results from Round 1 T&E to include completion of the reporting template and supporting raw data.
P1/M10	Upload of early version of software and models used to evaluate biomarkers and provide relevant biodosimetry outputs.
P1/M12, P1/M18, P2/M29, P3/M41	PI meetings with other performers, T&E, and USG transition partners present. Likely to occur within the DC metro area. Performers shall participate and provide final meeting documents, to include captured action items, within 15 calendar days following the meeting. Draft slides, for any presentations, are due 5 workdays prior to the meeting.
P1/M12	Performers provide limited, up to 100, number of samples from in-house models to T&E for 3rd party evaluation of protocols and biomarkers.
P1/M15	Report summarizing the updated biomarker list, optimized protocols for discovery/detection, self-assessment against Program Metrics and requested deviations or unique needs associated with upcoming T&E blinded samples. Raw analytical data to be included as well.
P1/M15	Finalized template for T&E reporting (developed in coordination with T&E teams).
P1/M15	T&E provide blinded samples to performers for Round 2 T&E
P1/M17	Results from Round 2 T&E to include completion of the reporting template and supporting raw data. Summary elements may be included in the Final Phase 1 report as an alternative to a separate deliverable.
P1/M17	Upload of working version of software and models used to evaluate biomarkers and provide relevant biodosimetry outputs.
P1/M17	Final Phase 1 summary report to include: executive summary, accomplishments (testbed, methods/protocol development, results – specific to Program Metrics and performer specific elements, and lessons learned), and Phase 2 research plans.
P2/M19	Updated Phase 2 research plan to include waypoints and relevant non-Program Metrics/Milestones.
P2/M20	T&E provides limited number of unexposed samples to performers.
P2/M24	T&E provides limited number of irradiated samples, to include standards, to performers.
P2/M26	Performers provide limited, up to 100, number of samples from in-house models to T&E for 3rd party evaluation of protocols and biomarkers.
P2/M27	Finalized template for T&E reporting (developed in coordination with T&E teams)
P2/M27	Summary of discovered biomarkers, to include self-reporting scores aligning to Program Metrics, protocols used for discovery and detection, and requested deviations or unique needs associated with upcoming T&E blinded samples. Raw analytical data to be included as well.
P2/M28	T&E provided samples for Round 3 T&E
P2/M29	Upload of updated, working version of software and models used to evaluate biomarkers and provide relevant biodosimetry outputs.

Phase/Month	Milestone/Deliverable
P2/M29	Results from Round 3 T&E to include completion of the reporting template and supporting raw data. Summary elements may be included in the Final Phase 2 report as an alternative to a separate deliverable.
P2/M29	Final Phase 2 summary report to include executive summary, accomplishments (testbed, methods/protocol development, results – specific to Program Metrics and performer specific elements, and lessons learned), and Phase 3 research plans.
P3/M31	Updated Phase 3 research plan to include waypoints and relevant non-Program Metrics/Milestones.
P3/M31	Finalized template for T&E reporting (developed in coordination with T&E teams)
P3/M34, P3/M38	Results from Round 4 and 5 T&E to include completion of the reporting template and supporting raw data.
P3/M41	Results from Round 6 T&E to include completion of the reporting template and supporting raw data. Summary elements may be included in the Final Phase 2 report as an alternative to a separate deliverable.
P3/M41	Upload of final version of software and models used to evaluate biomarkers and provide relevant biodosimetry outputs.
P3/M41	Final Program report to include executive summary, accomplishments (testbed, methods/protocol development, results – specific to Program Metrics and performer specific elements, future research directions, lessons learned, and transition requirements).
Monthly, by the 15th day of the following month	Monthly technical and financial reports and PDFs of invoices due to the Government. Templates provided by the Government.

Phase 1 (18 Months)	M1	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12	M13	M14	M15	M16	M17	M18
Program Kickoff	■																	
Establishment of Irradiation Testbed	■	■	■															
Research approvals (IRB, IACUC, Radiation H&S) achieved	■	■	■															
Biomarker discovery research (high-dose)		■	■	■	■	■	■				■	■	■	■				
Biomarker detection in-house					■	■	■	■	■	■	■	■	■	■	■	■	■	■
Site Visits			■					■								■		
PI Meetings												■						■
Test and Evaluation Round 1 (Samples from T&E to performer)									■	■								
T&E evaluation of performer samples and protocols (Performer to T&E samples)														■				
Test and Evaluation Round 2 (Samples from T&E to performer)																■	■	
Final Report																		■

Phase 2 (12 Months)	M19	M20	M21	M22	M23	M24	M25	M26	M27	M28	M29	M30
Phase Kickoff	■	■										
Update to Irradiation Testbed	■	■										
Renewal and updates to approvals	■	■										
Biomarker discovery research (high-dose)		■	■	■	■	■	■	■				
Biomarker detection in-house			■	■	■	■	■	■	■			
Site Visits				■					■			
PI Meeting											■	
T&E evaluation of performer samples and protocols (Performer to T&E samples)								■				
Test and Evaluation Round 3										■	■	
Final Report												■

Phase 3 (12 Months)	M31	M32	M33	M34	M35	M36	M37	M38	M39	M40	M41	M42
Phase Kickoff	■											
Update to Irradiation Testbed	■											
Renewal and updates to approvals	■											
Test and Evaluation Rounds 4, 5, & 6	■	■	■		■	■	■		■	■	■	
Performer Protocol updates				■				■				
Site Visit						■						
PI Meeting											■	
Final Report												■

Figure 3: Significant Program Events by Phase.

13 Meetings and Travel Requirements

Performers are expected to assume responsibility for administration of their project and to comply with contractual and Program requirements for reporting, including attendance at Program workshops and availability for site visits.

Program Meetings

All Performer teams are expected to attend workshops, to include key personnel from prime and subcontractor organizations. The TEI-REX program intends to hold a program Kick-off Meeting workshop in the first month of the program and Phase kick off meetings in the first month of each subsequent program phase. In addition, the program will hold a PI Review Meeting starting in Month 12 of Phase 1 and then similar workshops annually thereafter. Kick-off Meetings and PI Review Meetings may be combined for logistical convenience. The dates and locations of these meetings are to be specified at a later date by the Government, but for planning purposes, offerors should use the approximate times and locations listed in Figure 3. Both types of meetings will likely be held in the Washington, D.C. metropolitan area, but IARPA may opt to co-locate the

meeting with a relevant external conference or workshop to increase synergy with stakeholders. IARPA reserves the right to hold the meeting virtually for logistical or health and safety reasons.

Kick-off Meetings will typically be one day in duration and will focus on plans for the coming Phase, Performer planned research, and internal program discussions. PI Review Meetings will typically be two days in duration and will have a greater focus on communicating program progress and plans to USG stakeholders. These meetings will include additional time allocated to presentation and discussion of research accomplishments. In both cases, the workshops will focus on technical aspects of the program and on facilitating open technical exchanges, interaction, and sharing among the various program participants. Program participants will be expected to present the technical status and progress of their projects to other participants and invited guests. Individual sessions for each Performer team with the TEI-REX PM and T&E Team may be scheduled to coincide with these workshops. All research and data presented at these meetings should be considered non-proprietary information as these will be open meetings with other performers and partners.

Site visits by the Government Team will generally take place during the life of the program as outlined in Figure 3. These visits will occur at the Performer's facility. Reports on technical progress, details of successes and issues, contributions to the program goals, and technology demonstrations will be expected at such site visits. IARPA reserves the right to conduct additional site visits on an as-needed basis or reduce number of site visits for logistical or health and safety reasons.

Remote monthly meetings will be established at the TEI-REX kickoff wherein performers will present the previous month's research activities, review open action items, discuss upcoming research, and identify any concerns or issues which could impact the program. IARPA may establish remote meetings every two (2) weeks if, during contract negotiation or at program kickoff, it is determined by IARPA or, at the request of a performer, that bi-weekly meetings would be beneficial at any time during the program.

Research Conferences and Publications

Performers may plan to publish their research to academic journals or present their research at appropriate research conferences and may include in their proposal an expectation to participate in these events. During the program, a request to travel must be submitted to the contracting officer (CO), contracting officer's technical representative (COTR), and IARPA technical team. IARPA will expect a courtesy copy of publications, posters or presentations associated with TEI-REX research at least ten (10) days in advance of the submission deadline. All published material shall include the proper acknowledgement to IARPA and ARO, including contract information. IARPA and/or the Contracting Agent will provide appropriate language to use for acknowledgement of papers, presentations, and/or posters.