MODULE ANNOUNCEMENT

FOR

ADVANCED RESEARCH PROJECTS AGENCY FOR HEALTH ADVANCED ANALYSIS FOR PRECISION CANCER THERAPY (ADAPT)

ARPA-H-MAI-24-01-03

03/07/2024

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1. MODULE ANNOUNCEMENT OVERVIEW INFORMATION

FEDERAL AGENCY NAME: Advanced Research Projects Agency for Health (ARPA-H)

OPPORTUNITY TITLE: ADvanced Analysis for Precision cancer Therapy (ADAPT)

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- ***Module Announcement release date***: 03/07/2024
- ***Virtual Proposers' Day:*** 03/15/2024
- ***Questions & Answers (Q&A) due date***: 03/22/2024
- ***Questions & Answers (Q&A) release date:*** 04/01/2024
- ***Proposal due date***: 05/06/2024

2. OPPORTUNITY DESCRIPTION

The mission of the Advanced Research Projects Agency for-Health (ARPA-H) is to accelerate better health outcomes for everyone by advancing innovative research that addresses society's most challenging health problems. Awardees will develop groundbreaking new ways to tackle health-related challenges through high potential, high-impact biomedical and health research. ARPA-H seeks proposals to revolutionize new adaptive strategies for treating the evolution of cancer. The ADvanced Analysis for Precision cancer Therapy (ADAPT) Program will develop an adaptive cancer treatment platform that detects when tumors change, recommends updates to the treatment plan, and evaluates revised plans through a novel clinical trial design. The ADAPT program will examine a tumor's behavior as it changes and will then match each patient's evolving cancer with the best available therapy. ADAPT will revolutionize cancer care by bringing new science and medicine together to map and target tumor changes that improve survival for patients with metastatic cancer. This continuous and interconnected learning process fosters rapid innovation whereby tumor biology research provides evidence that rapidly informs and shapes clinical practice.

A. PROGRAM INTRODUCTION

Each year, 600,000 Americans die due to metastatic cancer, representing approximately 17% of all deaths.[1] Reducing this number requires appropriately matching treatments (e.g., chemotherapy, immunotherapy, targeted therapy, etc.) with a patient's particular tumor biology at multiple points in time as cancer progresses. Biomarkers measure indicators (e.g., genes, transcripts, proteins, etc.) of a tumor's biology, and can help clinicians assess the likelihood that a particular therapy will be effective for a given patient. Few new biomarkers have recently been discovered because cancer research has been constrained by using single data types (DNA, protein, imaging) rather than combining a broad range of tumor biology measurements and clinical data. Additionally, most biomarkers are based on single gene measurements, which limits predictive accuracy. Lastly, both the research and clinical domains have remained siloed, preventing sufficient patient data from enabling the discovery and validation of new predictive biomarkers. This chasm is particularly problematic when it comes to metastatic cancer, which requires that clinical decisions keep pace with rapidly evolving tumors. ADAPT utilizes advances in tumor biology measurement data, new data analysis methods and algorithms, and an innovative evolutionary clinical trial design to treat the right patient with the right drug at the right time.

Tumors are not static; instead, they mutate and change to keep growing, developing resistance to treatments that were initially effective. Today's static treatment regimens lead to deaths that could be avoided with a more dynamic treatment approach. To successfully combat cancer, treatment strategies need to adapt as tumors evolve. Advances in tumor measurement and analysis technologies make it possible to detect changes in tumor traits during growth with ever-increasing fidelity, scaling from single to multiple data

types. Novel measurements of tumor biology could be used to detect when cancer cells begin to resist treatment so that treatment plans can be adjusted. Armed with this information, doctors would then select more effective treatments that specifically target these new resistant traits. Selecting treatments with increased effectiveness would improve survival time for cancer patients so that they can live with metastatic disease instead of dying from it. Creating a standardized mechanism for selecting treatments that respond to changes in tumor biology is essential for prolonging the life of patients with metastatic cancers.

At its core, ADAPT will revolutionize predictive biomarkers for cancer and create the next generation of predictive biomarkers that capture changes in tumor biology over time, respond to resistant traits with better treatments, and extract insights from a diversity of tumor and patient data. Biomarkers will sequentially be discovered, tested, and implemented in the new evolutionary clinical trial to guide therapy selection as the tumor evolves pre- and post-treatments. The ADAPT program will examine a tumor's behavior as it changes and will then match each patient's evolving cancer with the best available therapy, with the goal of improving progression free survival (PFS) by 50% in at least one patient subgroup. Each patient's history of tumor adaptations to treatment will contribute to a collective knowledge base from hundreds of other patients with similar tumor types and treatment results. This collective evolutionary history and individual patient data will inform treatment through a new sequential evolutionary clinical trial approach that will enrich the precision and efficacy of patient care. ADAPT will revolutionize cancer care by bringing new science and medicine together to map and target tumor changes to improve survival for patients with metastatic cancer.

NATIONAL HEALTH IMPACT

Two million Americans receive a new cancer diagnosis annually with over 600,000 individuals currently living with metastatic cancer[2]. More than 90% of metastatic cancer patients develop resistance to therapy[3]. Advanced cancer is responsible for one in six deaths in the U.S., and one in three individuals is expected to encounter cancer in their lifetime[1]. The ADAPT program will apply these novel approaches to three leading causes of cancer related death in the United States: breast, lung, and colon cancers. Lung cancer is the third most common cancer, yet it is the leading cause of cancer related deaths in Americans[2]. Metastatic non-small cell lung cancer represents a significant area for treatment improvement, as response rates to therapy are less than 50% and survival time is less than one year from diagnosis of metastasis[4,5]. Colon cancer is the second leading cause of cancer related deaths in Americans, and response to second line therapy is less than 25% with a progression free survival (PFS) time of less than 6 months[6-7]. Breast cancer is the most diagnosed cancer, and the second leading cause of cancer related death in American women[1]. Among patients with metastatic estrogen receptor positive breast cancer, response rates to second line therapies are <25% with a PFS of less than one year[8-10].

The number of patients with metastatic and terminal cancer is on the rise; and the economic burden of metastatic cancer treatment is substantial, exceeding $200 billion in medical care costs in 2020 across all cancer types[11]. For example, metastatic breast cancer alone incurred over $35 billion in 2020, which is projected to surpass $86 billion annually by 2030[12]. Similarly, the combined costs for advanced and metastatic lung and colon cancers in 2020 was over 48 billion[11]. Alongside rising medical costs, significant productivity and other societal costs are also associated with cancer[13]. Importantly, based on an economic analysis of current precision oncology, using tumor biology data in treatment decisions significantly lowered average per week healthcare costs including inpatient and outpatient expenses, resource utilization, and end-of-life costs[14]. Based on the assessments of cost savings from precision care in this study, a conservative estimate of savings from the ADAPT program for breast, lung, and colon cancer is 6.8 billion dollars per year.

Substantial costs are also associated with drug development and approval. The cost of developing a new prescription drug that gains market approval is expected to exceed $2.6 billion[15]. Furthermore, the estimated

median cost of clinical trials supporting approval of oncology drugs was $45 million each based on oncology trials conducted in 2015-2017[16]. By advancing precision care through new technologies, expenses for drug development can be reduced while ensuring patients receive the most suitable therapy.

B. TECHNICAL AREAS (TA)

Due to significant advancements in tumor measurement and analysis techniques, tremendous opportunities exist to develop biomarkers that improve drug selection for patients. These innovations will enable the identification of optimal drug targets and treatment strategies for individual patients.

The ADAPT Program is comprised of three interconnected technology areas (TAs), outlined below and in Figure 1:

- TA1 – *Therapy Recommendation Techniques:* Develop data-driven methods that determine resistant cancer traits, discover new predictive biomarkers of drug response, and guide optimized treatments based on a tumor's genetic and phenotypic traits. TA1 comprises three sub-TAs including:
    - TA1.1: *Multi-Modal Data Fusion:* Combine information from multi-modal data types to create a unified representation of tumor data that offers a more comprehensive and accurate understanding than any single data source alone.
    - TA1.2: *Resistant Trait Modeling*: Develop tumor evolution models that increase number and precision at which resistant traits are discovered and that enable identification of new treatment strategies of targeting resistance traits.
    - TA1.3: *Biomarkers that Predict Drug Response*: Develop and test multi-modal biomarkers that will be implemented within an evolutionary clinical trial (TA2).
- TA2 – *Evolutionary Clinical Trial:* Design a trial that adjusts drug treatments based on how the tumor evolves during multiple sequences of therapy. TA2 comprises three sub-TAs including:
    - TA2.1: *New Tumor Measurement Technologies*: Collect a broad diversity of temporal tumor measurements from the evolutionary clinical trial (TA2.2) for resistance trait identification and predictive biomarker development in TA1.
    - TA2.2: *Evolutionary Trial Protocol:* Develop a centralized, modular, open-source protocol design capable of responding to tumor changes in near-real-time.
    - TA2.3: *Evaluation of TA1 Biomarkers:* Test and integrate predictive biomarkers and adaptation of subsequent lines of therapy into the evolutionary trial based on data collected from prior treatments.
- TA3 – *Treatment & Analysis Platform:* Create open-source collaboration space for developing, analyzing, and sharing data, models, and trial protocols between researchers and clinicians.

Performers may submit a single proposal addressing any one TA (TA1, TA2 or TA3) or sub-TA of TA1 (TA1, TA1.1, TA1.2, TA1.3) or performers may submit a single proposal addressing a combination of multiple TAs; (see Section 2C). All performers are expected to collaborate with each other; therefore, performers will have Associate Contractor Agreement (ACA) language included in their respective award; see Section G.

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B.1. TECHNICAL AREAS (TAS)

TA1 – THERAPY RECOMMENDATION TECHNIQUES

Tumors change their DNA, RNA, and proteins to keep growing, even during therapy. These changes can lead to drug resistance making it harder to treat cancer effectively. Data analysis methods have the capability to detect these changes and identify tumor resistance traits as well as develop biomarkers that

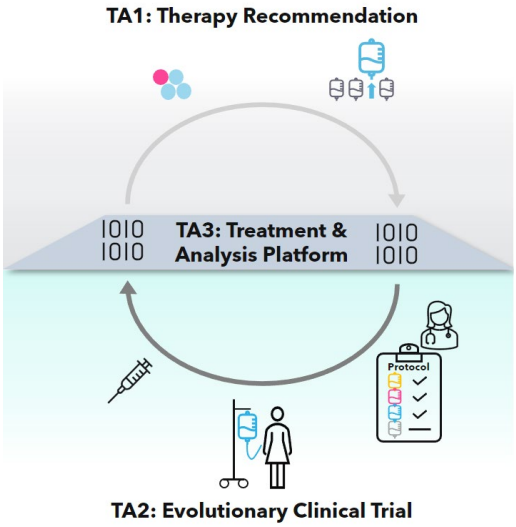

Figure 1. The ADAPT Program's TA1, TA2, and TA3 will jointly develop, test, share, and iteratively refine predictive biomarkers and new treatment regimens. TA1 will analyze tumor traits and build predictive biomarkers from multi-modal data derived from tumor measurements and clinical data collected by TA2. TA2 will develop a new type of clinical trial called an evolutionary clinical trial that will enable clinicians to dynamically adjust therapy and optimize drug selection based on near-real-time changes in tumor biology, allowing them to overcome tumor resistance and improve patient survival times. TA2 will take longitudinal tumor measurements to aid subsequent biomarker development, testing and implementation. Data and analysis algorithms will be shared in the treatment and analysis platform (TA3) to connect researchers and clinician teams as they develop new biomarker-driven drug strategies. This cycle, from tumor measurement and analysis to biomarker development, testing, and implementation within the evolutionary trial, enables a new approach in the treatment of cancer patients where data rapidly, consistently, and accurately informs patient care.

predict the most effective drug treatments. TA1 will include three parallel and interconnected subsections (sub-TAs): 1) multi-modal data fusion; 2) resistance trait modeling during tumor evolution; and 3) biomarkers that predict drug response. Performers will include systems biologists, biomedical data scientists, bioinformaticians, statisticians, and mathematicians working collaboratively to leverage assessments of tumor biology, including genetic and protein-level data (DNA- and RNA-sequencing, proteomics, and circulating tumor DNA/RNA/methylome data) along with clinical data (e.g., electronic health records (EHR), imaging, pathology, and blood-based tests). Collectively, these comprehensive tumor biology measurements will be termed multi-modal data.

- TA1.1 – *Multi-Modal Data Fusion:* Combine information from multi-modal data types to create a unified representation of tumor data that offers a more comprehensive and accurate understanding than any single data source alone.
- TA1.2 – *Resistant Trait Modeling*: Develop tumor evolution models that increase number and precision at which resistant traits are discovered and that enable identification of new treatment strategies of targeting resistance traits.
- TA1.3 – *Biomarkers that Predict Drug Response*: Develop and test multi-modal biomarkers that will be implemented within an evolutionary clinical trial (TA2).

As explained in Section B, proposers may submit a single proposal to one sub-TA or a single proposal for multiple sub-TAs for TA1. All TA1 proposals should describe how they plan to meet the metrics outlined in Table 1.

TA1.1 - MULTI-MODAL DATA FUSION

Multi-modal measurements enable the study of a tumor from different angles using high-dimensional data. However, the large amount of information derived across technology platforms poses multiple challenges

for data processing. Patient data can span different tumor measurements (e.g., DNA, RNA, single cell sequencing, proteomics) and clinical data (e.g., EHR and imaging data); however, biomarkers are historically established using a singular data modality. Further, obstacles such as a lack of usable data, sparsity of diverse data, and limited multi-modal interpretability and standardization hinder the discovery and analysis of new biomarkers. TA1.1 will devise data fusion methodologies that integrate multi-modal data types thereby enhancing the predictive efficacy of biomarkers developed by TA1.3.

Strong TA1.1 proposals should describe novel data fusion approaches that go beyond the state of the art. Proposers should describe how their fusion approach will integrate genomic, proteomic, and protein features from tumors and/or clinical data such as EHR, imaging, and pathological data. In addition, proposers should describe feature selection strategies that reduce the dimensionality of EHR, imaging, and multi-omic datasets from millions of dimensions down to the tens or hundreds that are most relevant to therapy recommendation.

To this end, TA1.1 proposals must describe the design, development, and evaluation of fusion techniques capable of generating a body of high quality, complex, and integrated features from multi-modal data that will enhance the quality of downstream biomarker development and resistant trait analysis. Strong proposals will describe data integration methodologies for both structured and unstructured data. TA1.1 performers will also standardize multi-modal data for mathematical and machine learning (ML) algorithms by rectifying distribution, variance, and structure differences across data sets. TA1.1 proposals must describe normalization and integration approaches, which may include but are not limited to early/middle/late fusion strategies, multimodal ML, transformer neural networks, perceiver architecture, and transfer learning methods. Fused data will be provided to TA1.2 and TA1.3 performers for resistant trait modeling and use in the development of predictive biomarkers.

The following multi-modal data fusion characteristics are required:

1. Approaches must address either early-data fusion, late-data fusion, or both including fusion of research-omic data and clinical data from TA2 performers as well as integration of biomarkers from individual data modalities into composite biomarkers.
2. Approaches that include multiple data types for fusion.
3. Methods must be reproducible and transparent.

The following multi-modal data fusion characteristics are out of scope:

1. Approaches that do not address early-fusion or late-fusion of research and clinical data.
2. Approaches that do not include multiple data types for fusion.
3. Methods that are not reproducible or transparent.

TA1.2 - RESISTANT TRAIT MODELING

To date, researchers have developed low-fidelity models of tumor progression; however, such efforts have been limited by the number of time samples collected, and work has predominantly focused on one or two data types at a time. TA1.2 performers will increase the fidelity of tumor models by expanding the breadth of data types captured in mechanistic models, improving the temporal resolution of models, and increasing the number of resistant traits identified. Such advances will convert discrete time series measurements into a continuous representation of tumor size and progression, enabling near-real-time treatment recommendations to optimize clinical decision making. TA1.2 proposals must describe different mathematical approaches to model tumor evolution and acquisition of drug resistant traits. These methods may include but are not limited to probabilistic generative long short-term memory, feed forward neural networks, causal artificial intelligence (AI), hierarchical generalized additive models, matrix analysis, Gaussian processes, clustering methods (point-wise distance-based, feature-based, model-base), ARIMA (autoregressive integrated moving average) and Hold-Winters (Triple Exponential Smoothing).

The following resistant trait modeling characteristics are required:

1. Approaches must analyze multi-modal data, including research and clinical data from TA2 performers, across multiple time points.
2. Approaches must identify pathway and gene/protein-level traits and drug targets that emerge during treatment.
3. Approaches must include dynamical/temporal modeling, tracking tumor evolution.
4. Methods must be reproducible and transparent.

The following resistant trait modeling characteristics are preferred:

1. Include both modeling (dry lab) components to identify resistant traits using multi-modal data from cancer patients as well as a pharmacology (wet lab) component to validate drug resistance mechanisms and drug efficacy.

The following resistant trait modeling characteristics are out of scope:

1. Approaches that only apply to a single data type.
2. Approaches that do not discover new drug resistant tumor traits.
3. Approaches that do not model tumor measurements over time.
4. Methods that are not reproducible and transparent.

Performers should not include data storage and analysis costs, as these will be covered by the ADAPT program and provided as a Government Furnished Resource.

TA1.3 - BIOMARKERS THAT PREDICT DRUG RESPONSE

TA1.3 seeks to build first-in-class biomarkers for standard therapies across at least three cancer types while increasing the accuracy of biomarkers to predict the right therapy for each patient using new advanced tumor characterization methods. Selecting an effective treatment plan hinges on accurately determining the current state of a tumor and predicting the best therapy; yet current clinical trials do not use biomarkers to adjust treatment regimens. To integrate biomarker discovery and evaluation with clinical trial design, TA1.3 performers will develop predictive biomarkers by analyzing comprehensive patient data such as genetic profiles, circulating tumor DNA in blood samples, medical imaging, and electronic health records from TA2 performers using advanced tumor characterization methods, which will then be tested and/or implemented in the TA2 clinical trial. TA1.3 proposals must provide detailed explanations of mathematical, statistical, and computational methods for evolutionary cancer analysis and biomarker development, which may include but are not limited to ML approaches (e.g., support vector machine (SVM), random forest, gradient and boosting, LASSO, ridge, elastic nets, deep neural networks), regression analyses (e.g., binary regression, mixed effect models, logistic regression), and mechanistic models (e.g., ordinary differential equations (ODEs), partial differential equations (PDEs), Lotka-Volterra equations, Ricker models, adaptive dynamic models, and reaction-diffusion equations). TA1.3 biomarkers will be evaluated based on the ability to accurately predict drug response in a clinical setting. Performers are welcome to propose approaches that leverage any of the aforementioned algorithms or others not on the list, so long as there is a sound plan to generate effective predictive biomarkers in clinically relevant timeframes.

The following biomarker characteristics are required:

1. Biomarkers must be developed using advanced mathematical and/or computational approaches (e.g., AI, ML, mechanistic models, etc.) for prediction of drug response. Algorithms for biomarker development should aim to be applicable in a diversity of cancer settings, facilitating generalizability of methods across cancer types and settings.
2. Approaches must use multi-modal data to test drug prediction capabilities through TA2's evolutionary clinical trial.

3. The method used to develop biomarkers must generalize to different cancer types.
4. Approaches must dynamically adapt to tumor response during treatment.
5. Biomarkers must predict drug response to a currently used therapy or drug class in metastatic cancer treatment.
6. Biomarkers must use a complexity of data for predictions with a minimum of >5 mutations, transcripts, or proteins.
7. All biomarkers used in ADAPT, whether pre-existing or novel, will be subject to rigorous independent validation to ensure efficacy and patient safety.
8. Approaches must be integrated into the TA3 platform and be testable by external reviewers.
9. TA1 performers must agree to collaborate to develop common Application Programming Interfaces (APIs) and data models to transfer algorithmic outputs and supporting data to TA2 and TA3, when applicable. By the end of the program, these open APIs and data models should form a foundation for future open standards. They should relevant open standards and data models, including Health Level 7 Fast Healthcare Interoperability Resources (HL7 FHIR) and United States Core Data for Interoperability Plus (USCDI+) whenever possible.

The following biomarker characteristics are preferred:

1. Existing biomarkers previously applied to patient data and have demonstrated significant predictive capability are welcomed. A general pipeline should be proposed for biomarker development; those already tested in patient data for at least one drug are preferred but not necessary.
2. Models that are informed by tumor biology/signaling.
3. Proposers must show evidence that they have developed at least one biomarker that has been independently validated in multiple patient cohorts as evidence of past performance.
4. Biomarkers developed during the ADAPT program should be interpretable, and they should reflect a tumor phenotype and biological cancer characteristics rather than empiric characteristics.

The following biomarker characteristics are out of scope:

1. Biomarkers that are not derived using state-of-the-art computational techniques including AI, ML, mechanistic models, and other advanced mathematical approaches.
2. Biomarkers that only include a limited number (<5) gene/mutations, transcripts, or proteins.
3. Biomarker development approaches that cannot be generalized to multiple therapies and/or tumor types.
4. Biomarkers that are not relevant for metastatic cancer.
5. "Black box" biomarkers that cannot be validated. All biomarker algorithms must be open for review.

Performers should not include data storage and analysis costs, as these will be covered by the ADAPT program and provided as a Government Furnished Resource.

TA2 – EVOLUTIONARY CLINICAL TRIAL:

Historically, cancer clinical trials have followed a uniform approach in which efficacy of a single treatment regimen is tested in patients by collecting sparse data, giving an incomplete picture of tumor biology and response. This design precludes adaptation of treatments to effectively address drug-resistant tumors. TA2 will improve cancer treatment by tightly integrating advanced tumor analysis methods from TA1.2 to identify resistant traits as they emerge so clinicians can adapt treatments to target these traits. This adaptive approach integrates the predictive biomarkers developed in TA1.3 for initial selection of optimal standard of care therapy, and subsequent identification of new treatments to overcome resistance. A single, institutional review board (IRB)-approved evolutionary clinical trial protocol will be used to test biomarkers

and drug treatments in sequence, thus promoting adaptation of this model.

TA2 is comprised of three subsections (sub-TAs):

- TA2.1 – *New Tumor Measurement Technologies*: Collect a broad diversity of temporal tumor measurements from the evolutionary clinical trial (TA2.2) for resistance trait identification and predictive biomarker development in TA1.
- TA2.2 – *Evolutionary Trial Protocol:* Develop a centralized, modular, open-source protocol design capable of responding to tumor changes in near-real-time.
- TA2.3 – *Evaluation of TA1 Biomarkers:* Test and integrate predictive biomarkers and adaptation of subsequent lines of therapy into the evolutionary trial based on data collected from prior treatments.

TA2.1 - New Tumor Measurement Technologies

Serial tumor measurements are required for understanding how a patient's unique cancer changes in response to treatment. Historically, data from tumor biology studies have been limited in precision, breadth, and duration, restricting the potential of personalized cancer treatments. Recent advancements in single cell analysis methods have enabled the holistic measurement of tens of thousands of individual cells within a tumor, while other biotechnological breakthroughs have enabled serial tumor measurements from blood collection. However, interpretation of these measurements requires computational resources and analysis expertise beyond the scope of randomized controlled clinical trials. TA2.1 performers will provide multiple tumor measurement data types for incorporation into predictive biomarkers, which will in turn be used to inform patient therapy selection.

TA2.1 performers will collect a broad diversity of temporal tumor measurements from the evolutionary clinical trial (TA2.2) for resistance trait identification and predictive biomarker development in TA1. TA2 proposals must describe multi-modal data collection approaches and tissue biopsy analysis methods that enable dynamical modeling and precise characterization of a tumor's biology. These approaches should be combined and may include but are not limited to bulk and single cell DNA- and RNA-sequencing, blood-based assays such as circulating tumor DNA/RNA/methylome sequencing, and spatial single cell assays (e.g., transcriptomics, proteomics, and mutation analysis). Proposals may also consider how the tumor environment contributes to drug response, as well as how the cancer and non-cancer cells interact to promote an environment that facilitates tumor growth. Proposals that leverage continuous patient health monitoring technologies will be considered relevant to the program. A list of required tumor measurement features is provided at the end of TA2.

TA2.2 - Evolutionary Trial Protocol

The TA2.2 clinical trial framework will ideally combine elements of several types of trials to treat patients sequentially during multiple lines of therapy while collecting tumor measurement and clinical data for biomarker development and implementation for drug response predictions. These elements could include randomized trials (a test of response between two different treatment regimens), classical adaptive trials (which allow for modifications to the trial protocols based on interim results), n-of-1 trials (where each individual patient is given a control and experimental treatment) and umbrella trials (where a variety of treatments are tested simultaneously on patients). In the ADAPT evolutionary trial, patients remain within a single clinical trial protocol transitioning between treatments based on their tumor's unique characteristics identified from serial samples taken throughout the trial. Performers should propose a cancer setting where biomarkers are needed to optimize patient response to sequential therapies, where new resistance mechanisms need to be discovered, and where patients have a short average progression free survival on current therapies. Examples are provided in Appendix A.

ADAPT will also allow modular clinical trial approaches that can be broadly enacted at diverse sites both

within the ADAPT program, but also can be repurposed and used independently by other clinical teams using the TA3 platform infrastructure. A list of required evolutionary clinical trial features for TA2 proposals is provided at the end of TA2. Performers will develop an evolutionary protocol for either metastatic breast, lung or colon cancer that follows patient treatments and response while collecting data to address critical needs for individualized and improved therapy decision capabilities. TA2 performers will work closely with TA1 performers to develop and test biomarkers. TA2 performers will select multiple sites for the clinical trial to enable diverse and rapid patient enrollment.

The ADAPT Program Manager team will select a Contract Research Organization (CRO) that is well suited to manage the regulatory affairs, data management, auditing, clinical trial planning, protocol management, site initiation, recruitment support, clinical monitoring, biomarker testing/integration, sample collection and distribution, among other centralized clinical trial components. TA2 proposals should not include CRO costs in their budgets, nor should they include data storage and analysis costs, as these will be covered by the ADAPT program.

TA2.3 - EVALUATION OF TA1 BIOMARKERS

The predictive accuracy of biomarkers developed by TA1.3 performers will be tested by TA2 performers, informing the iterative course of therapeutic regimens. This built-in process of biomarker identification and validation will be deployed across multiple lines of treatment and cancer types. Incorporating biomarker discovery and validation directly into the clinical trial process will improve their translational effectiveness.

Biomarkers will enter ADAPT at different levels of development and testing. The evolutionary trial will enroll patients in therapies that would benefit from biomarkers for drug selection and collect multi-modal data for biomarker development (TA1.3). Prior to biomarker testing in an evolutionary clinical trial arm, statisticians will pre-define the predictive accuracy needed for statistical significance. Once biomarkers are developed, they can be evaluated on patients independent from the biomarker development cohort within the same evolutionary trial protocol.

Proposers must provide the following information in TA2 proposals:

<u>TA2 proposal requirements</u>
(i) Tumor measurement characteristics:

1. Tissue or blood samples must be of sufficient mass and quality to support research data extraction (e.g., sequencing).
2. Planned tumor biology measurements should include a diversity of data types: bulk and single cell DNA- and RNA-sequencing, blood-based assays such as circulating tumor DNA/RNA/methylome sequencing, and spatial single cell assays (e.g., transcriptomics, proteomics, and mutation analysis). Measurements may be added to the clinical trial, if feasible, based on other performer capabilities.
3. Raw and summarized data from measurements will be made available to and used by performers and researchers.
4. Analysis of measurements must be feasible within one month from collection and processing.

(ii) Clinical trial characteristics:

1. Clinical trial for metastatic cancer patients.
2. Clinical trial that includes multiple lines of therapy under a single protocol.
3. Flexible clinical trial protocol that enables changes in design (e.g., randomized, adaptive, etc.).
4. Strong capability to collect tumor and blood-based measurements.

5. Possess a treatment line with a Progression Free Survival (PFS) rate of <9 months average.
6. The protocol must include mechanisms for biomarker evaluation.
7. Modular clinical trial design enabling rapid dissemination and protocol uptake by different sites.

(iii) General characteristics:

1. Details about key clinical needs being addressed (e.g., targeting chemotherapy resistance or endocrine therapy resistance).
2. Evolutionary clinical trial design examples (see Appendix A) and plans for rapid patient enrollment (see Metrics table 2).
3. Lines of treatments to be included in the clinical trial.
4. Plans for biomarker testing and integration into the clinical trial.
5. Historical clinical trial enrollment for 2020-2023 in the specific cancer type including patient demographic and diversity metrics. Proposers should detail a plan to initiate clinical trials and start enrolling patients within 6 months of funding.
6. Information about the ability to collect high quality patient samples, specifically tumor biopsies, blood, etc. Past successes should be detailed for large scale translational research that includes a diversity of patient samples and multi-modal data types.
7. Information about the ability to collect and use clinical data such as electronic health records (EHR), imaging data, pathology reports, genomics, clinical tests, etc. Note any restrictions on data use and/or sharing.
8. Whenever possible all relevant data should be structured and transferred in accordance with the HL7 FHIR standard.

Out of Scope for TA2 proposals
(i) Tumor measurement characteristics:

1. Research data that does not measure tumor biology.
2. Research data that cannot be made available to all performers and researchers.
3. Measurements that take >1 month to process for analysis by performers.
4. Patient data that does not directly contribute towards the research on or clinical application of cancer therapies.

(ii) Clinical Trial characteristics:

1. Clinical trials that do not include metastatic cancer patients.
2. Clinical trials that do not use a single protocol with multiple lines of therapy.
3. Clinical trials that do not allow for changes in therapies.
4. Clinical trials that do not collect serial samples.
5. Clinical trials that do not allow for integration of predictive biomarkers.
6. Protocols that do not include mechanisms for biomarker evaluation.

For additional information on the design and execution of evolutionary clinical trials, see Appendix A.

TA3 – TREATMENT AND ANALYSIS PLATFORM:
Currently many clinicians face a steep learning curve to find, access, explore, and analyze biomedical research data, especially multi-modal datasets, as the data are stored in siloed data repositories, and existing tools are designed for those with informatics skillsets. TA3 will fill this void by creating a collaborative, user-friendly platform, and testing ground that bridges the research and clinical domains to improve access

to data and toolsets that facilitate adaptive therapy recommendation techniques for cancer. The platform's data, algorithms, and clinical trial protocols will be made publicly available through the ADAPT portal thus creating a new standard for the field and alleviating roadblocks that have limited the impact of big data in basic and translational cancer research. To achieve this goal, TA3 performers will focus on five critical areas:

1. *Building a collaboration ecosystem:* TA3 performers will create a treatment and analysis platform that will bring together clinicians and multidisciplinary scientists and enable near-real-time availability of harmonized multi-modal and patient data, protocol distribution, and analysis of therapy regimens.

2. *Creating a comprehensive data lake:* performers will maintain a centralized repository (data lake) that encompasses various data types, enhancing data accessibility and management. The data lake will provide a scalable data management solution that stores the raw and processed data and will handle a wide array of data types and sources, utilizing cloud-based technologies for flexibility in storage and computing. The data lake will support various tools for data analysis, while also providing data governance and security to maintain data quality and compliance.

3. *Facilitate data processing:* TA3 performers will develop pipelines to rapidly process tumor biology measurement data, such as sequencing data, for use among TA1 performers. Processing of data will include quality control assessments (such as read counts, base quality scores, etc.), detection and mitigation of sampling biases across multi-source data, data curation, read alignment and mapping, variant calling and annotation, data summarization into user-friendly and standardized data formats, data de-identification (e.g., removal of personally identifiable information (PII) in text and images).

4. *Promote data standardization and linkage:* TA3 performers will implement data standardization and linkage processes to ensure compatibility and consistency across different tumor biology data types as well as link disparate data types across common sources using privacy-respecting common identifiers. TA3 proposals must describe prototype workflows for processing raw, multi-modal data to generate secondary and tertiary results that improve size, manipulability, and interpretability. Performers will standardize different data formats, units, and scales for consistency, transforming data for uniformity, and cleaning it to correct errors and inconsistencies. Performers will map and link data based on common identifiers, and ensure data conveys the same meaning across sources, and manage metadata for clarity and transparency. Regular quality assurance and control will be applied to maintain the integrity and usability of the harmonized dataset.

5. *Develop open APIs and toolsets:* TA3 performers will develop new open APIs to facilitate data access and sharing among stakeholders to promote broad use of the treatment and analysis platform. Proposals should describe the development of user-friendly interfaces that enable researchers and clinicians to access de-identified data and distribute evolutionary trial protocols to other users. The platform should enable the logical and efficient querying of biomedical data. Proposals should describe the design, development, and evaluation of these front-end and back-end platform interfaces. Similarly, proposers should explain how their approach will enable users to explore and make connections across multiple data types, including but not limited to multi-omics, imaging, longitudinal, and single cell datasets. Proposers are strongly encouraged to maximize the use of existing and emerging cloud-based technologies from the major cloud service providers. Proposers are encouraged to design, architect, develop, and implement intuitive AI-powered dashboards, user-friendly data exploration tools, and data visualization techniques. The key to data usability is understanding where and what data are available and obtaining enough context to understand how the data can be analyzed, explored, or used. To this end, TA3 performers will work with TA1 and

TA2 performers to ensure that dashboards, auto-report generation capabilities, and any other tools meet the needs of ADAPT performers and eventually the wider scientific and clinical communities. Data dashboards and other tools may provide near-real-time summaries of all data with a biomedical data ecosystem, including statistics by data type, disease type, number of patients, and other metrics.

The following treatment and analysis platform features are required:

1. A scalable data management solution that stores the raw and processed multi-modal data from cancer researchers and the evolutionary clinical trial.
2. A computational pipeline to rapidly process tumor biology measurements, perform quality control (QC) analysis, detect sampling bias, manage data curation, mapping, annotation, and linkage of disparate data types from the same patient.
3. Implementation plan for data harmonization to ensure compatibility and consistency across different data sources.
4. Development of open APIs, a data portal, and other tools for data access, sharing, analysis, querying, and visualization.
5. Whenever possible HL7 FHIR APIs and open data standards (e.g., USCDI+) should be leveraged.

The following treatment and analysis platform features are out of scope:

1. A limited data management plan that cannot store raw and processed patient data.
2. An inability to process patient data, perform QC analysis, detect sample biases, or curate, map and annotate data.
3. The lack of a data standardization and linkage plan for multi-modal data.
4. A data portal that does not enable data access, sharing, analysis, querying, and visualization with other performers as well as the public.

Performers should not include data storage and analysis costs, as these will be covered by the ADAPT program and provided as a Government Furnished Resource.

C. PROGRAM STRUCTURE AND INTEGRATION

The ARPA-H ADAPT program will develop and demonstrate an adaptive cancer treatment platform that integrates research and clinical practice to enable rapid improvements in cancer therapy. All TA1, TA2, and TA3 performers are expected to work together to achieve program goals. The ADAPT Program's TA1, TA2, and TA3 performers collaborate to create a system that enables advanced analysis methods to build biomarkers (TA1) that match the right patient to the right therapy at the right time by providing individualized cancer care in a new evolutionary trial (TA2). TA2 performers will collect a broad diversity of longitudinal tumor measurements and clinical data from the evolutionary clinical trial. TA1.1 performers will apply multi-model fusion methods to this data, which will enable resistant trait modeling by TA1.2 and resistant cancer biomarker development by TA1.3. In subsequent iterations, TA1.2 will provide resistance mechanism data and TA1.3 will provide therapy recommendations to TA2 performers based on biomarkers that predict drug response. TA2 performers will evaluate the predictive accuracy of the biomarkers throughout the course of the program. As such, TA2 will improve cancer treatment by tightly integrating advanced tumor analysis methods from TA1 to identify resistant traits as these emerge so clinicians can adapt treatments to target such traits. This adaptive approach uses the predictive biomarkers developed in TA1 for selecting the optimal standards of care therapies that best align with the biology of the patient's tumor in the initiation phases of clinical trials. Biomarkers are subsequently used for identifying new treatments to overcome emerging resistance.

In addition to data and process sharing, performers across TAs will be responsible for validation and verification efforts. TA3 performers will integrate the data and methods produced by TA1 and TA2 into the portal created in TA3 and ensure the TA1 algorithms run properly so that these algorithms can automatically process new TA2 data as it is delivered to the TA3 platform. TA3 will create a treatment and analysis platform that will enable near-real-time availability of curated and linked data, protocol distribution, and standardization of what constitutes a new biomarker. This platform and set of tools will allow clinicians and researchers to design, analyze, and share innovations from TA1 and TA2 including biomarkers, tumor genomic profiles, health records, models, treatment strategies, and trial protocols. TA3 performers will send the output from the algorithms to TA2 clinical teams so they can interpret the output and check for consistency. Performers from each TA are expected to work closely together, and proposals should address plans to incorporate data from other TAs and collaborate with those performers.

Cumulatively, the ADAPT program includes an infrastructure that enables continuous and iterative learning from patient care data collected and analyzed from the evolutionary trial. This constant and interconnected learning process between TA1-TA3 will foster rapid research innovation whereby clinical practice provides evidence for therapy recommendations and this evidence, in turn, will rapidly inform and shape clinical practice.

ARPA-H anticipates funding multiple performers for TA1-TA3. Proposers may submit a single proposal addresses any one TA (TA1, TA2 or TA3) or sub-TA of TA1 (TA1, TA1.1, TA1.2, TA1.3) or performers may submit a single proposal addressing a combination of multiple TAs. Four (4) to six (6) awards are anticipated for TA1. Four (4) performers are expected to be selected for TA2; TA2 proposals must address all TA2 sub-TAs (TA2.1, TA2.2, and TA2.3) and one of the following cancer types: breast (two performers), lung (one performer), or colon (one performer). Two (2) performers will be selected for TA3, with a planned down-selection to a single performer taking place at program month 12. Collaboration between multiple types of organizations, academic institutions and companies is highly encouraged.

D. Program Metrics

The overall program goals for ADAPT are to enroll and treat over 500 and up to 1,000 cancer patients with at least 95% compliance of multi-modal data collection during treatment, to identify a multitude of new drug resistance mechanisms, and to incorporate at least 3 new non-standard-of-care drug therapies based on predictive biomarkers that are derived from multi-modal data and computational analysis. New treatment indications should target resistant cancer traits based on tumor measurements and treat patients predicted to respond as assessed by the biomarker. The program will build, test, and implement multiple predictive biomarkers, and improve patient progression-free survival (PFS) by >50% in at least one clinical trial patient subgroup. Further, an open-source data portal will be populated with harmonized, audited and deidentified data that will be made available to the research and clinical communities. Metrics for each phase of each of the 3 TAs are outlined in the tables below.

Table 1. TA1 Metrics for Each Phase

TA	Metric	Description	Phase I, Stage I (0-6 mo)	Phase I, Stage II (7-36 mo)	Phase II (37-72 mo)
TA1.1	Data fusion pipeline	# of data types integrated from TA2	Target set by 6 months	≥ 50%	100%
TA1.2	Drug resistance models	# of resistance mechanisms discovered	Set up modeling algorithms	2-5	6-15
TA1.3	Therapy coverage	% therapies that have an associated multi-modal biomarker*	5%	≥ 30%	≥ 90%
TA1.3	Algorithm predictive accuracy	Accuracy of association between biomarker and whether patient responds to therapy*	20% - 50%	≥ 75%	≥ 90%
TA1.3	Cancer predictive biomarker development	# of novel predictive biomarkers discovered*	n/a	≥ 5	≥ 15
TA1.3	Biomarker processing speed	Time from availability of tumor measurement data to therapy recommendation	n/a	< 72 h	< 24 h

* Validated biomarkers must have a p-value of <0.05 or $R^2>0.8$

Table 2. TA2 Metrics for Each Phase

TA	Metric	Description	Phase I, Stage I (0-6 mo)	Phase I, Stage II (7-36 mo)	Phase II (37-72 mo)
TA2.1	Biological sample collection	# of sequential samples collected per patient during trial	n/a	≥ 2	≥ 3
TA2.1	'Omics data collection	% samples with 'omic data (ex. DNA-, RNA- sequencing) generated, processed, & uploaded	≥ 60%	≥ 80%	≥ 95%
TA2.1	Imaging data collection	# of images per patient	n/a	≥ 2	≥ 3
TA2.1	Collection of clinical trial data for data lake	% of clinical (ex. EHR, imaging, etc.) data made available to TA3	n/a	≥ 80%	≥ 95%
TA2.2	Clinical trial enrollment	# of patients enrolled in evolutionary trial	Approve protocol	200 - ≥500	500 - ≥1000
TA2.2	Clinical trial sites	# of new clinical trial sites	≥ 3 sites open	≥ 6 sites open	≥ 8 sites open
TA2.2	Patient diversity	% adherence to diversity rate for target population(s)	Demographic targets set by national averages for cancer type	< 10% deviation from population	< 5% deviation from population
TA2.3	Drug treatments	# of non-standard of care drug therapies used based on tumor resistance evolution	n/a	≥ 1	≥ 3
TA2.3	Clinical response	% improvement in progression free survival (PFS) rate	Measure PFS for standard of care	Measure PFS for biomarker-guided standard of care	≥ 50% for ≥ 1 patient subgroup using resistance targeting therapy

Table 3. TA3 Metrics for Each Phase

TA	Metric	Description	Phase I, Stage I (0-6 mo)	Phase I, Stage II (7-36 mo)	Phase II (37-72 mo)
TA3	Data quality assurance	% of data that has gone through ETL and quality assurance across data types	n/a	≥ 80%	≥ 98%
TA3	Ingest of clinical trial data to data lake	% of available data ingested	n/a	≥ 85%	≥ 95%
TA3	Portal engagement	# of unique visitors or users per year	n/a	≥ 100	≥ 500
TA3	User experience with platform	Likert scale assessment of usability by users	Target set by 6 months	≥ 80% approval	≥ 90% approval
TA3	Collaboration & support for TA1 & TA2	Likert scale assessment of satisfaction with support	Target set by 6 months	≥ 80% approval	≥ 90% approval

E. SCHEDULE/MILESTONES

The ARPA-H ADAPT program is a 6-year effort composed of 2 Phases. Phase I is divided into 2 Stages: an initial six-month Stage 1 to establish methods and infrastructure and a 30-month Stage 2. Phase II encompasses the remaining 36 months of the program. After program month 12, the ADAPT PM will evaluate and compare performance between the two TA3 performers using the metrics outlined above (Tables 1-3). Funding for Phase II is contingent upon approval by the ARPA-H director's office.

The ADAPT program will include annual in-person meetings, as well as monthly team meetings and separate working group meetings. ADAPT will feature the following management milestones to ensure success: (1) monthly technical and financial status reports that will be discussed with the ARPA-H Program Manager team; (2) end-of-phase final reports; (3) development of and adherence to regulatory strategy including meetings with the FDA; and (4) demonstration of a path to market for predictive biomarkers. ARPA-H may request performer data as deemed necessary throughout the program to validate technical progress. Performers that do not meet program metrics (Tables 1-3) or milestones (Figure 2) may be notified by the ARPA-H Agreement Officer that contract performance may no longer be necessary to reach the ADAPT program objectives and therefore negotiations may take place to end contract performance.

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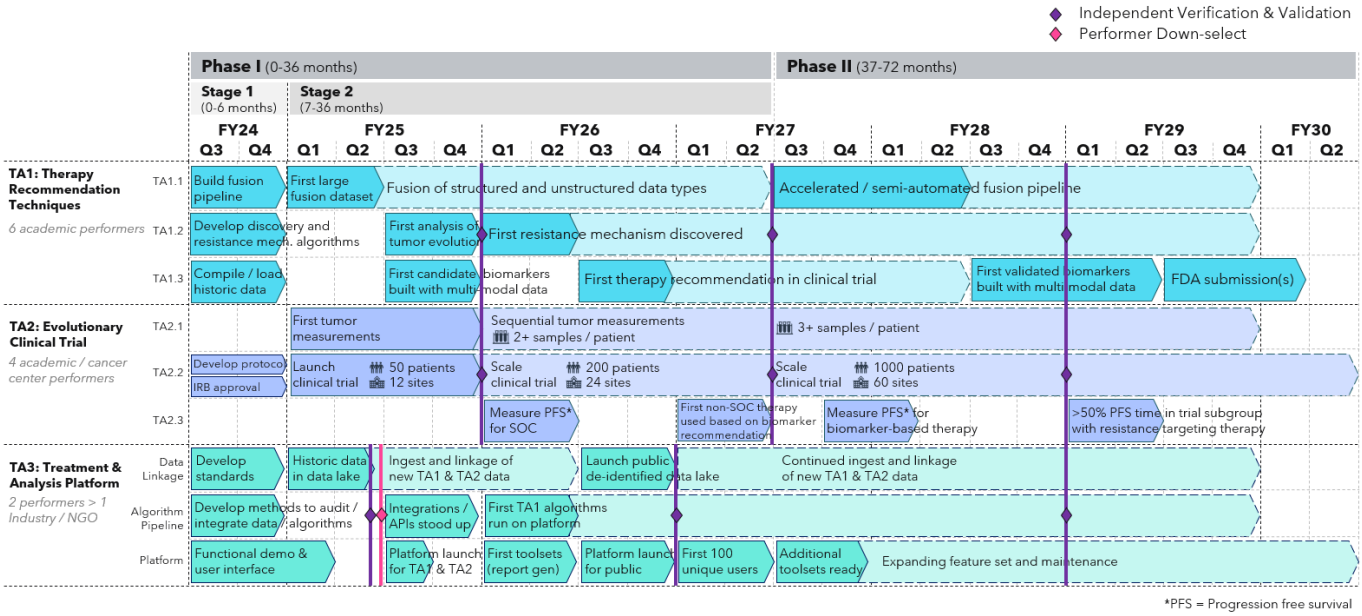

Figure 2. ADAPT milestones. Each TA has specific milestones to reach for Phase 1 and 2. Independent verification and validation will take place where purple lines are placed, and potential performer down-select will take place where the pink line is placed.

F. Policy Conformance, Software Component Standards, Open Standards, and Intellectual Property

Policy Conformance

Proposers will be expected to adhere to all relevant Government laws and policies applicable to data and information systems and technologies including but not limited to the following:

- Common IT Security Configurations
- Federal information technology directives and policies
- Section 508 of the Rehabilitation Act of 1973 (29 USC 794d) as amended by P.L. 105-220 under Title IV (Rehabilitation Act Amendments of 1998)
- HHS OCIO Policy for Information Technology (IT) Enterprise Performance Life Cycle (EPLC)

Software Component Standards

The health and healthcare data eco-system is complex and multi-dimensional with a variety of standards for data models, data transmission protocols, data routing methods etc. that are similar to and extend the International Standards Organization (ISO) Open Systems Interconnection Model (OSI)[1]. ARPA-H programs are likely to involve research that touches on multiple layers of the OSI model from low level radio frequency (RF) based protocols for transmission of data from implantable devices (potentially OSI layers 1-5), to secure and fault tolerant networking protocols for medical devices (potentially OSI layers 3-6) to the exchange of health information including Electronic Health Records, lab results and medical images related to a patient between healthcare facilities and health data brokers including but not limited to Health Information Exchanges (HIE) and Trusted Exchange Framework and Common Agreement (TEFCA) Qualified Health Information Networks using protocols such as HL7 FHIR (OSI Layer 7). This diversity requires careful consideration of the most appropriate standards to be used for the specific

[1] ISO/IEC 7498 https://www.iso.org/standard/20269.html

technologies in development and the layer at which they operate.

ARPA-H is committed to advancing interoperability in today's health ecosystem through the adoption of open, consensus driven standards and laying the foundation for emerging technologies to interoperate in the health ecosystem of the future through the evolution of these standards across all layers of the health data IT eco-system. With that in mind, we anticipate that potential performers will develop software and data communication components that fall into three categories: (1) components that can leverage today's existing standards without impeding the R&D, (2) components where extensions to existing standards will be necessary to unlock new capabilities in an interoperable way, and (3) components in areas where consensus-based standards do not yet exist or where use of standards would seriously limit the ability to efficiently conduct R&D.

Whenever such an existing standard is available that meets the scientific, technical, and research needs of the proposed effort, proposers must use the existing standard instead of creating their own. In cases where an existing standard provides only partial functionality, proposers should expand upon the existing standard, ideally in a way that does not prohibit or interfere with backward compatibility, and create sufficient documentation for Office of the National Coordinator for Health Information Technology (ONC), the U.S. Department of Health and Human Services (HHS) agencies or standards organizations, to evaluate extensions for potential inclusion in the standard (including open Application Programming Interfaces (APIs) and open data formats).

In the case of information relating health and healthcare data at higher layers of the OSI model, all health information technology (IT) components should adhere to or (as needed) expand upon applicable national standards adopted by HHS, including the ONC (e.g., Fast Healthcare Interoperability Resources (FHIR) and United States Core Data for Interoperability (USCDI)).[2]

Technical solutions that contain software elements, commercial-friendly open-source licenses (e.g., MIT, BSD, or Apache 2.0) are preferred. If an open, consensus-based standard does not yet exist, proposers should identify the aspects that lack an open standard, describe a plan to develop a general-purpose open data model and to prototype new open APIs. Strong proposals will explain how the performer will enhance data interoperability (including semantic interoperability) and expand the availability of open, consensus-based standards and data models.

Proposals must include a technical plan to align with applicable standards based on the OSI layer at which they are operating including but not limited to HHS-adopted health IT standards (45 CFR Part 170 Subpart B). For the full description of standards adopted in CFR Part 170, Subpart B, please review the complete text of the regulations when applicable, strong technical solutions will also outline integration with the Trusted Exchange Framework and Common Agreement (TEFCA). Adhering to international standard ISO/IEEE 11073 will enable broad support for current and future devices, especially those developed internationally. At other layers of the OSI model, and for software components operating outside the network stack e.g. health databases, Picture Archiving and Communication Systems (PACS) etc. other standards will be relevant and strong technical solutions will seek to utilize or expand upon appropriate open, consensus-based standards[3].

If a technical solution requires an extension of existing standards or development of technologies outside

[2] https://www.healthit.gov/sites/default/files/page/2022-07/Standards_And_Implementation_Specifications_Adopted_Under_Section_3004.pdf

[3] Examples of such open, consensus based standards include but are not limited to, the Digital Imaging and Communications in Medicine (DICOM) standard for medical image storage, the Global Alliance for Genomics and Health standards for storage of genomic data such as the Variant Call Format (VCF).

of the standards, the proposer must schedule a meeting with ARPA-H representatives to discuss the deviation to the standards prior to proposal submission.

OPEN STANDARDS

In concert with ARPA-H and partners, proposers should address innovative solutions to design, architect, develop, test, and implement, ARPA-H ADAPT tools and associated open standards as described in the TAs. It is expected that all performers will work together to converge on open standards and APIs to ensure interoperability across prototype capabilities.

All data developed, generated, and collected under the ADAPT program will be shared with ADAPT performers for research and/or clinical purposes and centralized on the ADAPT treatment and analysis platform.

INTELLECTUAL PROPERTY

The ARPA-H ADAPT program will emphasize creating and leveraging open-source technology and architecture. Intellectual Property rights asserted by proposers are strongly encouraged to be aligned with open-source regimes. A key goal of the project is to seed the establishment of a sustainable open-source ecosystem for translational oncology. Thus, it is desired that all non-commercial software (including source code), software documentation, and technical data generated by the project is provided as deliverables to the Government with open-source or unlimited rights, as lesser rights may negatively impact the potential for this biomedical data ecosystem to become self-sustaining. Open-source code is highly encouraged using permissive, business-friendly open-source licenses such as CC-BY, BSD, MIT, Apache 2.0 or similar. Approaches that inhibit this objective are not desired and would adversely affect the ADAPT program goals and objectives.

G. ELECTRONIC INVOICING AND PAYMENTS

Performers will be required to register in and to submit invoices for payment directly to Payment Management Services unless an exception applies.

H. PERFORMER COLLABORATION/ASSOCIATE CONTRACTOR AGREEMENT (ACA)

The ARPA-H ADAPT program will be developed by performers that include contractors and subcontractors, to include those with deep knowledge of key data assets as well as those selected through this announcement or through complementary funding mechanisms at partner organizations. Therefore, it is expected that performers will interact and work collaboratively with other performers.

To facilitate the open exchange of information described above, performers will have Associate Contractor Agreement (ACA) language included in their award. Each performer will work with other ADAPT performers to develop an ACA that specifies the types of information that will be freely shared across performer teams. The open exchange of scientific information will be critical in advancing the software research required to achieve the ADAPT objectives. The ACA will establish a common understanding of expectations to guide the open exchange of ideas and establish a collaborative foundation for the ADAPT project. Each performer will also work with other performers to converge on open standards and APIs to ensure interoperability across prototype capabilities.

3. AWARD INFORMATION

Multiple awards are anticipated under this announcement; however, the number of proposals selected for award will depend on the quality of the proposals received and the availability of funds. Proposals selected for award negotiations will result in an award of an Other Transaction.

See Section 1.4 of the MAI, ARPA-H-MAI-24-01 for additional information on award information.

4. ELIGIBILITY

See Section 2 of the MAI, ARPA-H-MAI-24-01 for eligibility requirements.

5. MODULE ANNOUNCEMENT RESPONSES

A. PROPOSAL CONTENT AND FORMAT

This Module Announcement is soliciting Stage 1 Volume 1 proposals. Stage 1 Volume 1 proposals must contain the following document submissions:

- TECHNICAL & MANAGEMENT
- BASIS OF ESTIMATE (BOE)
- TASK DESCRIPTION DOCUMENT
- ADMIN & NATIONAL POLICY REQUIREMENTS

If a Stage 1 proposal is selected for potential award, a proposer will be notified by the Government and required to submit a Stage 2 price/cost proposal for further consideration.

All proposals submitted in response to this announcement must comply with the content and formatting requirements of the Bundle of Attachments. Proposers should use the templates provided in the bundles associated with this announcement. Information not explicitly requested in the MAI or this announcement, applicable Bundles, may not be evaluated.

All submissions, including proposals, must be written in English. Content and formatting are disclosed in the Bundle of Attachments. Below is the page restriction for each Module category:

- **BIT Module** is ≤ $2,000,000: Volume 1 shall be limited to **10** pages.
- **BYTE Module** is > $2,000,000 ≤ $4,999,999: Volume 1 shall be limited to **15** pages.
- **KILO Module** is > $5,000,000 ≤ $10,000,000: Volume 1 shall be limited to **20** pages.
- **MEGA Module** is > 10,000,000 ≤ $25,000,000; Volume 1 shall be limited to **25** pages.

The following is the Government's estimation of Module category for each TA and TA sub-TA.

TA1: Individually proposed sub-TAs are anticipated at the **BYTE level.**
TA1: Combined proposal for **two** (2) sub-TAs is anticipated at the **KILO level**.
TA1: Combined proposal for all **three** (3) sub-TAs is anticipated at the **MEGA level.**
TA2: Proposals must address all sub-TAs therefore proposals are anticipated at the **MEGA level**.
TA3: Proposal are anticipated at the **MEGA level.**

Any proposals that combined TAs (TA1-TA2, TA2-TA3, TA1-TA3, etc.) are anticipated at the MEGA level.

NOTE: Strong proposals will select a cost point that is commensurate with the scale and complexity of the proposed approach. Proposals that simply align a proposed budget to the Module Category ceiling value is strongly discouraged. Thus, if a proposal is selected for Stage 2 submissions and the basis of estimate was simply aligned to the Module Category ceiling value, the Government will require a full cost proposal (i.e., direct and indirect rates, labor hours, equipment, material, other direct costs, etc.) that must be substantiated by salary documentation, indirect rate agreements, material and equipment quotations and a justification for proposed labor categories and hours that correlates directly to the proposed Task Description Document. The submission of a full cost volume will impact Stage 2 price/cost proposal timelines and will likely be followed by extensive cost negotiations.

DATA STORAGE AND ANALYSIS COSTS
Performers should provide data storage and analysis cost estimates; however, these values should not be included in budget totals, as these will be covered by the ADAPT program and provided as a Government Furnished Resource.

EQUITY REQUIREMENTS
ARPA-H is committed to equitable health care access irrespective of race, ethnicity, gender/gender identity, sexual orientation, disability, geography, employment, insurance, and socioeconomic status. To that end, we will follow the United States Food and Drug Administration's (FDA) guidance titled "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials". Accordingly, proposals addressing TA1.1, TA1.2, TA1.3, or TA2 must include an equity and accessibility plan outlined in the Bundle of Attachments, Volume 1 Technical & Management.

A key aspect of equitable access is ensuring that the population participating in clinical trials reflects the diversity of people who live in the United States and serves the patient population impacted by the disease. Proposers should indicate how their clinical enrollment strategy fulfills that goal. For instance, a road map to equity for the evolutionary cancer clinical trial would include enrolling, within 5% deviation (see Metrics Table 2), a patient profile that includes the affected population.

The United States has a diverse population of citizens (61% White (Non-Hispanic/Latino), 20% Hispanic or Latino, 12% Black or African American, 6% Asian, 1% American Indian and Alaska Native, and 4% two or more races (Multiracial)). Enrollment for the clinical trials will serve as an accurate demonstration of the correlation between race and cancer type in the US. For example, breast cancer incidence is 66% White, 14% Hispanic or Latino, 11% Black or African American, 8% Asian, and 1% American Indian and Alaska Native. As another example, patients diagnosed with NSCLC were 75.2% white, 12.1% black, 6.3% Asian or Pacific Islander, 5.8% Hispanic, and 0.5% American Indian or Alaskan Native. Sex and the socioeconomic status of the patients will also be recorded to ensure equitable access to the clinical trial.

B. PROPOSAL SUBMISSION INSTRUCTIONS

Proposal submissions requesting an OT against this Module Announcements shall be submitted to the electronic Contract Proposal Submission (eCPS)[4], ensuring receipt by the date and time specified in Section 5.C. of this Module Announcement.

Proposers should consider the submission time zone (Eastern Time) and that some parts of the submission process may take from one business day to one month to complete (e.g., registering for a SAM Unique Entity ID (UEI) number or Tax Identification Number (TIN); see Section 5.2.1 of the MAI for information on obtaining a UEI and TIN).

C. PROPOSAL DUE DATE AND TIME

Proposals in response to this notice are due no later than 1:00 PM ET on 05/06/2024. Full proposal packages as described in Section 5.A and 5.B must be submitted per the instructions outlined in this Module Announcement and received by ARPA-H no later than the above time and date. Proposals received after this time and date may not be reviewed.

[4] electronic Contract Proposal Submission (eCPS) is a component of an integrated, secure system for electronic submission, capture, tracking and review of contract proposals. Be advised eCPS requires user registration to submit a proposal response (https://ecps.nih.gov/).

6. PROPOSAL EVALUATION AND SELECTION

Proposals selected and evaluated in accordance with Section 4 of the MAI, ARPA-H-MAI-24-01. The Government reserves the right to decide which performers, if any, are selected for the award.

7. ADMINISTRATIVE AND NATIONAL POLICY REQUIREMENTS

Section 5.2 of the MAI, ARPA-H-MAI-24-01 provides information on Administrative and National Policy Requirements that may be applicable for proposal submission as well as performance under an award.

8. POINT OF CONTACT INFORMATION

ADAPT Module Announcement questions should be directed to:
ARPA-H Solutions
ATTN: ARPA-H-MAI-24-01-03

9. QUESTIONS & ANSWERS (Q&A)

All questions regarding this notice must be submitted to the link noted in Section 8. Emails sent directly to the Program Manager, or any other address will be **discarded**.

All questions must be in English. ARPA-H will attempt to answer questions in a timely manner; however, questions submitted within 10 business days of the proposal due date listed herein may not be answered.

In concert with this Announcement, ARPA-H will posted Q&As regarding the Module Announcement on SAM.gov and the ARPA-H ADAPT webpage. ARPA-H encourages all proposers to review the Q&As provided before submitting additional questions to the link noted in Section 8. The Government may not answer repetitive questions already answered in the posted Q&As.

10. APPENDIX A

Examples of potential evolutionary trials.

TA2 proposals must delineate the planned evolutionary trial approach. Proposers may synthesize aspects of different innovative clinical trial designs to create their novel evolutionary trial approach. While the evolutionary trial framework can be used for a diversity of disease types and treatments, in Figure 3 and below, we detail three use cases including metastatic breast, non-small cell lung and colon cancers. **Use cases are illustrative only**; proposers should highlight the novelty of their outlined approach. Proposals must indicate that patients are enrolled in a single clinical trial across a sequence of therapies, initiating with standard of care therapies given at time of enrollment followed by longitudinal data collection during treatment, and testing novel therapies targeting resistant traits in later lines. These resistance targeting therapies can include but are not limited to targeted therapies, immunotherapies and combinations of drugs based on tumor biology. Proposals must outline timing and incorporation of subsequent lines of therapy that are personalized to individual patients based on their specific tumor's biology using predictive biomarkers or directed at resistance mechanisms acquired during prior treatments.

Example 1: metastatic estrogen receptor positive (ER+) breast cancer

- ***Key clinical needs addressed:***
    - ER+ breast cancer is a leading cause of cancer death in the U.S.
    - Most patients with metastatic breast cancer lack therapy personalization.
    - Even when there are actionable mutations present in a tumor, the mutation status of these genes alone is often insufficiently accurate in predicting resistance.
- ***Biomarker testing and integration into the clinical trial:*** Patients will be stratified across treatment arms based on transcriptomic biomarker at enrollment. Therapies will be incorporated until either durable response is achieved or the patient progresses, at which time biopsy sample will be taken for

determination of the next therapy using biomarkers developed in TA1.3 and/or drug resistance mechanisms identified in TA1.2.

- ***Therapies incorporated***: Patients with metastatic ER+ BC have multiple possible standards of care therapies for second line treatment. Multi-modal data collected during this phase of the trial will be used to identify biomarkers of drug response, as not all patients have durable responses to these therapies. Tumor biopsies will be taken from patients who have progressed on the first drug regimen (endocrine therapy plus cell cycle inhibitor), and multi-modal data from these biopsies will be used to assign patients to one of four treatment arms: mTOR inhibitor (e.g., everolimus), endocrine therapy (e.g., fulvestrant), PI3K inhibitor (e.g., alpelisib), or chemotherapy (e.g., capecitabine) based on incorporation of TA1 biomarkers. Please note that first line metastatic therapy would not be a good treatment arm for the ADAPT evolutionary trial as time to progression is too long for the expected duration of the trial. Patients whose tumors are negative for targeted therapies will be assigned to the chemotherapy arm. In this way, we aim to substantially increase the percent of patients who receive therapy tailored to their specific cancer and response rates. As shown in the third breast cancer therapy sequence of Figure 3, if patients progress on these standard of care therapies, they will then be assigned to a randomized treatment strategy to compare therapies targeting the acquired resistant traits identified through mathematical modeling/machine learning approaches from TA1. In this example, a drug called "neratinib", which targets an acquired growth factor resistance pathway composed of Erbb activation, is tested as a treatment arm, as is activation of IL-15 with a therapy called N-803. In addition, new drugs that target the acquired resistant state identified through analysis of the multi-modal data collected can be included, thereby creating an iterative process where treatment decisions using advanced technologies are enacted in near-real-time.

Example 2: Metastatic non-small cell lung cancer (NSCLC)

- ***Key clinical needs addressed:***
  - Biomarkers to two classes of standard of care treatment, immunotherapies, and chemotherapies, remain insufficiently sensitive to predict durable drug response (defined as greater than one year of disease control) for most patients.
  - It is likely that multi-modal data will be needed to build accurate biomarkers, as to date single data types have had limited predictive accuracy.
- ***Therapies incorporated:*** Patients will be treated with front-line standard of care, including chemotherapy, immunotherapy (pembrolizumab) or oncogene directed targeted therapy (e.g., EGFR tyrosine kinase inhibitors for patients with mutations in EGFR).
- ***Biomarker testing and integration into the clinical trial:*** Patients will be assigned to initial immunotherapy treatment arm if PDL1 biomarker status is positive. Patients with EGFR mutations will be assigned to erlotinib treatment while patients with genetic alterations in p53 and/or Rb could be assigned to receive chemotherapy. Patients with combinations of these biological indications will receive combinations of the drugs on an alternating schedule. Upon progression, multi-modal data will be obtained via biopsy to identify resistance mechanisms and reassign patients to one of three second line trial arms: BCL2 inhibitor, Aurora kinase inhibitor, or PARP inhibitor + immunotherapy.

Figure 3. Example evolutionary clinical trial therapies.

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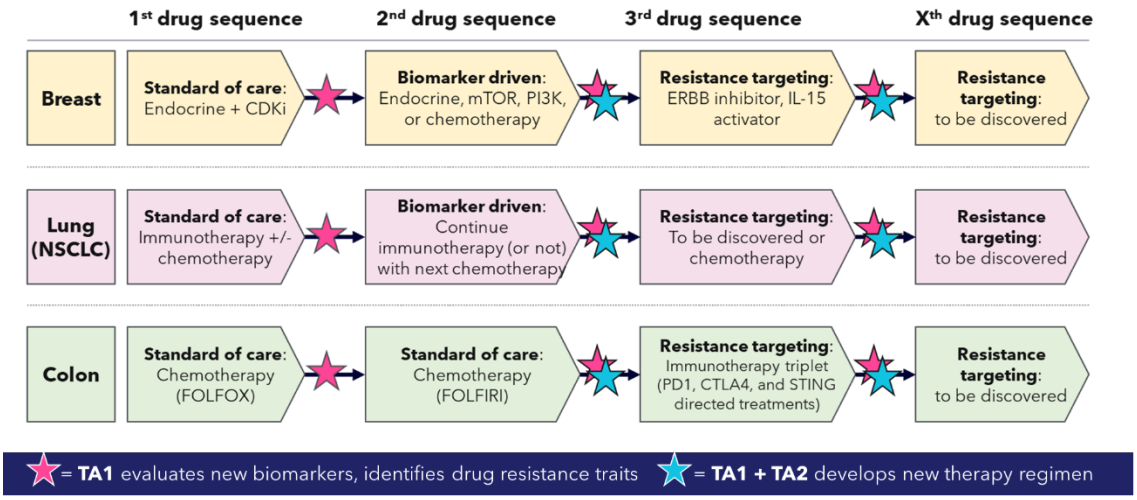

Example 3: Metastatic microsatellite stable (MSS) colon cancer

- ***Key clinical needs addressed***:
  - Emergent global epidemic of colon cancer among people younger than 50.
  - No personalized treatment options are available.
  - These patients also commonly present with metastatic disease and respond poorly to standard chemotherapies (with an overall response rate of 47% to first line chemotherapy and 21% to second line chemotherapy with a progression free survival (PFS) of 6.1 months).
- ***Biomarker testing and integration into the clinical trial***: Patients will be treated initially with standard of care FOLFOX (folinic acid, 5-fluorouracil, oxaliplatin) treatment. Upon relapse, patients will be assigned to standard of care FOLFIRI treatment (folinic acid, 5-fluorouracil, irinotecan). Multi-modal data will be collected to develop better biomarkers of FOLFOX and FOLFIRI response. Currently over half of patients receive no benefit from these therapies, suggesting they could be treated with a more effective treatment and avoid unnecessary toxic side effects of chemotherapy. Patients who progress on FOLFIRI will then be treated with immunotherapies targeting PD1, CTLA4, or STING in two or three drug combinations to predict which patients respond to doublet or triplet immunotherapy, as currently 75% of MSS colon cancer patients fail to respond to immunotherapies. If successful, we expect that most colon cancer patients will benefit from these biomarkers.

Together, these are examples of how the new ADAPT evolutionary clinical trial design, with multi-modal data and advanced technologies, can tackle important questions in cancer treatment. This design allows for identification of markers of sensitivity and response at each stage and for development of a comprehensive understanding and data-driven personalization of treatment that can better match the complexity of cancer.

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