INNOVATIVE SOLUTIONS OPENING

FOR

LYMPHATIC IMAGING, GENOMIC AND PHENOTYPING TECHNOLOGIES (LIGHT)

HEALTH SCIENCE FUTURES

ARPA-H-SOL-24-102

April 30, 2024

Contents

1. INNOVATIVE SOLUTIONS OPENING OVERVIEW INFORMATION

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

ISO SOLICITATION TITLE: Lymphatic Imaging, Genomic, and pHenotyping Technologies (LIGHT)

ANNOUNCEMENT TYPE: Solicitation

ISO SOLICITATION NUMBER: ARPA-H-SOL-24-102

DATES: (All times listed are Eastern Time)

- ***Proposer's Day: May 21, 2024***
- ***Questions & Answers (Q&A) due date***: May 29, 2024, 11:00AM ET
- ***Closing Date (Solution Summaries Due)***: June 18, 2024, 11:00AM ET

ANTICIPATED INDIVIDUAL AWARDS: Multiple awards

TYPE OF AWARD INSTRUMENTS: Other Transaction Agreements (OTs)

AGENCY CONTACT: LIGHT@ARPA-H.gov

Program Overview: LIGHT intends to shine a light on the lymphatic system, illuminating the unseen both literally via novel diagnostic approaches and figuratively through insight gained into the critical role the lymphatic system plays in health as well as its impacts when dysfunctional. LIGHT aims to improve the lives of tens of millions of Americans by creating agile tools that are scalable, accessible, accurate and clinically useful to detect lymphatic structure and function. Multiple diagnostic technologies will enable targeted interventions that result in better patient outcomes and reduced treatment costs, and will advance our understanding of lymphatic dysfunction, a key factor in the pathophysiology of many important diseases. Signs and symptoms of lymphatic dysfunction do not manifest until the disease has progressed, and current assessment tools neither adequately appraise lymphatic anatomy nor measure lymphatic function.

Today, patients with lymphatic disease may remain misdiagnosed or undiagnosed for years; some never get a diagnosis.

In the future, *with a comprehensive set of tools, the journey to diagnose lymphatic dysfunction will be measured in minutes.*

1.1 ACQUISITION STRATEGY

ARPA-H seeks proposals from all eligible entities (see Section 2 *Eligibility Information*) to accomplish the LIGHT Program goals as described in this solicitation package. Ultimately, ARPA-H intends to negotiate multiple OT agreements with proposers whose proposals are most advantageous to the Government and are poised to meet the goals of the LIGHT program.

Proposals are expected to use innovative approaches that may include both existing and novel technology, enabling revolutionary advances in medicine and healthcare. The LIGHT program aims to develop a comprehensive diagnostic toolkit to assess lymphatic structure and function, and potential performers should consider an approach to ensure the final technology includes an imaging modality plus biomarkers and/or genetic integration. Initially proposers should consider primary lymphatic diseases as the targeted disease state; however, consideration of other chronic conditions associated with lymphatic dysfunction is encouraged.

Specifically excluded are proposals that represent an evolutionary or incremental advance in the current state of the art, including clinical trials of an otherwise developed product. Additionally, proposals directed towards policy changes, traditional education and training, or center coordination, formation, or development, and construction of physical infrastructure are outside the scope of the ARPA-H mission.

1.2 SOLICITATION AND PROGRAM INFORMATION AVAILABILITY

This ISO will be solicited through the System for Award Management (SAM.gov) and posted on the ARPA-H website at https://arpa-h.gov/research-and-funding/programs. See Section 4 for Solution preparation and submission information.

1.3 AWARD INFORMATION

The Government reserves the right to select for negotiation all, some, one, or none of the proposals received in response to this ISO. If warranted, portions of resulting awards may be segregated into pre-priced options. In the event the Government desires to award only portions of a proposal, negotiations will commence upon selection notification. The Government reserves the right to fund proposals in phases with options for continued work, as applicable.

The Government reserves the right to request any additional, necessary documentation to support the negotiation and award process. The Government reserves the right to remove a proposal from award consideration should the parties fail to reach agreement on award terms, conditions, cost, and/or if the proposer fails to provide requested additional information in a timely manner.

In all cases, the Government will have sole discretion to negotiate all instrument terms and conditions with selectees. ARPA-H will apply publication or other restrictions, as necessary, if it is determined that the research resulting from the proposed effort will present a high likelihood of disclosing sensitive information including Personally Identifiable Information (PII), Protected Health Information (PHI), financial records, proprietary data, any information marked Sensitive but Unclassified (SBU), etc. Any award resulting from such a determination will include a requirement for ARPA-H concurrence before publishing any information or results on the effort.

2. ELIGIBILITY INFORMATION

2.1 ELIGIBLE APPLICANTS

All responsible sources capable of satisfying the Government's needs may submit a proposal to this ISO. Specifically, universities, non-profit organizations, small businesses and other than small businesses are eligible and encouraged to propose to this ISO.

2.1.1 FEDERALLY FUNDED RESEARCH AND DEVELOPMENT CENTERS (FFRDCs) AND OTHER GOVERNMENT ENTITIES

Federally Funded Research and Development Centers (FFRDCS) are not permitted to respond to this solicitation in any role on a proposed team, to include prime/lead or subperformer.

Government entities may not submit proposals to this solicitation as prime/lead performers but may participate on performing teams as a subperformer. Be aware, though, ARPA-H will not facilitate the establishment of the relationship between the prime/lead performer, performing team and the government entity that wishes to participate. Government entities and the prime/lead performer are

responsible for determining if the government entity is eligible to participate as a subperformer, prior to proposal submission. ARPA-H will not enter into a relationship directly with the government entity to facilitate performance on a specific team nor will ARPA-H reimburse the government entity directly for any participation. If the government entity wishes to be a subperformer, they must establish that relationship directly with the prime/lead performer to include receiving payment directly from the prime/lead performer.

Should a FFRDC or Government entity have a research idea that is within the technology area of this program, it should submit a statement of interest to LIGHT@ARPA-H.gov.

Individual government employees who wish to participate as part of a performing team should be aware that there may be significant statutory and/or regulatory ethical implications with such participation. Government employees contemplating such participation are highly encouraged to consult with their agency's legal counsel for guidance. ARPA-H will not provide such guidance. If a performing team includes a government employee, the prime/lead will be expected to do their due diligence and maintain on file a letter from the government employee's home agency that such participation is permissible. ARPA-H reserves the right to ask for a copy of this letter at any time during the evaluation or negotiation periods or during performance if selected.

2.1.2 NON-U.S. ENTITIES

Non-U.S. entities may participate to the extent that such participants comply with any necessary nondisclosure agreements, security regulations, export control laws, and other governing statutes applicable under the circumstances. However, non-U.S. entities are encouraged to collaborate with domestic U.S. entities. In no case will awards be made to entities organized under the laws of a covered foreign country (as defined in section 119C of the National Security Act of 1947 (50 U.S.C. § 3059)) or entities suspended or debarred from business with the Government.

2.2 SYSTEM FOR AWARD MANAGEMENT (SAM)

All proposers must have an active registration in SAM.gov in order for their proposal to be found conforming. Proposers must maintain an active registration in SAM.gov with current information at all times during which a proposal is under consideration or a current award from ARPA-H is held. Information on SAM.gov registration is available at SAM.gov.

NOTE: New registrations as well as renewals may take more than 14 business days to process in SAM.gov. SAM.gov is independent of ARPA-H and thus ARPA-H representatives have no influence over processing timeframes.

2.3. ORGANIZATIONAL CONFLICTS OF INTEREST (OCI)

Proposers are required to identify and disclose all facts relevant to potential or actual OCIs involving the proposer's organization and any proposed team member (proposed sub-awardee). Although the FAR does not apply to OTs, ARPA-H requires OCIs be addressed in the same manner prescribed in FAR subpart 9.5. Regardless of whether the proposer has identified potential or actual OCIs under this section, the proposer is responsible for providing a disclosure with its proposal. If a potential or actual OCI has been identified, the disclosure must include the proposers', and as applicable, proposed team members' OCI mitigation plans. The OCI mitigation plan(s) must include a description of the actions the proposer has taken, or intends to take, to prevent the existence of conflicting roles that might bias the proposer's judgment and to prevent the proposer from having unfair competitive advantage. The OCI mitigation plan will specifically discuss the disclosed OCI in the context of each of the OCI

limitations outlined in FAR 9.505-1 through FAR 9.505-4. The disclosure and mitigation plan(s) do not count toward the page limit.

2.3.1. Agency Supplemental OCI Policy

In addition, ARPA-H restricts performers from concurrently providing professional support services, or similar support services, and being a technical performer. Therefore, as part of the FAR 9.5 disclosure requirement above, a proposer must affirm whether the proposer or any proposed team member (proposed sub-awardee, etc.) is providing professional support services to any ARPA-H office(s) under: (a) a current award or subaward; or (b) a past award or subaward that ended within one calendar year prior to the proposal's submission date.

Proposers shall follow the instructions in, and complete, Volume III (see Appendix C) to address the requirements of this ISO Section.

Note: An OCI based on a proposer currently providing professional support services, as described above, cannot be mitigated.

GOVERNMENT PROCEDURES

The Government will evaluate OCI mitigation plans to avoid, neutralize, or mitigate potential OCI issues before award and to determine whether it is in the Government's interest to grant a waiver. The Government will only evaluate OCI mitigation plans for proposals selected for potential award based on the evaluation criteria and funding availability.

The Government may require proposers to provide additional information to assist the Government in evaluating the OCI mitigation plan.

If the Government determines a proposer failed to fully disclose an OCI; or failed to provide the affirmation of ARPA-H support as described above; or failed to reasonably provide additional information requested by the Government to assist in evaluating the proposer's OCI mitigation plan, the Government may reject the proposal and withdraw it from consideration for award.

3. THE PROGRAM

3.1 LIGHT OVERVIEW

The lymphatic system (LS) is an indispensable body system without which we could not survive. It consists of a complex network of lymphatic vessels, lymph nodes, and lymphatic organs that play a critical role in fluid balance, immune cell surveillance, and macromolecule homeostasis in almost every tissue of the human body. In contrast to the tools available for assessment of cardiovascular health (blood pressure, electrocardiography, echocardiography, etc.) there exist few means of assessing the structure and function of the LS. Lymphatic vessels are translucent, tiny, and fragile; additionally, they have low flow rates and pressures, making them difficult to visualize or assess using traditional tools such as blood pressure, visual inspection, or ultrasound. Today, clinicians have no easy-to-use, widely accessible, and safe tools to assess the health of the LS. As a result, the human LS has been largely ignored in the minds of clinicians and researchers alike and patients with primary lymphatic diseases are often undiagnosed or misdiagnosed, leading to avoidable morbidity and mortality. Further, patients whose lymphatic dysfunction underlies their chronic disease miss out on the benefit of early diagnosis and treatment.

The current, limited methods for the assessment of lymphatic anatomy and function include:

1. Physical exam and assessment for pitting and non-pitting edema (Stemmer Sign) and measurement of arm and leg circumference. The physical exam is rudimentary, non-quantitative, poorly standardized, and operator dependent. Additionally, it measures neither lymphatic anatomy nor lymphatic function.
2. Biomarkers are in development but are not yet standardized or in widespread clinical use.
3. Imaging – non-invasive imaging with bioimpedance, magnetic resonance imaging (MRI) or ultrasound (US), or invasive imaging via lymphoscintigraphy (LSG), dynamic contrast-enhanced MRI lymphangiography (DCMRL), intranodal CT lymphangiography (ICTL), conventional lymphangiography, and near-infrared (NIR) indocyanine green (ICG) lymphography. These imaging techniques lack deep tissue penetration, are unable to visualize small vessels due to limited resolution and lack organ specificity and dynamic functionality. Access is limited as they require a high level of expertise and expensive equipment. Importantly for the patient, many require risky invasive techniques.
4. Detection of genetic mutations (both inherited and somatic) are difficult and genomic approaches have not been fully explored.

LIGHT will address these limitations by extending and combining existing modalities to develop two important capabilities in the assessment of the lymphatic system:

1. The ability to image lymphatic structure in individual organs.

   The LS provides a one-way transport system from multiple organ-based subsystems (brain, eyes, lung, heart, gut, spleen, liver, skin, and soft tissue). To appreciate the entire lymphatic anatomy each lymphatic subsystem must be imaged.

   A variety of approaches may address this, including the identification of novel tracers through biomarker and genetic discovery that are specific to organ tissues and absorbed directly into the LS, combination of existing imaging modalities, and discovery of non-invasive imaging technologies. Additionally, the application of promising technologies used for other body systems has yet to be tried in the diagnosis of Lymphatic disease (LD). Examples may include but are not limited to microbubbles, small gas-filled lipid microspheres that are easily absorbed into the lymphatics and have acoustic properties suitable for use as an ultrasound contrast agent, and novel CT technologies such as high-resolution dual-energy CT that can visualize peristalsis of individual lymphatic vessels, enabling calculation of lymphatic flow and assessment of thoracic duct obstruction.

2. The ability to measure lymphatic function.

   Assessment of fluid dynamics and flow, permeability, pressure, and valvular function is an essential part of the evaluation of any vascular system. Administration of agents that accumulate in the tissue beds of different organs and are cleared via the LS could enable visualization and measurement of lymphatic flow in each organ. Development of such breakthrough methods would allow assessment of both lymph production and drainage via the LS, both of which can be causes and consequences of disease. Further, recent technological breakthroughs and computational approaches have revolutionized medical imaging and other diagnostic tools, and these approaches may be applied to the LS, unlocking meaningful measurement of lymphatic function.

3.2 TECHNICAL APPROACH AND STRUCTURE

3.2.1 TECHNICAL AREAS (TAs)

LIGHT performers will develop a comprehensive diagnostic toolkit to assess lymphatic structure and function. Potential performers must consider a revolutionary BIG (biomarkers, imaging, and genetic) approach to ensure the final diagnostic toolkit includes an imaging modality plus biomarkers and/or genetic integration. Performers should consider primary lymphatic diseases as the targeted disease state; however, consideration of other chronic conditions such as cancer, chronic heart, lung, kidney, liver, gastrointestinal, autoimmune (i.e., inflammatory bowel disease, rheumatoid arthritis), infectious diseases or transplantation, associated with lymphatic dysfunction is encouraged. To accomplish these goals LIGHT is structured into three technical areas (TAs), two tracks, and three phases. Phase 1 will encompass proof-of concept research (24 months), Phase 2 – Pre-clinical research (24 months), and Phase III – clinical validation (12 months). See Table 1. List of Primary Lymphatic Diseases and Chronic Diseases with Underlying Lymphatic Dysfunction.

Table 1.

Primary lymphatic diseases*	**Chronic disease with underlying lymphatic dysfunction***

• Lymphedema
  ○ Primary
  ○ Secondary (injury, trauma, infection, and surgery)
• Lymphatic anomalies
  ○ Tumors
  ○ Malformations (microcystic and macrocystic)
• Lipedema
	• Lipedema
	• Chronic kidney diseases
	• Chronic liver diseases
	• Inflammatory Bowel Disease (e.g. Chron's disease)
	• Cardiovascular diseases (e.g. heart failure and atherosclerosis)
	• Chronic lung disease
	• Metastatic cancer
	• Obesity
	• Infectious disease
	• Ocular diseases
	• Tissue transplantation
	• Autoimmune disease

*Performers may propose an alternative disease with justification. However, neurodegenerative diseases and other brain related disorders are outside the scope of LIGHT and should not be proposed.

Technical Area 1 (TA1): Diagnostics and Monitoring – *through biomarker development.*

TA1 focuses on the identification and development of specific biomarkers capable of diagnosing and monitoring lymphatic dysfunction. Approaches may include evaluation of novel biospecimens using traditional methodologies and implementation of innovative high throughput approaches. Biomarkers may consist of cells, proteins, peptides, metabolites, and nucleic acids, as well as physiologic measurements, such as bioimpedance. Additionally, LIGHT is supportive of proposals looking to mine existing data sets, such as public single-cell RNA-seq databases and patient registries, to identify novel markers of lymphatic phenotypes and disease indicators.

TA1 has three broad objectives:

Objective a: Discover and intelligently monitor biomarkers specific to lymphatic physiology, function, and LD. Performers may apply highly sensitive biomarker discovery methodologies to assess lymphatic dysfunction (i.e., nanosensors or aptamer scRNA-seq approaches) or use traditional methodologies to explore lymphatic biospecimens (i.e., interstitial fluid and lymph). Further, performers are encouraged to identify biological biomarkers that may inform the development of new tracers and contrast agents enabling novel imaging modalities (see Technical Area 2).

Objective b: Correlate biomarker expression with lymphatic function and dysfunction. Novel biomarkers could be used in conjunction with imaging of the LS to yield a new understanding of lymphatic pathophysiology. Performers are encouraged to carefully assess the fit of their novel biomarker(s) with the following categories: susceptibility/risk, diagnostic, monitoring, prognostic, predictive, pharmacodynamic/response, and safety.

TA1 will enable rapid and reliable diagnosis and accurate monitoring of LD using highly specific and sensitive biomarkers.

Technical Area 2 (TA2): Imaging Technologies

Advancing clinical care for lymphatic diseases is dependent on imaging systems capable of visualizing and measuring the LS of individual organs reliably and accessibly. New imaging technologies and approaches should represent a significant leap forward in capabilities compared to the current state-of-the-art in lymphatic imaging. Performers are encouraged to be bold while developing imaging technologies and may consider unorthodox approaches to understanding lymphatic anatomy, for example, cadaveric or novel humanized models. Performers are encouraged to choose from three potential approaches, below, but may suggest an alternative approach.

Potential Approach A.: Imaging tracer/contrast agent development and delivery. Performers will develop an imaging contrast agent in combination with an imaging modality that is specific to the LS and provides enhanced lymphatic imaging. Performers must carefully justify how the contrast agent will be delivered to minimize undesirable off target outcomes and improve patient experience.

Potential Approach B.: Combining multiple imaging modalities. Current lymphatic imaging approaches each have unique strengths and limitations. However, if the approaches were combined, it could significantly improve the current capabilities in lymphatic imaging. Performers will combine multiple imaging technologies or approaches to significantly improve their assessment of lymphatic function and/or provide earlier detection of dysfunction.

Potential Approach C.: Advancement of non-invasive imaging technology. Performers will apply emerging advancements in non-invasive imaging approaches, coupled with state-of-the-art computational approaches to image the LS without a contrast agent or dye. Examples of non-invasive imaging approaches that have been identified for potential application to lymphatic imaging are ultrasound imaging, non-invasive MRI, and optical coherence tomography.

TA2 will develop novel imaging technologies to assess whole-body lymphatic structure and function qualitatively and quantitatively at a cost and user-friendliness that will encourage widespread adoption.

Technical Area 3 (TA3): Prevention, Prediction & Diagnostic Confirmation – *through genetics, epigenetics, and models of lymphatic dysfunction.*

The various genetic and epigenetic variants of lymphatic disease (LD) and lymphatic dysfunction have yet to be fully explored; however, this discovery effort could revolutionize how we predict, diagnose, and treat LD. Performers must discover novel disease-causing genetic variants and develop accompanying models to enable prediction, prognosis, and risk assessment for personalized patient care.

TA3 has four broad objectives:

Objective a. Establish large scale databases. Performers will develop large databases and implement data sharing strategies to adequately address lymphatic diseases which are often relatively rare and may have somatic mutations with low allele frequency. Further, LIGHT encourages performers to apply state-of-the-art computational approaches to mine existing data sets for novel genetic variants associated with LD.

Objective b. Apply cutting edge approaches in discovering genetic or epigenetic variants to lymphatic disease and dysfunction. Performers will utilize emerging technologies to predict or discover genetic variants that have not been applied to lymphatic diseases on a wide scale. Performers will then explore the expression in both lymphatic diseases and in chronic disease with noted lymphatic dysfunction.

Objective c. Validate genetic targets with novel models of lymphatic dysfunction and disease. Performers will validate novel genetic and epigenetic variants identified in patients with LD with novel *in-vivo*, *in-vitro,* and *ex-vivo* models able to recreate key aspects of the LD. Models should focus on clinical and pre-clinical utility for translating novel diagnostic technologies.

Objective d. Apply radiogenomic (imaging genomics) or similar, methodologies to predict variant expression via imaging phenotype. Utilizing imaging technologies developed in TA2, performers must identify imaging features that can serve as a predictive surrogate for genetic testing and variant expression.

TA3 will identify genetic and epigenetic variants causing lymphatic dysfunction, allowing in combination with biomarkers and imaging for early and definitive diagnosis, prevention, prediction and refinement of prognosis and therapy.

Technical Requirements for All Performers:

All performers, regardless of technical area, must adhere to the following technical requirements:

A. Tissue Bed and LD Selection

In Phase I, performers must specify the organ/tissue bed and the LD for which their technology is best suited to address. Performers may propose a wide range of organs and tissue beds except for brain related lymphatics (i.e. meningeal lymphatics and the "glymphatic system").

In Phase II, performers must test the technology developed in Phase I in a relevant preclinical model to enable its clinical translation. Additionally, performers must conduct appropriate studies to test the technology in an alternative tissue bed, biofluid, or disease model. For example, a biomarker identified

in the interstitial fluid could be explored in blood or urine, or an imaging approach developed for central lymphatic imaging should be tested in an organ-specific lymphatic network.

B. Leveraging Computational Intelligence and Big Data Management

All performers should clearly outline how they are utilizing the latest, state-of-the-art, approaches in Artificial Intelligence (AI) and machine learning (ML) in order to increase the speed, efficiency, or predictiveness of their diagnostic technology in Phase I and Phase II of LIGHT. Additionally, across all phases of LIGHT, performers must leverage and share data in a smart and collaborative way using FAIR Data Principles (Findable, Accessible, Interoperable and Reusable) with the shared goal to advance lymphatic diagnostic technology and achieve commercial viability.

C. Product Development and Regulatory Science

At proposal submission, performers must identify a product development team (regulatory, reimbursement, and commercialization experts) as consultants or subcontractors for the award. Additionally, performers must include a brief commercialization plan to outline how their technology compares to current clinical options. Within the first 18 months of the award, performers, led by the product development team, must meet with appropriate regulatory bodies, such as the FDA, to develop and validate pre-clinical milestones for success. This will culminate in a full commercialization plan (≤ 8 pages) outlining a path for successful commercialization of their technology, including a market analysis, funding plan, pre-clinical testing, regulatory and reimbursement strategy, etc. LIGHT requires performers to revise the pre-clinical studies proposed at the time of submission to align with these regulatory findings. As appropriate for each Technical Area, the performer's commercialization plan should include a submission strategy to a relevant FDA approval program. For example:

- The Biomarker Qualification Program (BQP) for novel biomarkers
- A De Novo/510k/Premarket Approval (PMA) submission for imaging technologies
- An Investigation New Drug (IND) submission for injectable tracers and contrast agents

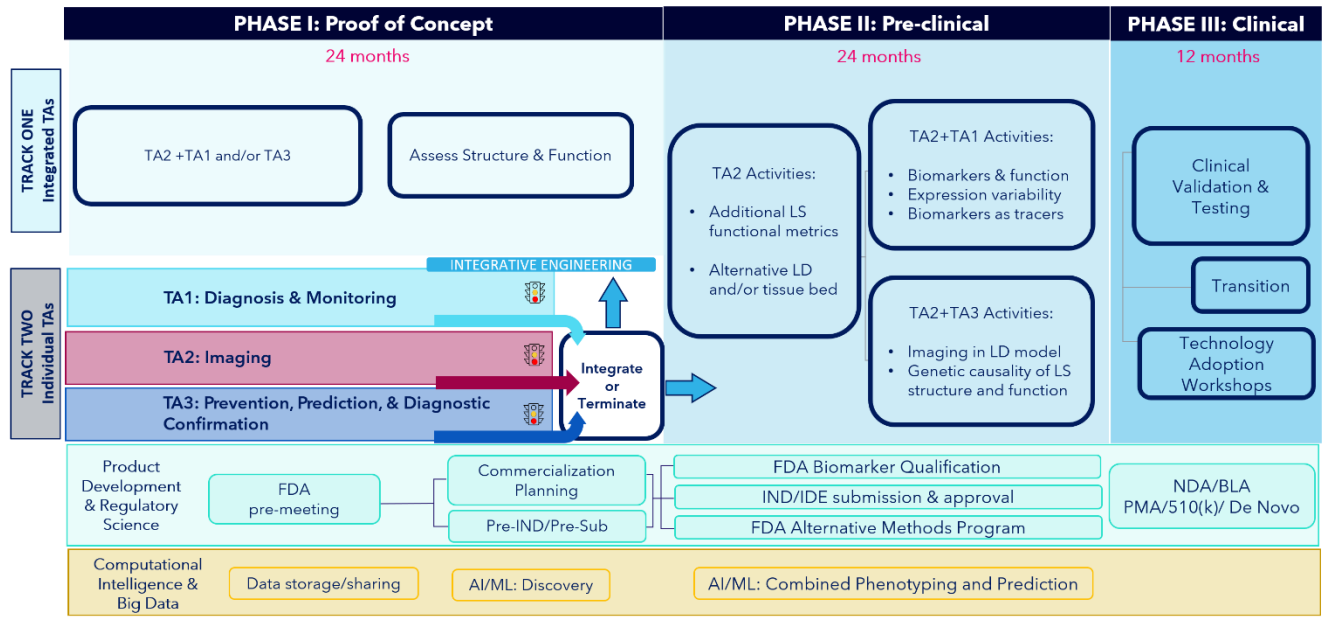
In Phase II, performers will implement the commercialization plan, and continue with regular engagement with intellectual property, reimbursement, and regulatory experts.

Proposals that fail to address the required technical areas and phase requirements may be deemed non-conforming and be rejected without further review.

Proposing teams must include data access plans and commercialization plans including FDA meeting milestones, technology transfer milestones to contract manufacturing organization (CMO) partners, preclinical proof of concept objectives, and market analysis and partnership models for commercialization. The proposed technology for TA1, TA2 and TA3 should meet the specifications listed in Section 3.3 Technical Area Metrics and Objectives.

3.2.2 PROGRAM STRUCTURE

Figure 1. Program Structure and Timeline



LS: Lymphatic System
LD: Lymphatic Disease
FDA: Food and Drug Administration
IND: Investigation New Drug
IDE: Investigational Device Exemption

NDA: New Drug Application
BLA: Biologics License Application
PMA: Premarket Approval
AI/ML: Artificial Intelligence/Machine Learning

Integrative Engineering:

1. Identify a Track One team with whom there is mutual interest to integrate; or.
2. Identify one or more Track Two performers with which to form a new performer team capable of addressing TA2 and at least one other TA.

LIGHT will be accomplished over three sequential phases: Phase I – proof-of concept research (24 months), Phase II – Pre-clinical research (24 months), and Phase III – clinical validation (12 months). Further, LIGHT has been structured to allow performers to choose from one of two tracks which will dictate the number of TAs and period of performance.

To encourage optimal collaboration and positive competition, all performers in both Track One and Track Two will be required to meet semiannually for Meeting of the Minds (M&M) virtual forum. Further, all performers from Track One and Track Two are required to present their discoveries at an internal innovations workshop hosted by LIGHT during Phase I at ~21 months. Guests from the NIH and the National Lymphatic Commission, FDA and other government agencies may be invited with the intended purpose of gathering insight into possible transition partners, commercialization strategies and importantly "shining a light" on the LS. **See all LIGHT meeting descriptions in Section 3.4.2 LIGHT Program Meetings and Attendance.**

Description of Tracks:

Track One: Integrated Technical Areas (60 months)

Proposers applying to Track One will enter Phase I (24 months) as an integrated team with a 5-year plan that must address at least two of three TAs: **TA2** (Imaging technologies) is required, and proposers can choose between **TA1** (Diagnostics and Monitoring) and/or **TA3** (Prediction and Prevention).

Track Two: Individual Technical Areas (24 months)

Cutting edge technical discovery approaches have yet to be applied to the LS. Many of these approaches appear promising but it is unclear which will most quickly produce translational clinical findings in the underexplored field of lymphatics. Track Two provides an option for individual performers who can contribute a piece of the puzzle to an integrated solution.

Proposers applying to Track Two will enter Phase I to address one technical area: **TA1** (Diagnosis & Monitoring – *through biomarker discovery*), or **TA2** (Imaging technologies), or **TA3** (Prevention, Prediction & Diagnostic Confirmation – *through genetic, epigenetic and models of lymphatic dysfunction*).

If a performer enters Track Two it is important to be aware this track ends at 24 months. Proposals for Track Two should be 24-month proposals that are responsive to the metrics and milestones outlined in Phase I of LIGHT. See below for additional information.

3.2.3 LIGHT GO/NO-GO PHASE I CHECKPOINT

By the end of Phase I, Track Two will end and LIGHT will down-select ensuring that the remaining performing teams develop the strongest diagnostic tools by the end of the program.

Selection Process:

In the last quarter of Phase I, there will be a down selection of teams based on performance against LIGHT Phase I metrics and milestones as described in the TA metrics and objectives tables (Section 3.3). Successful completion of Phase I metrics does not guarantee a Track One or Two team will continue to subsequent phases. Progression into future phases via exercise of Options 1 and 2 is determined by the ARPA-H PM and is based on performer progress toward current phase metrics and probability of success in future phases.

Track Two performers who remain in the program must meet all the minimal required metrics for Phase I of their specific TA. Assuming successful completion of Phase I metrics, Track Two performers may proceed through one of the two options below. LIGHT has coined this process: *Integrative Engineering – Integrate or Terminate.*

1. Identify a Track One team with whom there is mutual interest to integrate; or.
2. Identify one or more Track Two performers with which to form a new performer team capable of addressing TA2 and at least one other TA. This new Track One team must submit a Statement of Work (SOW) by month 22 of Phase I, to describe plans for Phase II and Phase III. The ultimate move from Track Two to Track One will be negotiated with ARPA-H.

Additionally, any performer that does not meet the equity, product development and attendance requirements may not progress to the subsequent phases.

3.2.4 DATA MANAGEMENT AND SHARING PLAN (DMSP)

LIGHT encourages all teams to consider the importance of data sharing opportunities that may be possible during the LIGHT program. All proposals are required to include a data management and sharing plan, that address the following points:

1. What type of data will be generated? Explain rationale for what scientific data will be preserved and what will be shared.
2. Will specialized tools, software, or code be needed to access or manipulate shared data, and if so, provide the purpose and rationale?
3. What are the common data standards that apply to scientific data and metadata to enable interoperability and safety?
4. What is the timeline for data preservation and access.
5. Outline your plan for data access, distribution, reuse, and privacy considerations.
6. Describe activities and individuals to ensure compliance and oversight.

Unless an exception is approved by the LIGHT PM, proposers will openly share deidentified/sanitized data acquired during the period of performance with the scientific community. Any member of the scientific community may have access to the deidentified/sanitized data; registration to a specific repository website is acceptable, but approval needs to be automatic. The specific repository where data will be deposited will be chosen in agreement with the ARPA-H Program Manager. The proposers will need to present explicit solutions to address the significant data storage and computing challenges presented by the program, with the understanding that the plans and repository may change later in the program. The DMSP must address any instances where open sharing of data may jeopardize the technology's commercial potential. With PM approval, proposers may restrict access to even the sanitized/deidentified data generated during the period of performance for up to 20 years following the award.

3.3 TECHNICAL AREA METRICS AND OBJECTIVES

ARPA-H will meet with LIGHT performers at least monthly to review progress towards the metrics and milestones defined below. Achievement of all metrics as agreed to by ARPA-H is part of the basis for initiation of moving to the next Phase. Key overall program metrics and milestones are listed in this section below. Performers may propose additional quantitative metrics and milestones for the Program Manager to consider that may be better suited for their specific technology. However, the performers must provide a justification for these additions to the metrics and milestones as specified below. A full target product profile (TPP), outlining the minimum and ideal functionality of the technology developed in each TA can be found in Appendix D.

OVERALL LIGHT PROGRAM GOALS

TA1: Diagnosis & Monitoring – *through biomarker discovery*	• Biomarkers will aid in early detection, monitoring of lymphatic dysfunction (providing real-time information about disease status and response to treatment (i.e., clinical trials: as companion diagnostics), inform treatment selection and decision making. • Identify or develop a biomarker capable of detecting lymphatic disease (a lymphatic anomaly or primary or secondary lymphedema) • Biomarkers will be correlated with specific lymphatic functions or modes of lymphatic dysfunction informing imaging diagnostic tools.

TA2: Imaging Technologies	• Doctors will have imaging modalities that allow organ specific assessment of lymphatic structure and function and the ability to monitor treatment response. • Develop an imaging modality that enables mapping of the local LS and measuring of LS functionality.
TA3: Prevention, Prediction & Diagnostic Confirmation – *through genetics, epigenetics, and models of lymphatic dysfunction*	• Genetics /epigenetics inform early diagnosis, prediction, targeted therapies, treatment response, and in combination with biomarkers and imaging confirms diagnosis. • Identification of new genetic variants strongly associated with LD. • Novel approaches and initiation of consortiums to identify genetic variants in patient samples. • Create a model of LD that represents greater physiological relevance to the human LS - to accelerate the development of novel diagnostic tools or interventions.
Tissue Bed and Disease Model Selection	• Performers will have developed a suite of diagnostic tools that allows for a more nuanced and comprehensive understanding of underlying disease mechanisms, differential diagnosis approaches and development of targeted therapeutic strategies. • Tools developed will be reliable, accessible, and affordable for assessing lymphatic structure and function in at least one tissue bed and/or for a specific LD. • Additionally, performers must translate their diagnostic tool to at least one alternative tissue bed and/or disease model.
Leveraging Computational Intelligence and Big Data Management	• Gather and mine large databases from multiple research centers (s.a. NIH HubMAP and All of Us Initiative) to determine novel insight into lymphatic physiology and pathology. • All performers must leverage and share data in a smart and collaborative way using FAIR Data Principles (Findable, Accessible, Interoperable and Reusable). • Apply current state-of-the-art approaches to leveraging Artificial Intelligence (AI) and machine learning (ML) approaches to increase speed, efficiency, or predictiveness of the team's diagnostic technology. • Leveraging computational intelligence with imaging, genetics and biomarkers will transform the diagnosis of lymphatic dysfunction using "the rising star" in cancer detection – Radiogenomics.
Product Development and Regulatory Science	• FDA evaluated and approved diagnostic tools to assess lymphatic structure and function. • Detailed commercialization plan for translating a diagnostic tool. • Igniting a market for a comprehensive toolkit used by clinicians across the world to assist when the differential diagnosis includes lymphatic dysfunction.
Equity Requirements	Performers must adhere to all equity requirements outlined in Section 3.4.3. This includes the following key milestones: • Identify a "Discovery Duo", consisting of a patient advocate and junior investigator, to join LIGHT's equity taskforce (aka OWL EASE taskforce).

	• Adhere to the key performance indicators developed by the equity taskforce and report back to the performing team. • Adhere to feedback from LIGHT's OWL EASE taskforce.
Dissemination	Disseminate new technology, models, documents, and other findings to the public and stakeholders through appropriate collaborations with private and government organizations (i.e., patient advocacy groups, and academic institutions).
Attendance and Participation	A collaborative environment, where all members are accountable and bring value-added contributions to drive Program success (as a result of the Mandatory Attendance Policy)

3.3.1 TA1 METRICS AND OBJECTIVES

The expected metrics per phase in TA1 are listed in the table below.

TABLE 1A. TA1 METRICS

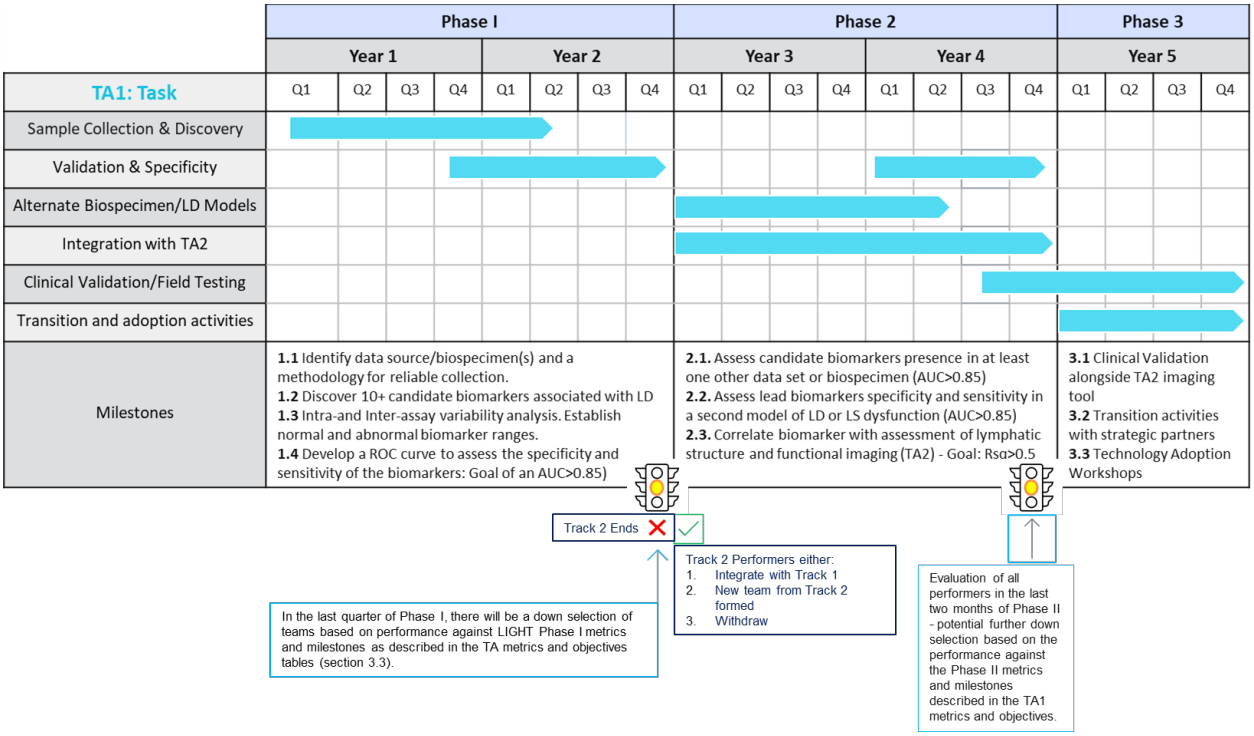
Phase I	
Sample Collection and Discovery	• Identify 10+ candidate biomarkers that are statistically correlated with LD. • Develop a methodology for reliable collection for healthy and LD samples. • Performers are strongly encouraged to gather and mine large databases from multiple research centers (i.e. patient repositories and NIH All of Us Initiative).
Validation and Standardizing	Establish normal to pathological ranges for the candidate biomarkers, as well as the most cost effective, reliable, and reproducible methodology for biomarker quantification. **Target Reproducibility:** • Minimal Acceptable Result: >90% of patients receive same diagnosis when evaluated twice in the same day. • Ideal Result: 100% of patients receive the same diagnosis when evaluated twice in the same day. **Target Stability** (for molecular and biological biomarkers): • Minimal Acceptable Result: 8hrs (20-22 ºC) / 72hrs (4-8 ºC) • Ideal Result: 72hrs (20-22 ºC) / 1 week (4-8 ºC)
Specificity and Sensitivity	Develop an ROC curve to assess the specificity and sensitivity of the biomarkers. • Minimal Acceptable Result: >1 biomarker in alternative biospecimen achieves Area Under the Curve (AUC) of **> 0.85 ± 0.05 (95% CI)** • Ideal Result: >1 biomarker with an **AUC > 0.90 ± 0.03(95%**

	CI)
Phase II	
Alternate Biospecimen Testing	Reassess biomarkers identified in Phase I in at least one additional dataset/biospecimen. • Minimal Acceptable Result: >1 biomarker in alternative biospecimen achieves **AUC > 0.85 ±0.05 (95% CI)**
Alternate Lymphatic Disease Testing	Assess candidate biomarkers expression in at least one additional model of LD. • Minimal Acceptable Result: >1 biomarker of additional LD achieves an **AUC > 0.85 ±0.05 (95% CI)**
Integration with TA2	Correlate candidate biomarkers with imaging assessment of lymphatic structure and function. • Ideal Result: **Rsq > 0.5** between at least one biomarker and one imaging based lymphatic functional metric.
Phase III	
Clinical Validation	• Develop or participate in a patient study where the biomarker's effectiveness will be further evaluated alongside an imaging technology in TA2. • Demonstrate that efficacy and accuracy in, matches or exceed Phase I/II metrics in patient study. Earliest Clinical Detection (in comparison to reference test): Minimal Acceptable Result: Detection following initial reporting of symptoms. Ideal Result: Pre-clinical detection of lymphatic dysfunction
Transition and Adoption	• Successfully transition to the clinic or larger commercial entities. • Develop workshops and showcases of technology for key stakeholders.

Scope and Equity Targets		
Product Target	**Minimal Acceptable Result**	**Ideal Result**
Intended Use	Detect and monitor primary lymphatic diseases (lymphedema and complex lymphatic anomalies)	Detect, monitor, and inform treatment of lymphatic dysfunction that is driving or contributing to a chronic disease.
Target User	Populations with primary lymphatic disease (performers must be able to accurately detect lymphatic disease in the presence of comorbid conditions and differentiate lymphatic disease from other	Populations with primary lymphatic diseases and general lymphatic dysfunction

	comorbid conditions).	
Accessibility	Results in ≤ 1 week	Results in ≤ 3 days
Affordability	<$100 to customer	Full coverage by healthcare insurance

TABLE 1B. TA1 MILESTONES & TIMELINE



3.3.2 TA2 METRICS AND OBJECTIVES

The expected metrics per phase in TA2 are listed in the table below.
Specific metrics for potential approaches are identified in the table below with the following designated letters:

A. Imaging tracer or contrast agent development and delivery
B. Combining multiple imaging modalities
C. Advancement of non-invasive imaging technology

Table 2A. TA2 Metrics

Phase I	
Selection and Development	Outline a specific LD and/or tissue bed that your solution is optimized for. Demonstrate that your approach will achieve or exceed at least 5 of the six metrics: • Minimal Acceptable Result: 1. Field of view (FOV) >12cm x 12cm 2. Spatial resolution: <1.0mm 3. Temporal resolution >1 scan of FOV/min

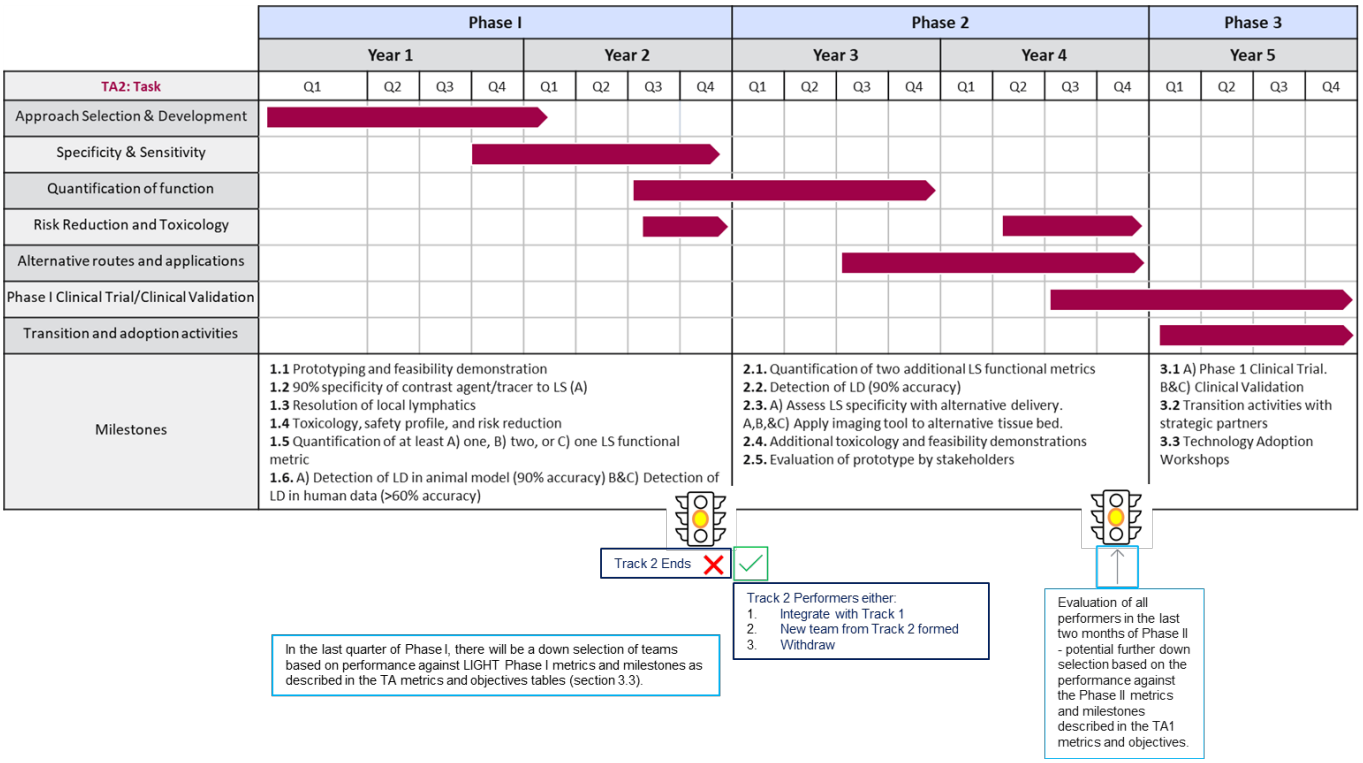
	4. Depth of imaging >2.0cm 5. Total procedure time <2 hours 6. Affordability <$1,200 per scan (cost to patient) • <u>Ideal Result:</u> 1. Field of view (FOV) > 1m x 15cm 2. Spatial resolution: <100µm 3. Temporal resolution >20 scans of FOV/min 4. Depth of imaging >6cm 5. Total procedure time <30 minutes 6. Affordability <$500 per scan (cost to patient)
Specificity and Sensitivity	Month 9 to 12: Submit project work record - demonstrate maintenance of a design history file (DHF) demonstrating capability of imaging LS >90% of patients, 90% specificity to the LS. <u>Minimal Acceptable Result:</u> A. Detection of LD with ≥ 90% accuracy in small animal models. B. Detection of LD with ≥ 80% accuracy in small animal models or ≥ 60% accuracy in human data. C. Detection of LD with ≥ 60% accuracy in human data.
Initial Performance Test	Resolution of LS anatomical structure in a tissue bed (in alignment with development targets above). Additionally, performers must develop imaging-based functional metrics (i.e. imaging biomarkers): A. At least 1 functional metrics of the LS B. At least 2 functional metrics of the LS C. At least 1 functional metrics of the LS Functional metrics for the LS include, but are not limited to: Lymph generation rate, transport rate to thoracic duct, vessel permeability, luminal pressure, flow rate, contractility, valve competence. Functional metrics must correlate with a performer determined reference (Target: r > 0.7)
Phase II	
Quantification of function	Quantification of at least two additional imaging-based functional metrics. <u>Minimal Acceptable Result:</u> Imaging based functional metrics should be correlated with LD state with a sensitivity of 75% and specificity of 90% in initial models.
Risk Reduction	Evaluate and mitigate barriers to adoption: Affordability, ease of use and integration into clinical workflow, size. If appropriate, further validate AI/ML approaches used for detection or functional measurement with additional testing and training sets. Additionally: A. Toxicology and PK/PD studies.
Alternative Strategies	Implement the imaging tool in an alternative tissue bed or LD to assess efficacy and universality of approach.

	Performance targets should align with the Phase I development goals for the six performance categories outlined. Additionally: A. Assess efficacy of a secondary delivery method to target the LS in the Phase I tissue bed.
Organ/Tissue Targeting	Minimal Acceptable Result: ≥ 2 organs/tissues Ideal Result: ≥ All organs / whole body
Performance Test	Detection of LD, or lymphatic associated tissue disease, with >**95%** accuracy in a large animal model or human data (in combination with diagnostic tools from TA1 and TA3)
Phase III	
Clinical Trial or Clinical Validation	Develop or participate in a phase I clinical trial (A) or patient study for clinical validation (B & C). Validate efficacy and accuracy in patient study.
Transition and Adoption	Successfully transition to the clinic or larger commercial entities. Develop workshops and showcases of technology for key stakeholders.

Scope and Equity Targets: Imaging Technology		
Product Target	**Minimal Acceptable Result**	**Ideal Result**
Intended Use	Detect and monitor primary lymphatic diseases (lymphedema and complex lymphatic anomalies)	Detect, monitor, and inform treatment of lymphatic dysfunction that is driving or contributing to disease.
Target User	Populations with primary lymphatic disease (i.e., ability to accurately detect LD in the presence of comorbid conditions and differentiate LD from other comorbid conditions).	Populations with primary lymphatic diseases and general lymphatic dysfunction.
Safety	Radiation Limit: <15mSV	No radiation
Accessibility	Available for use in suburban community hospitals	Available for use in rural and underserved hospitals.
Affordability	<$1200 per scan	Patient cost <$500 per scan
Ease of Use	Requires minimal training (<2 days of instruction for mastery)	No anesthesia <8 hours of instruction for mastery.

Scope and Equity Targets: Imaging-Based Metrics of Lymphatic Function		
Product Target	**Minimal Acceptable Result**	**Ideal Result**
Intended Use	Detect and quantify at least 3 distinct features of lymphatic vascular function and lymph flow	Detect and quantify at least 6 distinct features of lymphatic vascular function and lymph flow
Accessibility	Available as a free to use plug-in for the imaging technology.	Integrated into the imaging technology's software.

TABLE 2B. TA2 MILESTONES & TIMELINE



3.3.3 TA3 METRICS AND OBJECTIVES

The expected metrics per phase in TA3 are listed in the table below.

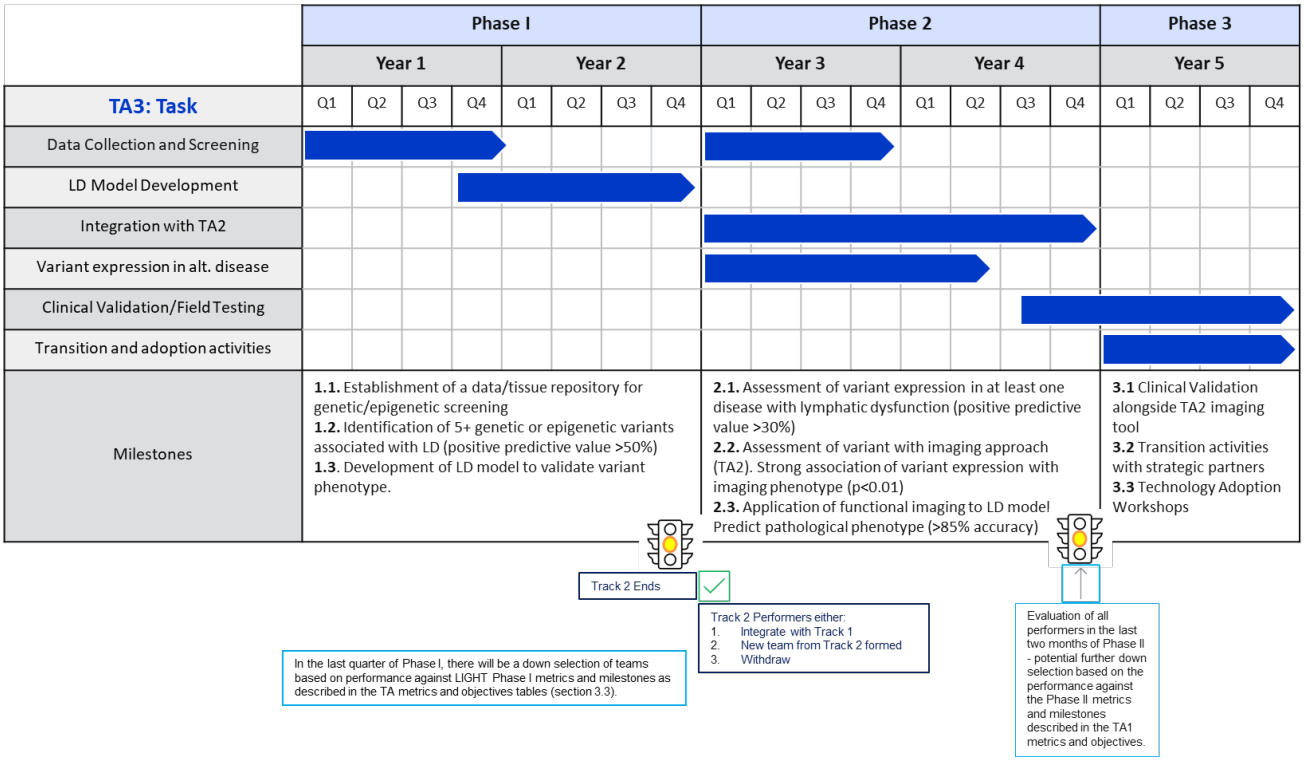
Table 3A. TA3 Metrics

Phase I	
Data Collection and Screening	• Establish and/or screen large scale genotyping datasets and tissue repositories to identify **5+** novel genetic and epigenetic variants associated with lymphatic disease and dysfunction. • Performers are strongly encouraged to gather and mine large databases from multiple research centers (i.e. NIH HubMAP and All of Us Initiative).
Application of novel genotyping or detection approaches	Apply novel approaches to sequencing or detecting variants associated with LD or dysfunction (ex. AI-powered genomic analysis). Minimally Acceptable Result:

	Positive predictive value >50%. Ideal Result: Positive predictive value > 70%
LD Model Development	Based on identified genetic or epigenetic variants of interest, develop an *in-vitro*, *ex-vivo*, or *in-vivo* model of LD that mimics all key aspects of the disease state.
Phase II	
Integration with TA2	Correlate genetic or epigenetic phenotype with imaging features or imaging-based functional metrics Minimally Acceptable Result: **$p \leq 0.01$** Ideal Result: **$p \leq 0.001$** Imaging approach must detect pathological phenotype in LD model. Minimally Acceptable Result: Diagnostic Accuracy>85% Ideal Result: Diagnostic Accuracy>95%
Alternate Disease Testing	Explore the expression of genetic variants associated with lymphatic disease or dysfunction in at least one model of chronic disease with lymphatic dysfunction (IBD, obesity, Alzheimer's Disease, etc.). Minimally Acceptable Result: Positive predictive value > 30% Ideal Result: Positive predictive value >50%
Process Optimization	Optimize protocol for patient sample collection and storage for genetic testing.
Phase III	
Clinical Validation	• Develop or participate in a patient study where the patient genotype is assessed in a patient dataset alongside the lymphatic imaging approach developed in TA2. • Validate efficacy and accuracy in patient study.
Transition and Adoption	• Successfully transition to the clinic or larger commercial entities.

	• Develop workshops and showcases of technology for key stakeholders.	
Scope and Equity Targets		
Product Target	**Minimal Acceptable Result**	**Ideal Result**
Intended Use	• Predicts likelihood of lymphatic dysfunction (Early Diagnosis and Prevention) • Informs incidence of LD • In combination with biomarkers and imaging – confirms diagnosis	Detects candidates for gene therapies or targeted therapeutics to improve lymphatic dysfunction
Target User	• Populations with primary lymphatic disease (i.e., able to accurately detect lymphatic disease in the presence of comorbid conditions and differentiate lymphatic disease from other comorbid conditions).	• Populations with primary lymphatic diseases and general lymphatic dysfunction • Detection of early lymphatic dysfunction in those with chronic common diseases.
Safety & Accessibility	Requires minimally invasive tissue samples	Available via saliva, blood or other less, or non-invasive samples
Affordability	Total cost <$4000.00	Total Cost <$1000.00

TABLE 3B. TA3 MILESTONES & TIMELINE



3.3.4 TECHNICAL REQUIREMENTS FOR ALL PERFORMERS

Phase I	
Tissue Bed and Disease Model Selection	Proposals should clearly articulate their fit for a specific tissue bed, biospecimen, or in the context of a specific lymphatic related disease. Brain-related lymphatics (i.e. meningeal lymphatics and glymphatics) are excluded from this solicitation. While proposals must display a strong fit for a specific use case, approaches with potential for cross-tissue utility will be preferred.
Leveraging Computational Intelligence and Big Data Management	1. Demonstrate usage of AI/ML approaches to enhance discovery, detection, categorization, or processing of data for the diagnostic tool. 2. Documented buy-in/approvals from key privacy and regulatory stakeholders. 3. Pilot demonstration with initial data cohort. 4. Submit initial database/warehouse/data lake design and plans for collaboration.

	5. Identification of scalability metrics (latency requirements, query rates/sec (QPS) limits).
Product Development and Regulatory Science	Performers are encouraged to include costs of regulatory and reimbursement consultations. By month 18, performers must produce a commercialization plan (≤8 pages) outlining the topics below: 1. Detailed SOW plan for concept prototype listing schedule, key risks to be retired, proof points, legal/regulatory/privacy hurdles, personnel required, key suppliers, key performance metrics. 2. Set clear IP guidelines for intellectual property and licensing agreements by the end of Phase I. 3. Complete a wide landscape analysis of competing technologies, market size, and potential investors (private or governmental organizations) 4. Functional early prototype of device or pilot data of approach.
Phase II	
Tissue Bed and Disease Model Selection	Technologies and approaches developed in Phase I must be tested in one or more disease models with pre-clinical relevance that will enable regulatory and coverage approval for use in humans. Performers are required to adjust their model selection based on the outcomes of the Product Development and Regulatory Science consultations to improve clinical relevance. Additionally, performers must explore a second tissue bed, biospecimen, or lymphatic disease as a use case for the developed technology or approach.
Leveraging Computational Intelligence and Big Data Management	1. Progress metrics on data acquisition. 2. Optimized data warehouse design. 3. Performance report on scalability metrics. 4. Detailed permissions and access workflows implemented. 5. Use/application demonstrations proving that approach is clinically user friendly with appropriate accuracy and reproducibility. 6. Utilize AI/ML to determine specific patterns of abnormal anatomy, flow or function and dysfunction of the LS across TAs.

	7. Provide external validity from objective third party.
Product Development and Regulatory Science	1. Entry into appropriate FDA regulatory programs and processes 2. Ongoing progress metrics against schedule, risks, proof points, legal/regulatory/privacy performance. 3. Verification and validation of prototype system design. 4. Safety analysis and detailed review of all risk mitigation plans. 5. Submit evidence that the protype helps advance imaging capabilities of 1 or more of the lymphatic subsystems. 6. Complete IRB and all regulatory processes to begin clinical validation by the start of Phase III.
Phase III	
Tissue Bed and Disease Model Selection	Demonstrate technology in human patient study for optimal tissue bed, biospecimen, and/or lymphatic disease.
Leveraging Computational Intelligence and Big Data Management	1. Final progress report on data warehouse size and scope. (i.e., Identify 150 centers w each treating ≥100 LD pts/year. 2. Initial and ongoing usage reports. 3. Proposal due for 30% use expansion including documentation, education, and broader integration, with other public databases. 4. Proposal due for future data cohort expansion.
Product Development and Regulatory Science	1. Final detailed demonstration of deliverable system. 2. Final cost and scalability assessment 3. Evaluation by potential stakeholders including providers, patients, and scientists. 4. Final safety and effectiveness report. Demonstrate efforts for collaboration – encourage this between academia, industry, and government to ensure there is ongoing support for research projects + facilitate sharing of knowledge and resources into the future.

3.4 GENERAL REQUIREMENTS

3.4.1 PROPOSING TEAMS

Proposals are expected to involve teams with the expertise needed to collectively achieve the goals of the proposed TA(s) specific content. Communications, networking, and team formation are the sole responsibility of the proposer. Proposers must submit a single, integrated proposal led by a Principal Investigator (PI), under a single prime awardee that addresses all program phases, as applicable.

Proposers may only submit one proposal as the prime proposer. Investigators may serve as the Principal Investigator under a single Prime proposal. Investigators may participate in multiple proposals within a sub-proposer/sub-awardee. If an entity, proposed as a sub-awardee, is part of multiple successful teams (i.e., award recipients), the Government may establish Associate Contractor Agreements (ACAs) with the applicable prime awardees. The requirement for an ACA will be dependent on the types of services/supplies provided by the sub-awardee, and the specific terms and conditions will be negotiated for each award (e.g., depending on the circumstances, subperformers may not receive

compensation in the form of ARPA-H funding for the same services more than once).

Additionally, an institution/organization can only submit one full proposal as a Prime. In terms of a university with multiple departments or a private or non-profit organization with multiple departments or divisions, each division/department may be counted as an institution who is eligible to submit a full proposal as the Prime proposer. Multiple solution summaries may be submitted from the same department/division but regardless of how many are encouraged, the department/division can only select one Solution to be submitted as a full proposal.

At minimum, each Performer Team must include the following individuals:

- **Lead Principal Investigator (PI)**
  The lead PI is responsible for overseeing and directing the project design, implementation, and reporting of results. Further the PI is responsible for organizing the entire performer team and ensuring compliance with LIGHT requirements.
- **Project Manager** (*Track One only, Optional for Track Two*)
  Track One performers must include a Project Manager who coordinates efforts across the team, ensuring compliance to timelines and programmatic goals. The Project Manager will assist the lead PI in day-to-day project operations and execution as well as financial management and reporting.
- **Product Development Lead (PDL)**
  The Product Development Lead is a co-investigator with the background necessary to manage the commercialization and regulatory efforts. This includes oversight of the "product development team"; regulatory, reimbursement, and commercialization experts who can act as either consultants or subcontractors. While the Government may offer to augment the proposers' team with additional commercialization experts post award (e.g., Regulatory Consultants), the Proposer must propose a team capable of meeting LIGHT's translational/commercialization goals.
- **Discovery Duo Program**
  The Discovery Duo program is designed to further engage the patient community in our research efforts by pairing a patient or parent ambassador with an early-stage scientific investigator who is within the first 10 years of receiving their doctoral degree. The early-stage investigator is designated as the performer's Justice, Equity, Diversity, and Inclusion (JEDI) representative for the performing team. The background or expertise of the Discovery Duo should align with the technology and disease area of the performing team's proposal. Discovery Duos will work directly with the lead PI and PDL, who in turn will provide oversight and guidance.

  The goal of the Discovery Duo program is to center the "patient experience", encouraging researchers and clinicians to be advocates for lymphatic disease and empowering patients and patient ambassadors with a better understanding of the research process. The partnership will bidirectionally inform and motivate each other while engaging the patient community exposing researchers and clinicians to those who live with lymphatic disease and allowing the patient and/or parent to learn about the day in a life of a researcher.

  As key members of LIGHT's equity taskforce (see Section 3.4.2), the Discovery Duo will help to ensure that affordability, accessibility, and user experience is centered in the program. These Duos are tasked with conducting patient centered customer discovery, which should include meetings with specialized hospital settings, patient advocacy organizations, medical

associations, and more. Each Duo is responsible for outlining their own approach and timeline to complete at least 50 meetings with these organizations and groups by the end of Phase I in preparation for the Equity Workshop in Phase II. Ultimately, Discovery Duos will integrate their findings into their program's structure through direct involvement in the study review, ensuring accessibility, affordability of new technologies, equity, data sharing, and informed consent in clinical trials. The proposals must allocate funding for both members of the Discovery Duo and to include expenses related to these efforts (such as travel expenses) in the program budget. LIGHT requires this stipend to be, at minimum, $2,500/each per year of the Period of Performance (i.e., minimum of $5,000 per Duo).

3.4.2 LIGHT PROGRAM MEETINGS AND ATTENDANCE

- **Monthly Status Reports (MSR) with Program Manager/LIGHT Team** – Each team lead performer and project manager (if team has one) will be required to meet with the PM/LIGHT Team monthly (estimated as 1hr each meeting) for an update and review (e.g., Project metrics and progress).

- **Meeting of the Minds (M&M)** – In an effort to promote collaboration and learnings from all, the lead PI, Discovery Duo, Product Development Lead (PDL), and the Project Manager from each performer team must meet semiannually throughout the LIGHT program at a virtual Meeting of the Minds (M&M) where discovery and technology will be discussed among all performers of the LIGHT program. Additional members of each performing team are welcome to join M&M.

- **LIGHT's Innovative Technology Workshop** – In the final months of Phase I (at ~ 21 months), LIGHT will host an Internal Tech workshop - *Lympho Sphere: Exploring Diagnostic Innovations.* This will be an in-person workshop (site TBD) where all performers will present progress and updates on their technology and will have the opportunity to meet FDA, NIH, and DoD representatives. Further, this workshop will act as an opportunity for those in Track Two to either integrate into Track One or form their own team among performing teams in Track Two.

- **The Equity Taskforce Meetings and Workshop**
  The *Officials Watching over Lymphatics to establish Equity, Advocacy, and Stakeholder Education - OWL EASE Taskforce* will meet within the first quarter of each of the three phases. The meeting will be mandatory for the lead PI, Discovery Duos, the PDL, and the project manager of each performer. The findings from the Equity Taskforce Meetings will inform the Equity Taskforce Workshop.

  During the first 12 months of Phase II, the Equity Taskforce will hold an Equity Workshop to establish Key Performer Indicators (KPIs) and to which all performers will be invited to attend to share the findings from the Equity Taskforce Meetings.

- **Attendance**
  Attendance at all meetings will be recorded and is expected to be no less than 90% of the mandatory performer attendees annually. The 90% mandatory attendance policy will establish accountability and encourage a collaborative LIGHT ecosystem to support overall Program success.

3.4.3 DIVERSITY IN CLINICAL TRIAL POPULATIONS FOR LIGHT PHASE III

While following the guidelines outlined by FDA on clinical trials, ARPA-H is also committed to equitable healthcare access irrespective of race, ethnicity, gender/gender identity, sexual orientation, disability, geography, employment, insurance, and socioeconomic status. Lymphatic dysfunction does not discriminate by age, sex, gender, socioeconomic status, religion, or ethnicity. LIGHT will ensure that all performers follow the FDA's guidance titled "Diversity Plans to Improve Enrollment of Participants from Underrepresented Racial and Ethnic Populations in Clinical Trials" and that Phase I clinical trial participants mirror the proportions of the US population that suffers from the specified primary lymphatic disease or the chronic condition with an underlying lymphatic dysfunction (±5%).

3.4.4 EQUITY REQUIREMENTS

Lymphatic disease spares no one and knows no borders. LIGHT will ask lead PIs from each team to prioritize diversity, adopting intentional inclusion practices, addressing systemic inequities, and ensuring a wide range of voices within core research teams. ARPA-H is committed to equity inclusive of diverse and underrepresented scientists, clinicians, students, and patients. In an intentional effort to build capacity for research/innovation among underrepresented communities, LIGHT performers are highly encouraged to involve qualified junior investigators, graduate students and undergraduates inviting them as team members or offering research opportunities that they may not otherwise have to explore the field of lymphatic medicine. Such creative solutions may include – availability of scholarships, internships, and stipends for summer projects.

Further, ARPA-H is committed to equitable health care access irrespective of race, ethnicity, gender/gender identify, sexual orientation, disability, geography, employment, insurance, and socioeconomic status. ARPA-H will review all proposals, and performers throughout the program, to ensure that metrics and milestones prioritize end-user needs regarding equity, affordability, and accessibility.

***Overview of Equity Responsibilities as a LIGHT performer*:**
All proposers must describe how they will engage specific stakeholder groups (e.g., patients and community organizations) to maximize health equity. **All performers must articulate how they will incorporate equity considerations** (e.g., diverse user demographics) into design, development, and testing of prototypes to ensure equal access and mitigation of bias.

Performers who may collect patient data in support of research deliverables must collect data elements that enable assessment of health equity and disparity indices (e.g., race, ethnicity, sex, foreign-born, rural, and other demographic data). **Performers must designate one Discovery Duo members (preferably an early investigator or postdoctoral student) as the primary point of contact for equity activities** and considerations, then remain responsive to communication and coordination with LIGHT's team.

Performers involved in the handling of personalized and/or identified demographics or health data must ensure appropriate privacy and security standards are met. All proposers should outline anticipated risks and potential ramifications of not meeting equity goals. The Equity Officer (EO) will be involved in reviewing all milestone reports and evaluations and will advise on how equity issues can be strengthened throughout the program.

LIGHT Equity Taskforce

The LIGHT program will develop the *Officials Watching over Lymphatics to establish Equity, Advocacy, and Stakeholder Education (OWL EASE) Taskforce*. Under the guidance of expertise from ARPA-H, each performer team's Discovery Duo and PDL must serve as members on the OWL EASE Taskforce. Performers can recommend additional members, such as community hospital administrators or representatives of patient advocacy organizations, to join the taskforce with PM approval.

The OWL EASE Taskforce's mission will be to ensure equity, diversity, inclusion, and justice in the form of accessibility and affordability as well as advocacy and stakeholder education among all teams under LIGHT.

Responsibilities of Taskforce:

- Attend PM team meetings, workshops, participate in "Patient Voice Sessions".
- Advocate for insurance, accessibility, clinical trial equity and central data sharing.
- Work with the Customer Experience Network and Investor Catalyst Network Hubs providing a patient perspective.
- Hold an Equity symposium in collaboration with LIGHT, within the first 12 months of Phase II.
    - **Goal** -Define equity Key Performance Indicators (KPI's) for the taskforce. Resulting in a Road Map to Equity report.
    - Disseminate Road Map to Equity Report across the United States (i.e., hospitals, clinics, patient advocacy organizations, CMS, CDC, NIH and the National Lymphatic Commission, private insurers, FDA, Centers of Excellence, professional societies).

Stakeholder Education and Dissemination

Each PI is required to give at least one lecture centered on lymphatics per year during the LIGHT program. The lectures should be directed to either a medical school, graduate, undergraduate school audience (preferably of underserved or rural academic centers) and/or patient advocacy group or professional society. Further, LIGHT will encourage collaborative efforts of the performer teams with the ARPANET-H hub and spoke system. This may include formative user studies offering a diverse array of stakeholders, customer discovery to inform product design and patient voice sessions including interactions with the FDA to include patient-led research.

The interactions and communications of the performing teams with various professional societies, advocacy groups and students will strengthen and intentionally build formative educational opportunities, and capacity among the lymphatic community engaging all stakeholder and consumer communities and therefore yielding more inclusive technologies and management of disease.

4. SOLUTION SUMMARY AND PROPOSAL PREPARATION AND SUBMISSION INFORMATION

4.1 SOLUTION SUMMARY PREPARATION INSTRUCTIONS

Solution Summary submissions are required. See Appendix A for the recommended format.

4.2 SOLUTION SUMMARY AND PROPOSAL SUBMISSION INFORMATION

NOTE: Non-conforming submissions that do not follow ISO instructions may be rejected without

further review at any stage of the process.

All solution summaries and proposals submitted in response to this solicitation must be written in English and must be consistent with the content and formatting requirements of Appendix A (Solution Summary Format and Instructions) and Appendix B (Full Proposal Format and Instructions).

All solution summaries and full proposals shall be submitted via the ARPA-H Solution Submission Portal[1].

4.3 SOLUTION SUMMARY AND PROPOSAL SUBMISSION DEADLINES

The closing date of this solicitation, as established in Section 1, is the date Solution Summaries are due.

The full proposal submission deadline will be provided to proposers at the time of Solution Summary feedback (i.e., encourage/discourage submission of full proposal). See Appendix B (Full Proposal Format and Instructions) for the recommended full proposal format. Proposal packages must include Volumes I-III. To emphasize, whether the Government encourages or discourages submission of a full proposal, proposers must have submitted a Solution Summary to be eligible to submit a full proposal.

4.4 PROPRIETARY INFORMATION

Proposers are responsible for clearly identifying proprietary information. Submissions containing proprietary information must have the cover page and each page containing such information clearly marked with a label such as "Proprietary."

NOTE: "Confidential" is a classification marking used to control the dissemination of U.S. Government National Security Information as dictated in Executive Order 13526 and should not be used to identify proprietary business information.

5. SOLTUION SUMMARY REVIEW AND EVALUATION OF FULL PROPOSALS

5.1 CONFORMING SOLUTION SUMMARY AND PROPOSAL SUBMISSIONS

Conforming submissions contain all requirements detailed in this ISO. Solution summaries or full proposals that fail to include required information will be deemed non-conforming and may be removed from further consideration. A solution summary or proposal will be deemed non-conforming under this ISO if it fails to meet one or more of the following solicitation requirements:

- The proposed concept is applicable to the LIGHT Program.
- The proposers meet the eligibility requirements.
- The solution summary/proposal meet the submission requirements.
- The solution summary/proposal meet the content and formatting requirements in the attached instructions.
- The proposer's concept has not already received funding or been selected for award negotiations for another funding opportunity (whether from ARPA-H or another Government agency)

[1] The ARPA-H Solution Submission Portal requires user registration to submit solution summaries and proposals (https://solutions.arpa-h.gov/).

Non-conforming solution summary and proposal submissions may be removed from consideration. Proposers will be notified of non-conforming determinations via email correspondence.

5.2 SOLUTION SUMMARY REVIEW PROCESS

ARPA-H will review and respond to all proposers submitting solution summaries**.** At a minimum the response will indicate whether a proposer is encouraged or discouraged from submitting a full proposal. Feedback will be provided to the administrative and technical points of contacts noted on the solution summary cover page.

5.3 FULL PROPOSAL EVALUATION CRITERIA FOR AWARD

All full proposals will be evaluated using the following evaluation criteria, listed in descending order of importance, except as described below in Section 5.4.2.

5.3.1 CRITERIA 1: OVERALL SCIENTIFIC AND TECHNICAL MERIT

The proposed technical approach is innovative, feasible, and complete. Task descriptions and associated technical elements provided are complete and in a logical sequence with all proposed deliverables clearly defined such that a final outcome that achieves the goal can be expected as a result of the award. The proposal identifies major technical risks and planned mitigation efforts are clearly defined and feasible. In addition, the evaluation may take into consideration the extent to which the proposed intellectual property (IP) rights structure will potentially impact the Government's ability to transition technology.

5.3.2 CRITERIA 2: PROPOSER'S CAPABILITIES AND/OR RELATED EXPERIENCE

Factors considered may include: the proposed technical team has the expertise and experience to accomplish the proposed tasks; the proposer's prior experience in similar efforts clearly demonstrates an ability to deliver products that meet the proposed technical performance within the proposed budget and schedule; the proposed team has the expertise to manage the cost and schedule and; similar efforts completed/ongoing by the proposer in this area are fully described, including identification of other Government entities.

5.3.3 CRITERIA 3: PRICE ANALYSIS

Proposals will be evaluated to determine the reasonableness of the estimated budget proposed to accomplish the work in the SOW. Cost realism analysis may be performed to ensure proposed costs are realistic for the technical and management approach, accurately reflect the technical goals and objectives of the solicitation, the proposed costs are consistent with the proposer's Scope of Work and reflect a sufficient understanding of the costs and level of effort needed to successfully accomplish the proposed technical approach. The costs for the prime proposer and proposed subawardees should be substantiated by the details provided in the proposal (e.g., the type and number of labor hours proposed per task, the types and quantities of materials, equipment and fabrication costs, travel and any other applicable costs including the basis for the estimates).

It is expected the effort will leverage all available relevant prior research to obtain the maximum benefit from the available funding. For efforts with a likelihood of commercial application, appropriate direct cost sharing may be a positive factor in the evaluation. As noted in Section 3.2, ARPA-H recognizes that undue emphasis on cost may motivate proposers to offer low-risk ideas with minimum uncertainty and to staff the effort with junior personnel in order to assume a more competitive posture. ARPA-H discourages such cost strategies.

5.4 REVIEW, EVALUATION, AND SELECTION PROCESS

It is the policy of ARPA-H to ensure impartial, equitable, comprehensive evaluations based on the evaluation criteria listed above, and to select the proposals whose solutions are most advantageous to the Government.

ARPA-H will conduct a scientific and technical review of each conforming solution summary. ARPA-H will evaluate each eligible and conforming full proposal based solely on the evaluation criteria.

NOTE: Solution Summaries will be reviewed based on their own individual merit and not compared with other submissions. Proposals will not be evaluated against each other during the scientific review process, but rather evaluated on their own individual merit to determine how well the submission meets the criteria stated in this ISO.

5.4.1 SELECTABLE OR NON-SELECTABLE DETERMINATION

A selection for award negotiations will be made to proposers whose proposal is determined to be most advantageous by the Government. For the purposes of this solicitation, selectable and non-selectable are defined as follows:

SELECTABLE: A selectable proposal is a proposal that has been evaluated by the Government against the evaluation criteria listed in this ISO, and the positive aspects of the overall proposal outweigh its negative aspects.

NON-SELECTABLE: A proposal is considered non-selectable when the proposal has been evaluated by the Government against the evaluation criteria listed in this ISO, and the positive aspects of the overall proposal do not outweigh its negative aspects.

5.4.2 NON-SELECTABLE CRITERION 1 SOLUTIONS

Should a full proposal be evaluated as non-selectable related to Criterion 1, the Government may not evaluate Criteria 2 and 3.

5.4.3 REVIEW AND EVALUATION TIMELINES

ARPA-H's intent is to review solution summaries and proposals as soon as possible after they arrive.

5.5 HANDLING OF COMPETITIVE SENSITIVE INFORMATION

It is the policy of ARPA-H to protect all solution summaries and proposals as competitive sensitive information and to disclose their contents only for the purpose of evaluation and/or only to screened personnel for authorized reasons, to the extent permitted under applicable laws. Restrictive notices notwithstanding, during the evaluation process, submissions may be handled by ARPA-H support contractors for administrative purposes and/or to assist with technical evaluation.

All ARPA-H support contractors are expressly prohibited from performing ARPA-H sponsored technical research and are bound by appropriate nondisclosure agreements. Input on technical aspects of the solution summaries and proposals may be solicited by ARPA-H from non-Government consultants/experts who are strictly bound by appropriate non-disclosure requirements. No submissions will be returned.

6. POLICY REQUIREMENTS AND AWARD ADMINISTRATION INFORMATION

6.1.1 INTELLECTUAL PROPERTY

Proposers must provide a good faith representation that the proposer either owns or possesses the appropriate licensing rights to all intellectual property (IP) that will be utilized for the proposed effort. ARPA-H strongly encourages IP rights to be aligned with open-source regimes. Further, it is desired that all non-commercial software (including source code), software documentation, and technical data generated and/or developed under the proposed project is provided as a deliverable to the Government. IP delivered to the Government should align with project or program goals and should be aligned with the level of Government funding provided to generate and/or develop the IP.

NOTE: IP rights assertions will be reviewed under evaluation criterion 1 stated in Section 5.3.1.

6.1.2 HUMAN SUBJECTS RESEARCH

All entities submitting a proposal for funding that will involve engagement in human subjects research (as defined in 45 CFR § 46) must provide documentation of one or more current Assurance of Compliance with federal regulations for human subjects protection, including at least a Department of Health and Human Services (HHS), Office of Human Research Protection Federal Wide Assurance. All human subjects research must be reviewed and approved by an Institutional Review Board (IRB), as applicable under 45 CFR § 46 and/or 21 CFR § 56. The entities human subjects research protocol must include a detailed description of the research plan, study population, risks and benefits of study participation, recruitment and consent process, data collection, and data analysis. Recipients of ARPA-H funding must comply with all applicable laws, regulations, and policies for the ARPA-H funded work. This includes, but is not limited to, laws, regulations, and policies regarding the conduct of human subjects research, such as the U.S. federal regulations protecting human subjects in research (e.g., 45 CFR § 46, 21 CFR § 50, § 56, § 312, § 812) and any other equivalent requirements of the applicable jurisdiction.

The informed consent document utilized in human subjects research funded by ARPA-H must comply with all applicable laws, regulations, and policies, including but not limited to U.S. federal regulations protecting human subjects in research (45 CFR § 46, and, as applicable, 21 CFR § 50). The protocol package submitted to the IRB must contain evidence of completion of appropriate human subjects research training by all investigators and key personnel who will be involved in the design or conduct of the ARPA-H funded human subjects research. Funding cannot be used toward human subjects research until ALL approvals are granted.

6.1.3 ANIMAL SUBJECTS RESEARCH

All entities submitting a proposal for funding that will involve engagement in animal subjects research (Award recipients performing research, experimentation, or testing involving the use of animals) must comply with the laws, regulations, and policies on animal acquisition, transport, care, handling, and use as outlined in: (i) 9 CFR parts 1-4, U.S. Department of Agriculture rules that implement the Animal Welfare Act of 1966, as amended, (7 U.S.C. § 2131-2159); (ii) the Public Health Service Policy on Humane Care and Use of Laboratory Animals, which incorporates the "U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training," and "Guide for the Care and Use of Laboratory Animals" (8th Edition)."

Proposers must provide documentation of a current Animal Welfare Assurance (AWA) on file with the Office of Laboratory Animal Welfare (OLAW).

Proposers must complete and submit the Vertebrate Animal Section (VAS) for all proposed research anticipating Animal Subject Research. A guide for completing the VAS can be found at https://olaw.nih.gov/sites/default/files/VASchecklist.pdf worksheet for all proposed research anticipating Animal Subject Research.

All Animal Use Research must undergo review and approval by the local Institutional Animal Care Use Committee (IACUC) prior to incurring any costs related to the animal use research. For all proposed research anticipating animal use, proposals should briefly describe plans for IACUC review and approval.

6.1.4 ELECTRONIC INVOICING AND PAYMENTS

Performers will be required to submit invoices as described in the award document.

6.1.5 GOVERNMENT-FURNISHED PROPERTY/EQUIPMENT/INFORMATION

Government-furnished property/equipment/information may be provided to selected performers. Any instances of GFP/GFE will be specifically negotiated.

7. ISO QUESTIONS AND ANSWERS

All questions regarding this ISO should be submitted to LIGHT@arpa-h.gov. ARPA-H will post Q&As to the ARPA-H ISO Website on an on-going basis. All questions must be in English and must include the name, email address, and telephone number of a point of contact.

ARPA-H will attempt to answer questions in a timely manner; however, questions submitted after the due date may not be answered.

8. OTHER INFORMATION

ARPA-H will host a Proposers' Day in support of the LIGHT Program as described in Special Notice ARPA-H-SN-24-105. The purpose is to provide potential proposers with information on the LIGHT program, promote additional discussion, and encourage team networking.

Interested proposers are not required to attend, and materials formally presented at Proposers' Day will be posted to SAM.gov.

ARPA-H will not reimburse potential proposers for participation at the Proposers' Day or time and effort related to submission of solution summaries or full proposals.

APPENDIX A: SOLUTION SUMMARY FORMAT AND INSTRUCTIONS

A. General Instructions

All solution summaries must use a font type not smaller than 11-point font. Smaller font may be used for figures, tables, and charts. Margins may be no less than one inch in width. Solution Summaries are limited to four (4) pages, exclusive of a cover page and Rough Order of Magnitude. No tables of content shall be provided. The Government may not review pages beyond four (4); and any Solution Summary submitted that exceeds four (4) pages will only be reviewed at ARPA-H's discretion.

B. Cover Page

The cover page should follow the format below. The cover page does not count towards the page limit.

Solicitation #	ARPA-H-SOL-24-102
Solution Summary Title	
Submitter Organization	
Type of Organization	**Choose all that apply:** Large Business, Small Disadvantaged Business, Other Small Business, HBCU, MI, Other Educational, or Other Nonprofit
Technical Point of Contact (POC)	Name: Mailing Address: Telephone: Email:
Administrative POC	Name: Mailing Address: Telephone: Email:
Total Estimated Budget	Total: $
Place(s) of Performance	
Other Team Members (subawardees, including consultants) if any	Technical POC Name: Organization: Organization Type:

C. Concept Summary

Describe the solution summary concept with minimal jargon and explain how it addresses the technical areas of the LIGHT program. Clearly identify the problem(s) to be solved and the outcome(s) sought with the proposed technology concept. Describe how the proposed effort represents an innovative and potentially revolutionary solution to the technological challenges outlined in LIGHT. Explain the concept's potential to be disruptive compared to existing or emerging technologies and how the proposed approach will go far beyond current commercial capabilities. To the extent possible, provide quantitative metrics in a table that compares the proposed technology concept to current and emerging technologies and includes:

- A progression of increasingly complex technical challenges.
- State of the art / emerging technology "baseline."
- Aggressive developmental metrics for each year of the program.
- Targets for the proposed technology in its final, commercializable form
    - Patient population, integration into clinical workflow, user experience, etc.

D. Proposed Work

Describe the final deliverable(s) for the project, one or two key interim milestones, and the overall technical approach used to achieve project objectives. Discuss alternative approaches considered, if any, and why the proposed approach is most appropriate for the project objectives. Describe the background, theory, simulation, modeling, experimental data, or other sound engineering and scientific practices or principles that support the proposed approach. Provide specific examples of supporting data and/or appropriate citations to scientific and technical literature. Identify adoption challenges to be overcome for the proposed technology to be successful. Describe why the proposed effort is a significant technical challenge and the key technical risks. At a minimum, the solution summary should address:

- Does the approach require one or more entirely new technical developments to succeed?
- How will technical risk be mitigated?
- What use cases and data types will be featured?

E. Team Organization and Capabilities

Indicate the roles and responsibilities of the organizations and key personnel that comprise the Project Team. Provide the name, position, and institution of each key team member and describe in 1-2 sentences the skills and experience they bring to the team.

F. Rough Order of Magnitude (ROM)

Please include a basis of estimate (BOE) to support the proposed project budget, as well as the total project cost including cost sharing, if applicable. The BOE should also include a breakdown of the work by direct labor, labor hours, subcontracts, materials, equipment, other direct costs (e.g., travel), profit, cost sharing, and any other relevant costs. The below table may be used for this breakdown:

Categories	**Phase I Amount**	**Phase II* Amount**	**Phase III* Amount**	**Total**
Direct Labor (Fully burden)				
Labor hours				
Subawardees				
Materials				
Equipment				
Travel				
Other Direct Costs				
Profit				
Total				
Cost Sharing (if applicable/appropriate)				

*Track Two proposers should only complete the Phase I column.

Proposers must ensure the BOE encompasses all applicable costs and should modify the above to best reflect the proposer's expected costs. The BOE does not count toward the page limit.

NOTE: Delete all formatting and content instructions prior to submission.

APPENDIX B: FULL PROPOSAL FORMAT AND INSTRUCTIONS

Full proposals must be in the format given below. The typical proposal should express a consolidated effort in support of one or more related technical concepts or ideas. Disjointed or unrelated efforts should not be included in a single proposal. Proposals shall consist of three volumes:

1) Volume I, Technical and Management Proposal,
2) Volume II, Cost Proposal, and
3) Volume III, Administrative and Policy Requirements Submission

Cover Pages should be no more than one (1) page in length.

The page limitation includes all figures, tables, and charts. All pages shall be formatted for printing on 8-1/2 by 11- inch paper. Margins must be 1-inch on all sides, font size should be no less than 11 pt (Arial or Times New Roman), and page numbers should be included at the bottom of each page.

Documents must be clearly labeled with the ISO number, proposer organization, and proposal title/proposal short title (in the header of each page). Use the following Title Format: "Volume I_XYZ Institution", "Volume II_XYZ Institution", "Volume II_Supporting Documents", etc.

I. Volume I, Technical and Management Proposal

The maximum page count for Volume I is thirty (30) pages. This includes sections A-E described below (Executive Summary, Goals and Impact, Technical Plan, Management Plan and Capabilities). Sections F-I below are not included in the page count (Statement of Work (SOW), Schedule and Milestones, Technology Transfer Plan, and References). However, for all sections, ARPA-H encourages conciseness to the maximum extent practicable. No other supporting materials may be submitted for review. Volume I should include the following components:

Cover Page

1. ISO number ARPA-H-SOL-24-102;
2. Technical area;
3. Proposal title;
4. Prime Awardee/entity submitting proposal;
5. Unique Entity Identifier of prime proposer/awardee (UEI)
6. Type of organization, selected among the following categories: LARGE BUSINESS, SMALL DISADVANTAGED BUSINESS, OTHER SMALL BUSINESS", Historically Black Colleges and Universities (HBCUs), Minority Institution (MI), OTHER EDUCATIONAL, OR OTHER NONPROFIT (including non-educational government entities) (NOTE: The Small Business Administration's (SBA) size standards determine whether or not a business qualifies as small.). Size standards may be found here: https://www.ecfr.gov/current/title-13/chapter-I/part-121#121.201
7. Date of submission;
8. Other team members (if applicable) and type of organization for each;
9. Technical point of contact (POC) to include: salutation, last name, first name, street address, city, state, zip code, telephone, email;
10. Administrative POC to include: salutation, last name, first name, street address, city, state, zip code, telephone, email; and

11. Total funds requested from ARPA-H, and the amount of cost share (if any).

A. **Executive Summary:** Provide a synopsis of the proposed project, including answers to the following questions:

- What is the proposed work attempting to accomplish or do?
- How is it done today, and what are the limitations?
- What is innovative in your approach?
- What are the key technical challenges in your approach, and how do you plan to overcome these?
- Who or what will be affected, and what will be the impact if the work is successful?
- How much will it cost, and how long will it take?

B**. Goals and Impact:** Clearly describe what the team is trying to achieve and the difference it will make (qualitatively and quantitatively) if successful. Provide an overview of the current and previous research and development (R&D) efforts related to the proposed research and identify any challenges associated with such efforts, including any scientific or technical barriers encountered during such efforts or challenges in securing sources of funding, as applicable. Describe the innovative aspects of the project in the context of existing capabilities and approaches, clearly delineating the uniqueness and benefits of this project in the context of the state of the art, alternative approaches, and other projects from the past and present. Describe how the proposed project is revolutionary and how it significantly rises above the current state-of-the-art. Describe the deliverables associated with the proposed project as well as how the project will integrate into existing clinical workflows and successfully improve patient care.

C. **Technical Plan:** Outline and address technical challenges inherent in the approach and possible solutions for overcoming potential problems. This section should provide appropriate measurable milestones (quantitative if possible) at intermediate stages of the program to demonstrate progress, a plan for achieving the milestones, and a simple process flow diagram of the final system concept. The technical plan should demonstrate a deep understanding of the technical challenges and present a credible (even if risky) plan to achieve the program goal. Discuss mitigation of technical risk.

D. **Management Plan:** Provide a summary of the expertise of the team, including any subawardees, and key personnel who will be doing the work. A PI for the project must be identified, along with a description of the team's organization, including the breakdown by TA. All teams are strongly encouraged to identify a Project Manager/Integrator to serve as the primary POC to communicate with the ARPA-H PM team and OT/Contracts equivalent for each award instrument (e.g., Contracting Officer), coordinate the effort across co-performer, vendor, and sub-awardee teams, organize regular performer meetings or discussions, facilitate data sharing, and ensure timely completion of milestones and deliverables. Provide a clear description of the team's organization including an organization chart that includes, as applicable: the programmatic relationship of team members; the unique capabilities of team members; the task responsibilities of team members, the teaming strategy among the team members; and key personnel with the amount of effort to be expended by each person during each year. Provide a detailed plan for coordination, including explicit guidelines for interaction

among collaborators/subawardees of the proposed effort. Include risk management approaches. Describe any formal teaming agreements required to execute this program.

E. Capabilities: Describe organizational experience in relevant subject area(s), existing intellectual property, specialized facilities, and any Government-furnished materials or information. Describe any specialized facilities to be used as part of the project, the extent of access to these facilities, and any biological containment, biosafety, and certification requirements. Discuss any work in closely related research areas and previous accomplishments.

F. Statement of Work (SOW): The SOW should provide a detailed task breakdown, citing specific tasks for each TA, and their connection to the milestones and program metrics. Each Phase of the program should be separately defined. The SOW must not include proprietary information. The SOW will not pe part of the technical evaluation.
For each task/subtask, provide:

- A detailed description of the approach to be taken to accomplish each defined task/subtask.
- Identification of the primary organization responsible for task execution (prime awardee, sub-awardee(s), by name).
- A measurable milestone, i.e., a deliverable, demonstration, or other event/activity that marks task completion. Include completion dates for all milestones. Include quantitative metrics.
- A definition of all deliverables (e.g., data, reports, software) to be provided to the Government in support of the proposed tasks/subtasks.

It is recommended the SOW be developed so that each TA and Phase of the program is separately defined.

G. Schedule and Milestones: Provide a detailed schedule showing tasks (task name, duration, work breakdown structure element as applicable, performing organization), milestones, and the interrelationships among tasks. The task structure must be consistent with that in the SOW. Measurable milestones should be clearly articulated and defined in time relative to the start of the project.

H. Commercialization Plan: Briefly outline your current understanding of your technologies target market and the size of that market. Identify 2-3 key competitive technologies operating in the market and their limitations. Outline ownership plans for existing and future IP across the team. Identify ideal partners (e.g. private industry, investors, etc), that may be pursued to secure funding, manufacturing, and marketing following the award period. Finally, identify members of the proposed team that will be responsible for development and submission of the mature commercialization plan required in Phase I of the project.

Note: The commercialization plan at this stage should be brief **(recommend NTE 4 pages).**

I. Data Management and Sharing Plan (DMSP) (recommend NTE 2 pages)
The DMSP shall include all information included in the 6-Element plan format recommended by the National Institutes of Health (to view the 6-Element suggested format visit https://grants.nih.gov/grants/forms/data-management-and-sharing-plan-format-page)

J. References: Add a list with the cited literature.

II. Volume II, Cost Proposal

There is no maximum page count for Volume II. The Cost Proposal shall be comprised of the editable Excel Cost Proposal spreadsheet and associated supporting materials, ideally provided in a single attachment (e.g., Adobe pdf) led by a Cover page as follows.

Cover Page

1. ISO number ARPA-H-SOL-24-102;
2. Technical area;
3. Prime Awardee/entity submitting proposal;
4. UEI of prime awardee/proposer:
5. Type of organization, selected among the following categories: LARGE BUSINESS, SMALL DISADVANTAGED BUSINESS, OTHER SMALL BUSINESS", Historically Black Colleges and Universities (HBCUs), Minority Institution (MI), OTHER EDUCATIONAL, OR OTHER NONPROFIT (including non-educational government entities)
6. Other team members (if applicable) and type of organization for each;
7. Proposal title;
8. Technical POC to include: salutation, last name, first name, street address, city, state, zip code, telephone, email;
9. Administrative POC to include: salutation, last name, first name, street address, city, state, zip code, telephone, and email;
10. Total proposed cost separated by base and option(s) (if any);
12. Name, address, and telephone number of the proposer's cognizant auditor (as applicable);
13. Date proposal was submitted;
14. Commercial and Government Entity (CAGE) Code;
15. Proposal validity period (Minimum of 120 days).

A. Cost Proposal Spreadsheet: ARPA-H Standard Excel Cost Proposal Spreadsheet shall be provided with all full proposals. All tabs and tables in the cost proposal spreadsheet should be developed in an editable format with calculation formulas intact to allow traceability of the cost proposal. The cost proposal spreadsheet must be used by the prime organization and all subawardees at any tier. Subawardee cost proposal spreadsheets may be submitted directly to the Government by the proposed sub-awardee via email to LIGHT@ARPA-H.gov. NOTE: Track Two proposers should only complete the Phase 1 section of the spreadsheet while Track One proposers must complete the entire spreadsheet.

B. Cost and Pricing Data Support: In addition to using the cost proposal spreadsheet, the cost proposal must include documentation to support the proposed price/budget. Supporting documentation must be in sufficient detail to substantiate the summary cost estimates and should include a description of the method used to estimate costs. For other direct costs (ODCs) (e.g., equipment, IT) with unit costs greater than $10,000, proposers must provide screenshots/quotes or other independent substantiation. For indirect costs, provide the most current indirect cost agreement (e.g., Colleges and Universities Rate Agreement, Forward Pricing Agreement, Provisional Billing Rates, etc.).

C. **Subawardee Proposals:** The awardee is responsible for compiling and providing all sub-awardee proposals with its proposal (or by ensuring direct submission to the Government from the subawardee as noted above). Subawardee proposals should include Interdivisional Work Transfer Agreements or similar arrangements between the awardee and divisions within the same organization as the awardee. All proprietary subawardee proposal documentation, prepared at the same level of detail as that required of the proposer's proposal and which cannot be uploaded with the proposer's full proposal, shall be provided to the Government either by the proposer or by the subawardee when the proposal is submitted. Subawardee proprietary proposals may be submitted directly to ARPA-H at LIGHT@ARPA-H.gov. See Section 4.2. of this ISO for Proposal Submission information.

D. **Value Analysis Supporting Information:** Respondents to the ISO should include any additional information regarding value-added resources or conditions that are not immediately obvious in the Cost Proposal Spreadsheet or the Supporting Cost and Pricing Data section (e.g., intended intellectual property terms and conditions with perceived future value).

APPENDIX C: ADMINSTRATIVE AND POLICY REQUIREMENTS

The Administrative and Policy Requirements submission must be completed in full and included as the Volume III proposal submission. Proposers must include all elements of Appendix C in their submission. All pages shall be formatted for printing on 8-1/2 by 11-inch paper with 1-inch margins and font size not smaller than 11 point. Smaller font sizes may be used for figures, tables, and charts. There is no page limit for this Volume.

The Administrative and Policy Requirements document must be in .pdf, .odx, .doc, or .docx formats.

<PRIME ORGANIZATION LOGO (OPTIONAL)>

ADMINISTRATIVE AND NATIONAL POLICY REQUIREMENTS

Proposal Title	
Proposer Organization	
Technical Point of Contact (POC)	Name: Address: Telephone: Email:
Administrative POC	Name: Address: Telephone: Email:
Date Proposal was Prepared	
Proposal Validity Period (minimum 120 days)	

TEAM MEMBER IDENTIFICATION

[Using the table below as a template, provide a list of all entities as well as specific individuals included on the Performer Team as specified in Section 3.4.1. Note: Consultants (e.g., 1099s) are considered subawardees]

PRIME				
Individual Name:	**Organization:**	Non-U.S. Organization: Non-U.S. Individual:	☐ Yes ☐ Yes	☐ No ☐ No
SUBAWARDEES, INCLUDING CONSULTANTS				
Individual Name:	**Organization:**	Non-U.S. Organization: Non-U.S. Individual:	☐ Yes ☐ Yes	☐ No ☐ No
Individual Name:	**Organization:**	Non-U.S. Organization: Non-U.S. Individual:	☐ Yes ☐ Yes	☐ No ☐ No

ORGANIZATIONAL CONFLICT OF INTEREST AFFIRMATIONS AND DISCLOSURE

a. Are any of the proposed individual team members or their respective organizations (whether prime or subawardee) currently providing support services to ARPA-H? ¨ No ¨ Yes
b. Did any of the proposed individual team members or their respective organizations (whether prime or subawardee) provide support services to ARPA-H within one calendar year of this proposal submission? ¨ No ¨ Yes

   [If you answered "Yes" to a OR b, provide the following information for each applicable team member:
   - The name of the ARPA-H office receiving the support;
   - The prime contract number;
   - Identification of proposed team member (subawardee) providing the support; and
   - An OCI mitigation plan.]

c. Are there any other potential or actual Organizational Conflicts of Interest involving any of the proposed individual team members *or* their respective organizations (whether prime or subawardee)?
   ¨ No ¨ Yes

   [If yes, provide the following information for each applicable team member:
   - Identification of applicable team member; and
   - An OCI mitigation plan.]

NATIONAL SECURITY DISCLOSURE

[In accordance with National Security Presidential Memorandum (NSPM)-33 and the associated White House Office of Science and Technology Policy Implementation Guidance, which requires certain individuals to disclose potential conflicts of interest (COI) and commitment (COC), individuals designated as PIs and other senior/key personnel (see Section 3.4.1) under prime and subawardees are required to complete the Common Form for Current and Pending (other) Support as well as the Common Form for Biographical Sketch[2]:]

a. For PIs and other senior/key personnel (in both prime and subawardees, including consultants), please list:
   i. Other organizational affiliations and employment
   ii. Other positions and appointments[3]
   iii. Participation in any foreign government-sponsored talent recruitment program(s)[4]

[2] Other Support: https://www.nsf.gov/bfa/dias/policy/researchprotection/commonform_cps.pdf; Biographical Sketch: https://www.nsf.gov/bfa/dias/policy/researchprotection/commonform_biographicalsketch.pdf
[3] Both foreign and domestic, including affiliations with foreign entities and governments. This includes titled academic, professional, or institutional appointments whether or not remuneration is received, and whether full-time, part-time, or voluntary (including adjunct, visiting, or honorary).
[4] The term "foreign government-sponsored talent recruitment program" or "foreign government-sponsored talent recruitment programs" means an effort directly or indirectly organized, managed, or funded by a foreign government or institution to recruit S&T professionals or students (regardless of citizenship or national origin, and whether

iv. Current and pending support/Other support. For researchers, "Other Support" includes all resources made available to a researcher in support of and/or related to all of their professional R&D efforts, including resources provided directly to the individual rather than through the research organization, and regardless of whether or not they have monetary value (e.g., even if the support received is only in-kind, such as office/laboratory space, equipment, supplies, or employees).] This support includes:

1. all resources made available, or expected to be made available, to an individual in support of the individual's research and development efforts, regardless of (i) whether the source is foreign or domestic; (ii) whether the resource is made available through the entity applying for a research and development award or directly to the individual; or (iii) whether the resource has monetary value;
2. in-kind contributions requiring a commitment of time and directly supporting the individual's research and development efforts, such as the provision of office or laboratory space, equipment, supplies, employees, or students. This includes resource and/or financial support from all foreign and domestic entities, including but not limited to, (i) gifts provided with terms or conditions, (ii) financial support for laboratory personnel, and (iii) participation of student and visiting researchers supported by other sources of funding; and
3. Private equity, venture, or other capital financing.

b. For consultants, please additionally list the following (Note: current, pending, and other support not required):

i. Other organizational affiliations and employment

ii. Other positions and appointments**Error! Bookmark not defined.**

iii. Participation in any foreign government-sponsored talent recruitment program(s)

NOVELTY OF PROPOSED WORK

Has the proposed work been submitted to any other Government solicitation? ¨ No ¨ Yes
If yes, provide the following information:

- Solicitation number _____
- Agency/Office _____
- Proposed work has already received funding or a positive funding decision.
  ¨ No ¨ Yes □ Decision pending

INTELLECTUAL PROPERTY (IP)

[Provide the following information, as applicable. *Note: The Government will assume unlimited rights to all IP not explicitly identified as restricted in the proposal.*]

a. TECHNICAL DATA AND COMPUTER SOFTWARE

Are you asserting any IP restrictions on any technical data or computer software that will be delivered to the Government? □ No ¨ Yes

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having a full-time or part-time position). Compensation could take many forms including cash, research funding, complimentary foreign travel, honorific titles, career advancement opportunities, promised future compensation, or other types of remuneration or consideration, including in-kind compensation.

[If yes, list all anticipated proprietary claims to results, prototypes, deliverables, or systems supporting and/or necessary for the use of the proposed research, results, prototypes and/or deliverables. Provide a short summary for each item asserted with less than unlimited rights that describes the nature of the restriction and the intended use of the intellectual property in the conduct of the proposed research. Use the following format for these lists.]

NONCOMMERCIAL				
Technical Data and/or Computer Software To be Delivered with Restrictions	**Summary of Intended Use in the Conduct of the Research**	**Basis for Assertion**	**Asserted Rights Category**	**Name of Person Asserting Restrictions**

COMMERCIAL				
Technical Data and/or Computer Software To be Delivered with Restrictions	**Summary of Intended Use in the Conduct of the Research**	**Basis for Assertion**	**Asserted Rights Category**	**Name of Person Asserting Restrictions**

b. PATENTS

Does the proposed effort involve using patented inventions that are owned by or assigned to the proposing organization or individual? ¨ No ¨ Yes

[If yes, provide documentation proving ownership or possession of appropriate licensing rights to all patented inventions to be used for the proposed project. If a patent application has been filed for an invention, but it includes proprietary information and is not publicly available, provide documentation that includes: the patent number, inventor name(s), assignee names (if any), filing date, filing date of any

related provisional application, and summary of the patent title, with either: (1) a representation of invention ownership; or (2) proof of possession of appropriate licensing rights in the invention (i.e., an agreement from the owner of the patent granting license to the proposer).]

a. ABILITY TO MEET PROGRAMMATIC GOALS WITH IP/PATENT IMPLICATIONS

[Describe how IP assertions and/or patent implications impact the applicable ARPA-H programmatic goals.]

HUMAN SUBJECTS RESEARCH

Does the proposed work involve Human Subject Research? ¨ No ¨ Yes

[If yes, provide the Federalwide Assurance (FWA) number and the plan for Institutional Review Board (IRB) review and approval.]

ANIMAL SUBJECTS RESEARCH

Does the proposed work involve Animal Subject Research? ¨ No ¨ Yes

[If yes, provide the Animal Welfare Assurance (AWA), the Vertebrate Animals Section (VAS), and the plan for Institutional Animal Care and Use Committee (IACUC) review and approval.]

REPRESENTATIONS REGARDING UNPAID DELINQUENT TAX LIABILITY OR A FELONY CONVICTION UNDER ANY FEDERAL LAW

[Complete the following statements.]

The Proposer represents that –

(i) It is [ ] is not [ ] a corporation that has any unpaid Federal tax liability that has been assessed, for which all judicial and administrative remedies have been exhausted or have lapsed, and that is not being paid in a timely manner pursuant to an agreement with the authority responsible for collecting the tax liability,

(ii) It is [ ] is not [ ] a corporation that was convicted of a felony criminal violation under a Federal law within the preceding 24 months.

APPENDIX D: TARGET PRODUCT PROFILE (TPP) FOR TA1, TA2, TA3

Target Product Profile for Technical Area 1: Diagnosis & Monitoring		
Product Target	**Minimum Acceptable Result**	**Ideal Results**
Scope and Equity Targets		
Intended Use	Detect and monitor primary lymphatic diseases (lymphedema and complex lymphatic anomalies)	Detect, monitor, and inform treatment of lymphatic dysfunction that is driving or contributing to a chronic disease.
Target User	Populations with primary lymphatic disease (performers must be able to accurately detect lymphatic disease in the presence of comorbid conditions and differentiate lymphatic disease from other comorbid conditions).	Populations with primary lymphatic diseases and general lymphatic dysfunction.
Accessibility	Results in ≤ 1 week	Results in ≤ 3 days
Affordability	<$500 to customer	Full coverage by healthcare insurance
Performance Characteristics		
Sensitivity	70	85
Specificity	90	97
AUC	>0.85	>0.90
95% confidence interval (AUC)	0.05	0.03
Reproducibility	90% of patients receive same diagnosis when evaluated twice	100% of patients receive the same diagnosis when evaluated twice
Stability	8hrs(20-22 ºC) / 72hrs(4-8 ºC)	72hrs(20-22 ºC) / 1wk(4-8 ºC)
Limits of the detection	$\text{mean}_{\text{blank}}$ +(SD)	$\text{mean}_{\text{blank}}$ +2(SD)
Measurement range	$\text{mean}_{\text{disease}} \pm 3$(SD)	$\text{mean}_{\text{disease}} \pm 4$(SD)
Earliest clinical detection (in comparison to reference test)	Detection following initial reporting of symptoms.	Pre-clinical detection of lymphatic dysfunction
$\text{mean}_{\text{blank}}$: Average detected expression in a sample set without the disease marker. $\text{mean}_{\text{disease}}$: Average expression of biomarker in patients with disease.		

Target Product Profile for Technical Area 2: Imaging Technology		
Product Target	**Minimum Acceptable Result**	**Ideal Results**
Scope and Equity Targets		
Intended Use	Detect and monitor primary lymphatic diseases (lymphedema and complex lymphatic anomalies)	Detect, monitor, and inform treatment of lymphatic dysfunction that is driving or contributing to disease.
Target User	Populations with primary lymphatic disease (performers must be able to accurately detect lymphatic disease in the presence of comorbid conditions and differentiate lymphatic disease from other comorbid conditions).	Populations with primary lymphatic diseases and general lymphatic dysfunction.
Safety	Radiation Limit: < 15 mSV	No radiation
Accessibility	Available for use in suburban community hospitals.	Available for use in rural and underserved hospitals.
Affordability	Patient cost <$1200 per scan	Patient cost <$500 per scan
Ease of use	• Requires minimal training (<2-days of instruction for mastery)	• No anesthesia • <8 hours of instruction for mastery
Performance Characteristics		
Spatial Resolution	<1.0mm	<100µm
Temporal Resolution	>1 scan of FOV/min (0.016Hz)	>20 scans of FOV/min (0.33 Hz)
Depth of imaging	>2.0cm	>6cm
Field of View (FOV)	12cmx12cm	1mx15cm
Total Procedure Time	<2 hours	<30 min
Organ/Tissue Targeting	≥ 2 organs/tissues	All organs/whole body

Technical Area 2: Imaging-Based Metrics of Lymphatic Function		
Product Target	**Minimum Acceptable Result**	**Ideal Results**
Scope and Equity Targets		
Intended Use	Detect and quantify at least 3 distinct features of lymphatic vascular function and lymph flow	Detect and quantify at least 6 distinct features of lymphatic vascular function and lymph flow
Target User	Populations with primary lymphatic disease (performers must be able to accurately detect lymphatic disease in the presence of comorbid conditions and differentiate lymphatic disease from other comorbid conditions).	Populations with primary lymphatic diseases and general lymphatic dysfunction.
Accessibility	Available as a free to use plug-in for the imaging technology	Integrated into the imaging technology's software.
Performance Characteristics		
Sensitivity	75	90
Specificity	90	97
Diagnostic Accuracy	>90%	>95%
95% confidence interval	5%	3%
Correlation with reference (r)	>0.7	>0.85

Target Product Profile for Technical Area 3: Prevention, Prediction & Diagnostic Confirmation		
Product Target	**Minimum Acceptable Result**	**Ideal Results**
Scope and Equity Targets		
Intended Use	Predict likelihood of lymphatic dysfunction or incidence rate for LD	Reveal candidates for gene therapies to improve lymphatic dysfunction
Target User	Populations with primary lymphatic disease (performers must be able to accurately detect lymphatic disease in the presence of comorbid conditions and differentiate lymphatic disease from other comorbid conditions).	Populations with primary lymphatic diseases and general lymphatic dysfunction.
Safety & Accessibility	Requires minimally invasive tissue samples.	Available via saliva, blood, drain fluid or other non-invasive samples
Affordability	Total Costs < $4000	Total Costs < $1000
Performance Characteristics		
Correlation with imaging metrics (p-value)	<0.01	<0.001
Positive predictive value (primary LD)	>50%	>70%
Positive predictive value (lymphatic dysfunction)	>30%	>50%