Response to ARPA-H July 17 Letter Re Submission Requirements

(1) BAA number (75N99223S0001)
(2) Technical areas: Health Science Futures, Scalable Solutions, and Proactive Health
(3) Lead organizations submitting proposal: Society for Heart Attack Prevention & Eradication (SHAPE) and HeartLung.AI Corporation
(4) Type of organization: NONPROFIT (SHAPE) and C CORPORATION (HeartLung.AI)
(5) Proposer's reference number (if any): N/A
(6) Other team members (if applicable) and type of organization for each:

Participating Longitudinal Cohorts from Academic Institutions	
Daniel Levy	Framingham Heart Study
Philip Greenland	MESA
Raimund Erbel	HNR (Heinz Nixdorf Recall Study)
Valentin Fuster	PESA/BioImage / HRP Study
Amit Khera	Dallas Heart Study
Herman Taylor	Jackson Heart Study
Tatiana Kouznetsova	FLEMENGHO Study
Khurram Nasir	MiHeart Study
Harry de Koning	ROBINSCA
Michael Blaha	ARIC and Brazilian MESA
Jes Sanddal Lindholt	VIVA
Axel Diederichsen	DANRISK and DANCAVAS
Oscar Franco	Rotterdam Heart and Erasmus Age
Paul Elliot	UK Biobank
Wolfgang Koenig	BiomarCaRE

(7) Proposal Title: Developing an Artificial Intelligence System to Forecast Near-Term Sudden Cardiac Death and Cardiovascular Events in Asymptomatic Individuals with no History of Cardiovascular Disease (CVD)

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(10) Total funds requested from ARPA-H, and the amount of cost share (if any): $39,600,000
(11) Date proposal was submitted: May 12, 2023
(12) Keywords: Cardiovascular Disease, Heart Attack, Stroke, AI

ARPA-H Proposal Abstract:

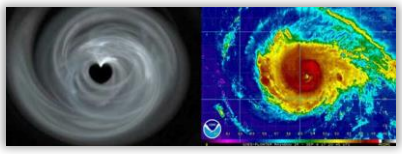
Developing an Artificial Intelligence System to Forecast Near-Term Sudden Cardiac Death and Adverse Cardiovascular Events in Asymptomatic Individuals with no History of Cardiovascular Disease (CVD)

Concept Summary: We aim to use AI to detect who will have a cardiovascular event, such as sudden cardiac death, heart attack, or stroke, within a year (detect the Vulnerable Patient). **AI will be trained based on a rare collection of existing data from numerous longitudinal studies throughout US, Europe, and South America. Each study contributes a unique set of data from asymptomatic individuals who shortly (i.e. hours, days, or weeks, up to 12 months) after their medical visit had a sudden cardiac death or an adverse CVD event.** During the medical visit, they must have had a blood draw (banked), and their medical records must include a complete clinical evaluation along with a coronary artery calcium (CAC) scan, a coronary CT angiography (CCTA), or a chest CT scan obtained within 2 years prior to the event. By applying deep learning techniques to this set of rare data, we will train AI to identify individuals at very high risk for a near-term event. For the first time, the field of cardiology will be able to predict who will have a heart attack, stroke, or an adverse CVD event within 12 months.

Background: CVD has been the #1 cause of death and healthcare costs in the US for decades. Every year over 600,000 first-time heart attacks unexpectedly hit asymptomatic Americans. Currently less than 3% of US adults aged 20-79 years have an optimal cardiovascular risk factors profile defined as: total cholesterol <200 mg/dL (5.17 mmol/L), blood pressure <120/<80 mm Hg, non-smoker, body mass index (BMI) <25 kg/m2, fasting plasma glucose <100 mg/dL (5.56 mmol/L). Nonetheless, the awareness on CVD risk factors is above 95% meaning almost all US adults are aware of the risk associated with these risk factors. Clearly, new strategies are needed.

Innovation and Impact: No longitudinal cohort or biobank in the world, by itself, has enough cases for this project. Hence, we have invited all prospective cardiovascular epidemiological studies worldwide to participate in this study, and we have 14 large cohorts committed so far that will amount to about 1,000 cases.

State of the Art: Since the pioneering Framingham Heart Study in 1960s introduced CVD risk factors, the practice of preventive cardiology has been based on long-term CVD risk prediction. Physicians tell their patients that based on their risk factors (age, gender, blood pressure, cholesterol, diabetes, smoking etc.) their risk of developing cardiovascular disease in the next 10 years is X. The median and mean for X are 2.7% and 5.2% respectively. *Although such a long-term risk assessment is necessary, it is not enough. It does not trigger immediate preemptive actions and cannot detect asymptomatic patients who are vulnerable to a near-term CVD event.* A layman's analogy to this scenario would be a TV weather broadcaster announcing that, over the next 10 years, a catastrophic hurricane will hit an area. Such an announcement would hardly change behaviors. However, when the weatherman displays a hurricane eye coming in a narrow path in the near future, it can cause immediate preemptive actions. A medical analogy would be finding a tumor in a cancer patient that gets serious attention and triggers immediate interventions to improve outcomes. Having such a predictive tool in cardiology can cause a paradigm shift resulting in developing new treatments. Developing this highly desired tool is the purpose of our ARPA-H "moonshot" proposal.



Proposed Work: We will utilize the Framingham Heart Study, MESA, ARIC, UK Biobank, HNR, BioImage, and the Dallas Heart Study for AI training. External validation to test for discrimination and calibration will be conducted using other longitudinal observational studies that provide adjudicated cardiovascular event information, such as MiHeart, JHS, DANRISK and ROBINSCA. Additionally, we will use AI to characterize individuals who, despite high conventional risk due to hyperlipidemia, hypertension, diabetes, smoking and obesity have lived over 80 years with no CHD events (the Invulnerable Patient). We expect to discover new targets for drug and possibly vaccine development. We will make the AI algorithms available as an open-source tool to collect additional data over time and increase AI's predictive value.

Topic Area of BAA	How Proposal Addresses Topic
Health Science Futures	Dramatically improves upon the current practice of preventive cardiology and provides opportunities not only for accurate risk assessment but also has the potential to yield new therapeutic targets including vaccine for heart attacks.
Scalable Solutions	The AI tool resulting from this proposal will be a SaaS product therefore readily scalable to access worldwide.
Proactive Health	Alerting the very high-risk individuals who have no symptoms and are completely unaware of their high risk of a catastrophic health event in the near future will likely cause immediately proactive and preemptive actions.
Health Outcome(s) Sought	The primary health outcome will be significant reductions in sudden cardiac death, acute coronary syndromes, and cerebrovascular events.
Innovative and Revolutionary	This AI-enabled approach in preventive cardiology will be revolutionary and highly innovative. Nonetheless it is based on proven track record in cancer treatment where a detection of a malignant tumor can trigger rapid response and immediate compliance to intensive treatments such as chemotherapy. Whereas today, preventive cardiology faces poor compliance with over half of statin prescriptions not filled after the first year.
Disruptive	The proposed AI-enabled solution can cause a paradigm shift in preventive cardiology and disrupt some of the current imprecise population-based risk assessment and therapeutic strategies with such high NNT (number needed to treat). Instead, highly effective personalized preemptive therapies (coronary artery bypass graft) can be applied to a small number of very high-risk patients.
Positive Impact:	The proposed AI-enabled solution will impact millions of lives worldwide as CVD is the number 1 killer in most countries and kills over 17 million annually.
Quantitative Metrics:	As shown in the modality table below, the quantitative jump from the existing solution to the proposed solution will be on the order of magnitude (approximately 40 times more precise). Furthermore, we will make the AI algorithms available as an open-source platform to collect additional data over time and increase AI's predictive value.
Value Add:	The proposed solution will greatly enhance the accuracy of targeted therapy and will reduce unnecessary waste of healthcare resources. It will result in added millions of productive life years for human beings that will contribute to the world's economy.

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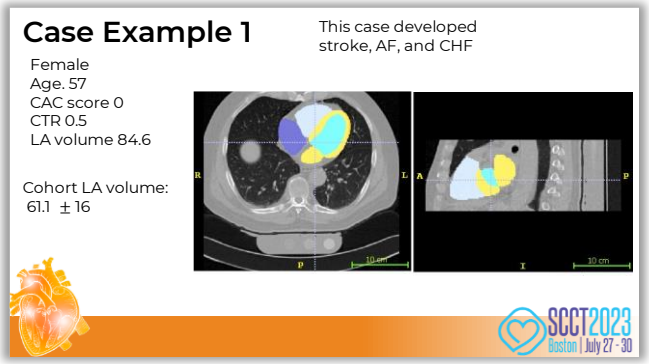
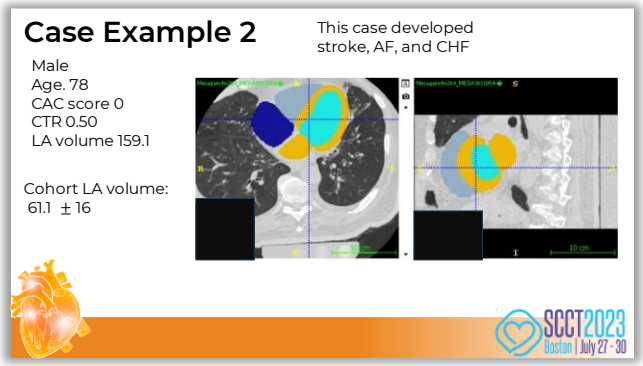
Illustrative Example: As an illustrative example, HeartLung.AI's breakthrough AutoChamber™ AI Software as a Medical Device (SaMD) can detect high risk patients for heart failure and stroke. It uses deep learning algorithms to visualize chambers volume in non-contrast cardiac CT scans which human eyes cannot detect. This technology is currently under review by FDA Breakthrough Designation committee.





Anticipated Outcome and Impact: Preliminary data indicates for this ARPA-H project, we can expect to be able to develop algorithms and a Software as Medical Device (SaMD) that will provide a patient with a forecast of approximately 20% chance of near-term sudden cardiac death and adverse cardiovascular events in asymptomatic individuals with no history of cardiovascular disease (CVD) within the next 12 months. This is far more compelling and actionable than average 5.2% within the next 10 years. We expect the FDA filing to be initiated within 9 months, with anticipated clearance as "**Breakthrough Medical Device Designation**" within 16 months.

Modality	Method	Forecast	Time Frame
Existing	Risk Factors, Polygenic Risk Score, Coronary Artery Calcium Score	Average 5.2%	10 years (120 months)
Proposed	AI-Enabled Event Forecaster Comprising Existing Modality and New Biomarkers	About 20%	1 year (12 months)

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Society for Heart Attack Prevention and Eradication
SHAPE
Mission: Eradicating Heart Attacks

HeartLung.AI

Rough Order of Magnitude (ROM) Budget:

Cost Category	Amount
Direct Labor	$5,000,000
Subcontractors	$26,300,000
Materials	$500,000
Equipment	$1,000,000
Travel	$200,000
Other Direct Costs	$3,000,000
Profit	10%
Cost Sharing	$0
Total	**$39,600,000**

Participating Longitudinal Cohorts from Academic Institutions (Subcontractors)		Expected Number of Cases*	Cost
Daniel Levy	Framingham Heart Study	127	$3,175,000
Philip Greenland	MESA	68	$1,700,000
Raimund Erbel	HNR (Heinz Nixdorf Recall Study)	77	$1,925,000
Valentin Fuster	PESA/BioImage / HRP Study	28	$700,000
Amit Khera	Dallas Heart Study	44	$1,100,000
April Carson	Jackson Heart Study	38	$950,000
Tatiana Kouznetsova	FLEMENGHO Study	24	$600,000
Khurram Nasir	MiHeart Study	18	$450,000
Harry de Koning	ROBINSCA	29	$725,000
Michael Blaha	ARIC and Brazilian MESA	82	$2,050,000
Jes Sanddal Lindholt	VIVA	31	$775,000
Axel Diederichsen	DANRISK and DANCAVAS	98	$2,450,000
Oscar Franco	Rotterdam Heart and Erasmus Age	87	$2,175,000
Paul Elliot	UK Biobank	282	$7,050,000
Wolfgang Koenig	BiomarCaRE	19	$475,000
	Total (Estimated)	**1052**	**$26,300,000**

*Each case is defined as existing data including a blood or serum sample from a longitudinal study participant, an asymptomatic individual who shortly (i.e. hours, days, or weeks, up to 12 months) after their medical visit had a sudden cardiac death or an adverse CVD event.