

**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**:

<table>
<thead>
<tr>
<th>Participating Longitudinal Cohorts from Academic Institutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daniel Levy</td>
</tr>
<tr>
<td>Philip Greenland</td>
</tr>
<tr>
<td>Raimund Erbel</td>
</tr>
<tr>
<td>Valentin Fuster</td>
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<tr>
<td>Amit Khera</td>
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<tr>
<td>Herman Taylor</td>
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<tr>
<td>Tatiana Kouznetsova</td>
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<tr>
<td>Khurram Nasir</td>
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<tr>
<td>Harry de Koning</td>
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<tr>
<td>Michael Blaha</td>
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<tr>
<td>Jes Sanddal Lindholt</td>
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<tr>
<td>Axel Diederichsen</td>
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<tr>
<td>Oscar Franco</td>
</tr>
<tr>
<td>Paul Elliot</td>
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<tr>
<td>Wolfgang Koenig</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>8) Technical point of contact:</th>
<th>9) Administrative point of contact:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Naghavi, Morteza, TMC Innovation, 2450 Holcomb Blvd, Houston, TX 77021, Tel: (650) 414-5057 Email: <a href="mailto:mn@shapesociety.org">mn@shapesociety.org</a></td>
<td>Mr. Montes, Marlon, Dr. Naghavi, Morteza TMC Innovation, 2450 Holcomb Blvd, Houston, TX 77021, Tel: (650) 263-7636 Email: <a href="mailto:marlon@heartlung.ai">marlon@heartlung.ai</a></td>
</tr>
</tbody>
</table>

8. **Total funds requested from ARPA-H, and the amount of cost share (if any)**: $39,600,000
9. **Date proposal was submitted**: May 12, 2023
10. **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 ROBINS.CA. 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.

<table>
<thead>
<tr>
<th>Topic Area of BAA</th>
<th>How Proposal Addresses Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health Science Futures</td>
<td>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.</td>
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<tr>
<td>Scalable Solutions</td>
<td>The AI tool resulting from this proposal will be a SaaS product therefore readily scalable to access worldwide.</td>
</tr>
<tr>
<td>Proactive Health</td>
<td>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.</td>
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<tr>
<td>Health Outcome(s) Sought</td>
<td>The primary health outcome will be significant reductions in sudden cardiac death, acute coronary syndromes, and cerebrovascular events.</td>
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<tr>
<td>Innovative and Revolutionary</td>
<td>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.</td>
</tr>
<tr>
<td>Disruptive</td>
<td>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.</td>
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<tr>
<td>Positive Impact:</td>
<td>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.</td>
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<tr>
<td>Quantitative Metrics:</td>
<td>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.</td>
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<tr>
<td>Value Add:</td>
<td>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.</td>
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</table>
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.

**Case Example 1**
- Female
- Age: 57
- CAC score 0
- CTR 0.5
- LA volume 84.6
- Cohort LA volume: 61.1 ± 16

This case developed stroke, AF, and CHF

**Case Example 2**
- Male
- Age: 78
- CAC score 0
- CTR 0.50
- LA volume 159.1
- Cohort LA volume: 61.1 ± 16

This case developed stroke, AF, and CHF

**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.

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

**Executive Director:** Morteza Naghavi, M.D.

**Steering Committee:** Valentin Fuster, M.D., Ph.D., Philip Greenland, M.D., Daniel Levy, M.D., David Maron, M.D., Jagat Narula, M.D., Ph.D., Michael Blaha, M.D., M.P.H., Michael Pencina, Ph.D., David Yankelevitz, M.D.

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Nathan Wong, M.P.H., Ph.D.
Professor of Epidemiology and Director, Heart Disease Prevention Program, University of California, Irvine, CA

David Yankelevitz, M.D.
Professor of Radiology, Carl Icahn Mount Sinai School of Medicine, Founding Director of Lung Cancer Screening Cohort IELCAP, New York
Rough Order of Magnitude (ROM) Budget:

<table>
<thead>
<tr>
<th>Cost Category</th>
<th>Amount</th>
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<tbody>
<tr>
<td>Direct Labor</td>
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<tr>
<td>Subcontractors</td>
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<tr>
<td>Materials</td>
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<tr>
<td>Equipment</td>
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<tr>
<td>Travel</td>
<td>$200,000</td>
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<tr>
<td>Other Direct Costs</td>
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<td>Profit</td>
<td>10%</td>
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<tr>
<td>Cost Sharing</td>
<td>$0</td>
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<tr>
<td>Total</td>
<td>$39,600,000</td>
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</table>

Participating Longitudinal Cohorts from Academic Institutions (Subcontractors)  

<table>
<thead>
<tr>
<th>Participating Cohorts</th>
<th>Expected Number of Cases*</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daniel Levy, Framingham Heart</td>
<td>127</td>
<td>$3,175,000</td>
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<tr>
<td>Philip Greenland, MESA</td>
<td>68</td>
<td>$1,700,000</td>
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<tr>
<td>Raimund Erbel, HNR (Heinz Nixdorf</td>
<td>77</td>
<td>$1,925,000</td>
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<tr>
<td>Valentin Fuster, PESA/BioImage /</td>
<td>28</td>
<td>$700,000</td>
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<td>Amit Khera, Dallas Heart Study</td>
<td>44</td>
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<td>April Carson, Jackson Heart Study</td>
<td>38</td>
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<td>Tatiana Kouznetsova, FLEMENGO</td>
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<td>Axel Diederichsen, DANRISK and</td>
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<tr>
<td>Oscar Franco, Rotterdam Heart and Erasmus Age</td>
<td>87</td>
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<tr>
<td>Paul Elliot, UK Biobank</td>
<td>282</td>
<td>$7,050,000</td>
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<td>Wolfgang Koenig, BiomarCaRE</td>
<td>19</td>
<td>$475,000</td>
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<tr>
<td><strong>Total (Estimated)</strong></td>
<td><strong>1052</strong></td>
<td><strong>$26,300,000</strong></td>
</tr>
</tbody>
</table>

*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.