Pre-Application Webinar for RFA-TR-21-008: Question & Answer Session

Q1: What is considered a “broad” array of rare diseases?
A1: The intent of the funding opportunity announcement (FOA) is to identify, escalate, and accurately diagnose as many rare disease patients who are hard-to-diagnose as possible. A broad array is intended to mean rare diseases generally or categories of rare diseases inclusive of, for example, clusters of related diseases, such as generalized seizures or motor impairment, because they involve many different rare diseases within the cluster.
- Example: Augmented reality software to analyze gait abnormalities, applicable to multiple neuromuscular diseases, would be considered responsive.
- Example: Machine-assisted algorithms using clinical characteristics or disease-specific attributes to identify patients with one rare disease would not be considered responsive.

Q2: What is considered a “multi-disciplinary” team?
A2: In view of the goals of this FOA, applicants should assemble a multi-disciplinary team with expertise in medical informatics, genetic analysis, rare diseases, and front-line healthcare when preparing the application.

Q3: What are some key elements to consider in an application for this UG3/UH3 activity code?
A3: The transition plan with clear go/no-go criteria and meeting the UG3 milestones are crucial to continued funding to the UH3 phase. NIH can consider ending support and negotiating an orderly close-out of the award if at any time the project fails to make progress toward meeting milestones.

Establish a robust milestone plan with clear quantifiable measures of success. A timeline (Gantt chart) including milestones is required for all components of the diagnostic strategy. Quantitative milestones are required in order to provide clear indicators of a project's continued success or emergent difficulties and will be used to evaluate consideration of the awarded project for funding of non-competing award years.

Q4: Given the amount of the award budget, what should be accomplished in the UG3 phase?
A4: The primary focus of the UG3 phase should be on planning and developing a diagnostic process for rare diseases. Pilot testing of critical experimental parameters in a single front-line healthcare setting should also be evaluated with quantifiable outcome measures.

Q5: For the UH3 phase, what is considered another clinical setting?
A5: The UH3 phase is intended to expand the diagnostic strategy beyond the initial front-line healthcare setting so it is not too customized for any one clinical setting, and should include at least one other front-line healthcare site, such as (including, but are not limited to):
- An affiliate community site
- A satellite primary care clinic
- A local secondary care specialist clinic or office

Ideally, this would include clinical care settings which reflect health disparities, and which differ with regard to demographic, geographic (e.g., rural versus urban), and socioeconomic factors.
Q6: What is the role of the front-line healthcare provider?
A6: Front-line healthcare providers are more likely to interact with rare disease patients earlier in their diagnostic journey. The intent of this FOA is to integrate better diagnostic strategies into the clinical care workflow of front-line healthcare providers in order to more rapidly identify, escalate, and accurately diagnose these patients.

The FOA allows for flexibility; it is up to the multi-disciplinary team to determine how best to incorporate each of the 3 required areas into the overall proposal and fit the strategies into the workflow of front-line healthcare providers.

Q7: Do "front-line" providers need to be primary care providers? Could hospital-based providers (e.g., hospitalists, intensive care clinicians) be considered front-line?
A7: Secondary care levels may also be considered front-line healthcare providers. The intent of the FOA is to accelerate diagnosis by reaching the front-line healthcare providers who see a broad array of patients in the community. It is possible to put together a proposal including hospital-based providers as long as the primary intent of the FOA is met.

Q8: Does using commercially available genetic testing options count sufficiently towards the genomic analysis component?
A8: It is up to the PI to make the case.

Q9: Can you elaborate more on the machine-assistance aspect of the FOA?
A9: Artificial intelligence, including machine learning or other information technology (IT), components of the project may include the development of algorithms that computationally make predictions based on data. Machine-assistance strategies may be applied to the EMR or other healthcare system databases, genomic data, imaging data, and other biological domains. Methods may include knowledge extraction, such as natural language processing; or machine capture and interpretation, such as facial recognition.

The goal would be to develop and apply algorithms that could identify potential rare disease patients on the basis of, for example:
- Medical utilization patterns (e.g., high-utilizers, young age)
- Sentinel characteristics or other features (e.g., abnormal gait, facial features, delayed development)
- Imprecise diagnosis (e.g., neurologic disorder not otherwise specified, failure to thrive)
- Clusters of diseases that are related in some way (e.g., generalized seizures, motor impairment)

Q10: Could activities of this type fall under the definition of a clinical trial?
A10: Yes, it could.

Q11: Have any specific groups been given advanced notice about this FOA?
A11: No, everyone was notified at the same time through publication of RFA-TR-21-008 in the NIH Guide.

Q12: Is it possible that meritorious proposals might be awarded beyond NCATS by another NIH Institute or Center?
A12: There are no other NIH institutes or centers signed onto the FOA at this time, but NCATS would consider interest from other NIH Institutes and Centers.
Q13: How does NIH intramural intend to take the application or innovation and implement or expand upon it?
A13: This is an extramural program, and the NIH intramural program is not involved in this initiative. It is our hope that some of these strategies could be disseminated and adapted by other places, including NIH as well as other academic and community healthcare centers around the U.S.

Q14: Do you expect the application to have all three components—clinical strategies, machine-learning, and genomic analysis?
A14: Yes, the overall approach must include all three required components within the application.