

Grand Challenges in Global Health



Grand Challenges in Global Health *Diagnostics*

***To develop technologies that help assess multiple
conditions or pathogens at point-of-care***

Phase I

Global Health Discovery

Bill & Melinda Gates Foundation

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1 INTRODUCTION

We are continuing the mission set forth in the Grand Challenges in Global Health initiative and continuing to invest in solutions to Grand Challenge 14: *Develop Technologies that Allow Assessment of Multiple Conditions and Pathogens at Point of Care*. Specifically, we seek to create a new class of point-of-care (POC) diagnostics that will be easy to use, low cost and otherwise appropriate so that these new tools achieve significant impact and rapid uptake in resource-poor settings.

2 BACKGROUND

In the developing world, tools are not available to easily and accurately assess a person's health status, and the risks of various illnesses and treatment options. In addition, little information about the burden of disease is available to guide population health decisions. This severely impacts the care that people receive. A solution, according to studies conducted by the Diagnostics Forum¹, is to move toward a common point-of-care (POC) diagnostic platform for global health. POC diagnostics are not only intended to be used in a laboratory or clinic by a trained user. They also need to be operated by minimally trained community health workers in limited infrastructure settings. The platform we envision will have the ability to assess multiple pathogens and health conditions using a set of common technical, logistical, and medical decision-making approaches. The combination of 1) a point of decision test, and; 2) a common platform, will ultimately result in better health outcomes.

The challenge for these POC diagnostic platforms for global health is to define and achieve the needed performance characteristics of rapid, accurate assessment of individuals' health status, including robust, simple-to-use technologies for achieving parallel, multi-pathogen, reliable and valid clinical measures in developing world settings. High throughput approaches to genomics, proteomics, metabolomics and the measurement of other analytes, coupled with novel technologies of miniaturization and multiplexing create the possibility of radically new ways to detect and diagnose health and disease states in individuals, even in remote or impoverished settings with limited infrastructure. The coupling of new and existing validated biomarker signatures with microfluidic platforms could place effective diagnostics within reach of unskilled users in the developing world.²

Improved diagnostics platforms hold the benefit of potential:

- Unequivocal identification of pathogen type and subtype
- Rapid assessment of susceptibility and immunity to health threats
- Rapid diagnosis of exposure and disease
- Rapid detection of emerging pathogens
- Rapid parallel diagnosis of multiple infectious agents
- Accurate assessment of disease stage and prognosis
- Better detection and management of outbreaks and emerging acute and chronic health threats

¹See set of call to action papers in Nature Supplemental at <http://www.nature.com/diagnostics>

² *Requirements for high impact diagnostics in the developing world*, Mickey Urdea et al., Nature S1, pp 73-79 (23 November 2006). doi:10.1038/nature05448

Quantification of disease incidence in endemic countries

Program Goal

We seek to create point of care platforms that share common standards for use, development and integration. This will enable diagnostic devices that are lower cost, easier to use, more readily accepted, more thoroughly disseminated and more appropriate for health care in the developing world.

We hope to achieve the design and initial proof-of-principle for a POC platform with a target product profile (TPP) that includes the following characteristics:

- Quick time-to-answer
- Simple readout
- Low cost
- Good sensitivity and specificity
- Able to be used by minimally trained personnel
- The ability to function above 30 °C and at high humidity
- The ability to be stored for long periods of time without refrigeration
- The ability to conduct tests without the need for local reagents/water and/or specialized laboratory equipment
- The ability to detect multiple pathogens or to distinguish between different pathogens and/or strains and subtypes

Key Objectives

In order to create common diagnostic platforms with common performance, training and logistics aspects suitable for low resource settings, it is important to achieve the following objectives:

1. Develop a framework for collaboration by recommending a common set of technical and business standards for the development and integration of diagnostics components
2. Advance the state of the art in critical component technologies consistent with the business and technical standards developed under this program
3. Integrate best-in-class component technologies into diagnostic platforms under the framework of standards developed in this program

Phase I of this effort will be focused mainly on achieving Objectives 1 and 2: developing standards related to component integration, user experience and logistics requirements and conducting proof-of-principle investigations into component technologies. Phase II will be dedicated to integrating component technologies from Phase I or elsewhere to demonstrate POC platform concepts, performance, and operation.

The Role of Collaboration

There will be three groups working to achieve the objectives of this program.

- A Science and Technology Advisory Group (STAG) will be responsible for developing a framework for collaboration by recommending a common set of technical and business standards for the development and integration of diagnostics components. For a more detailed description of the STAG, please refer to Appendix A.
- Component Builders (CB) who will advance the state of the art in critical component technologies. This will be done consistent with the business and technical standards developed by the STAG.
- Systems Integrators (SI) who collaborate with Component Builders (both from within and outside of this program) to develop new POC diagnostic platforms consistent with the standards developed by the STAG.

Phase I will include Component Builders (CB) who will advance the state of the art in component technologies. In Phase II, Systems Integrators (SI) will work with Component Builders (CB) to integrate the best-in-class component technologies into viable POC diagnostic platforms. Some organizations may have the capacity to participate at both levels. The STAG will be active through both phases in creating a common set of standards allowing the Component Builders and System Integrators to collaborate on novel platforms. The STAG will operate concurrently with Phase I Component Builders.

Group	Acronym	Function
Science & Technology Advisory Group	STAG	Objective 1 - Provide framework for collaboration by creating common set of technical and business standards
Component Builders	CB	Objective 2 - Advance the state of the art in critical component technologies
System Integrators	SI	Objective 3 - Integrate best-in-class component technologies into competing diagnostic platforms

2.1 Advance State of the Art in Critical Component Technologies

One of the assumptions from systems engineering is that it would be possible to disaggregate the complex diagnostics research and development problem into more manageable and focused challenges. This new *Grand Challenges* effort has been structured in such a way that individual research groups can submit proposals that provide best-in-class innovations for each of the key components. Those groups will be encouraged to focus their efforts on significant innovations on the key components that limit performance. Phase I is designed to allow Component Builders to play to their strength(s) in component technologies without having to rush into suboptimal integration of solutions to the POC platform. The main goal of the Component Builder will be to show proof-of-principle operation and data for their component technology. As long as the component is optimized while conforming to the standards being defined by the STAG, the technology will be compatible with any future platform built

upon this concept. Also, in keeping with the spirit of this program, the Component Builders will be encouraged to collaborate with other Phase I participants.

2.2 Integrate Component Technologies into Platforms

We hope to have a sizable number of component technologies that will operate in a “plug-and-play” fashion, allowing Systems Integrators to work with Component Builders to create optimized platforms based on best-in-class component technologies, but also paying attention to the requirements of forming a target product profile (TPP) from the platform concept. We are not currently setting a specific cost target; however, the Systems Integrator will have to understand the interplay between the cost of goods for instrumentation, cost per test for consumables, and costs for reagent storage, distribution and disposal. The ease-of-use metric may include automation, lowering the need for trained personnel, easy interpretation of results, and streamlined workflow for batch processing. Goals for minimal infrastructure may include minimizing needs for electricity and water, and little or no supporting lab instrumentation like centrifuges, microscopes, thermocyclers, or autoclaves. By trying to meet all these requirements, we can better ensure the adoption of the diagnostic platform for developing world applications.

2.3 Collaborative Framework

In parallel to the funding of the individual technical innovations, we will fund through a separate activity the convening of a group of diagnostics and standards setting experts as a Science and Technology Advisory Group (STAG) to develop a common set of technical and business standards that will guide the Phase II call for proposals. The STAG will recommend common standards of component integration, performance and user experience to help reduce regulatory and business obstacles to collaboration and product uptake. Through this process, we will ensure the groups funded under this initiative (as well as other stakeholders we may identify) agree to common standards for overall performance and interfaces between the components and agree to a common Global Access Strategy that significantly lowers barriers for access to diagnostics in the developing world. These performance standards will allow us to compare how well one approach works against another and will permit investigators attempting to integrate comprehensive platforms to choose from alternative approaches at the component level. The interface standards should also include considerations with regard to the eventual integration with health information systems and automated, mobile communications technologies.

3 APPROACH

3.1 Program Scope for Phase I

The focus of this RFP will be exclusively on Phase I. We describe some details regarding Phase II to give applicants insight into how we will likely shape the program in years 4-6. However, due to the changing landscape for technologies, the actual implementation of Phase II may be somewhat different than what we envision today.

Length of Award: It is anticipated, subject to satisfactory attainment of negotiated milestones, that the length of the award to grantees will be three years for Phase I.

Size of Award: The total available funds to support a portfolio of responses to this *Grand Challenge* RFP are \$30 million USD, to be awarded over three years in Phase I.

Topic Areas

Each Component Builder applicant must classify his or her proposal in one of the following four Topic Areas. In the proposal, applicants must explicitly link their technical goals with a specific set of improvements they plan to achieve for the proposed component. The improvements can be described in the form of new target performance specification or in the form of desired goals. Component builders can submit more than one proposal to different Topic Areas, but each proposal should only address one Topic Area.

3.1.1 Topic Area #1: Sample collection, concentration, and preparation (SCCP)

Sample collection, concentration and preparation are critical components for diagnostics development. Challenges in the area of **sample collection** include different protocols for sample volume, sample type (e.g. blood, urine, tissue, sputum, saliva, feces), and waste disposal. Sample volumes for infants and children are frequently limited and therefore new technologies should lower the collection volume required. In the area of **sample concentration**, we will invest in innovative approaches that are simple, require minimal reagents and power (e.g. no centrifuges). In the area of **sample preparation** extraction, separation and cleanup protocols that work across a wide variety of sample types (e.g. blood, urine, tissue, sputum, saliva, feces), require minimal to no reagents and match downstream analysis sub-systems. It is very important for the sample preparation chemistry to be compatible with downstream detection assays. For example, Component Builders should understand that downstream detection assays are potentially prone to interferences like detergents and salts, may have a narrow range of acceptable pH or temperature, need to maintain protein viability (storage), or require a certain level of DNA purity.

3.1.2 Topic Area #2: Amplification and detection technologies

In this topic area, we are looking for detection and amplification methods that advance the state of the art in terms of simplicity, performance and cost. In spite of the expected gains from advances in sample preparation, the copy numbers or concentration of target molecules available for detection will frequently remain low. Therefore, a sensitive molecular detection and analyte or signal amplification stage is likely to be needed for metabolite, nucleic acid and protein markers. One particular area of interest would be amplification methods that eliminate the need for thermal cycling. We also welcome other innovative approaches with superior characteristics such as assay ruggedness, high specificity, quick time-to-answer, reduced cost and complexity, multiplexing, and quantitation capabilities.

3.1.3 Topic Area #3: Readout and signal transduction

In this topic area, we will invest in innovative methods to transduce the recognition of protein markers, biomolecular binding events, or amplification products into detectable readout signals. We are particularly interested in platforms and technologies that enable multiplexed and multi-analyte readouts.

3.1.4 Topic Area #4: Enabling technologies for diagnostics

Under this topic area we will invest in additional innovations in critical components including micro-fluidic handling, packaging, power management, reagent handling, waste handling, bioinformatics not captured under the previous three Topic Areas.

3.2 Program Structure

This RFP is soliciting proposals from Component Builders for Phase I under the aforementioned four topic areas. Phase I will run for a total of 3 years with milestones proposed by each of the Component Builders that will demonstrate proof-of-principle for their technology. The Component Builders must specify which Topic Area they will work in and propose how they will improve the state of the art for that component technology. Although the Component Builders within each technical area will work largely independently from one another, they will be required to participate in the standards setting process spearheaded by the STAG. The STAG will formulate a communications plan to disseminate the details from the standards that are being formed to the Component Builders. In addition, the STAG will offer channels for Component Builders to contribute to the development of the standards. Near the end of Phase I, we will evaluate the component technologies within each of the technical areas for demonstration of proof-of-principle, potential for compliance to the standards created under the STAG and readiness for integration into a next generation of POC platforms. During the course of Phase I, we will also create opportunities for collaboration between the Component Builders.

In years 3-6 which will comprise the second phase of this initiative we will solicit proposals to build integrated point-of-care diagnostic platforms consistent with the standards established during the first phase of activities. This follow-on call for proposals will be open to all the successful awardees from the first phase, but will also be open to any prospective applicants who could deliver superior performance at either a system or component level consistent with the standards set during Phase I. It is through this combination of advancing the key technologies and developing standards under which they can be integrated and continuing innovation can be nurtured that we believe we will be able to meet our objectives for transformational point-of-care diagnostics that will meet the objectives of the foundation's global health mission.

4 ACTIVITIES & DELIVERABLES

The Component Builders funded under this effort will be expected to engage in the activities and provide specific deliverables listed below. The overall goal is to deliver scientific and engineering

advances on critical components to improve performance, cost, and ease-of-use metrics. In the proposal, the applicants must link their technical goals to specific improvement in component technology and present a plan to demonstrate those improvements. In addition to engaging in investigative activities related to their component technologies, the Component Builders will be expected to

- Refine their project plan with a proposed set of critical milestones to achieve technical goals and meet standards set through the STAG.
- Actively participate in STAG task force for developing standards.
- Develop and commit to a Global Access Strategy consistent with the principles of Global Access described in Section 6.8 below.

The deliverables listed below will help demonstrate the project's progress and success.

- Annual progress report detailing the technical and programmatic achievements (written and site visit)
- A clear proof-of-principle demonstration described in the original proposal and documented as part of final report. This final report will also provide detailed documentation of the technical work accomplished and success and lessons learned from Phase I projects. Instructions for the annual report and final report will be provided to selected awardees..

5 RULES AND GUIDELINES

5.1 Program Direction

The Bill & Melinda Gates Foundation staff will be substantially involved in shaping this initiative over time. In consultation with independent external experts, global health staff will review and select specific projects from among the solicited proposals. Assuming proposals of sufficient scientific merit, the level of funding requested should be adequate to assure completion of the goals in a three-year time frame for Phase I. If this program produces promising interim results, authorization will be sought to move forward with issuing a Phase II RFP prior to the end of Phase I.

Assuming a sufficient number of proposals of sufficient merit, this competition is expected to fund between 10-14 grants for an aggregate total cost of \$30 million USD over three years.

5.2 Application Instructions & Review Process

Full invited applications must propose clear project goal(s), including one (or more) final product(s) during the award period. The applicant must clearly state the interim objectives (proof-of-principle milestones) to be achieved during the project, identify impediments or critical decision points

that could require a revision in the work plan or milestones, and provide a detailed scheduled or time line for the attainment of each milestone and/or goal.

This RFP will make use of a mandatory two-step application process:

Step 1: Submission of a Letter of Inquiry (LOI) to The Bill & Melinda Gates Foundation. There is a five (5) page limit on the LOI. Applicant organizations submitting an LOI MUST fully meet the eligibility criteria listed on page 12. The Bill & Melinda Gates Foundation staff will evaluate the LOIs. Those applicants who are eligible and have projects of further interest to The Bill & Melinda Gates Foundation will be contacted directly and will be invited to submit a full proposal.

- Letters of Inquiry must be submitted electronically, using the forms and process described at the following address: www.grandchallenges.org/diagnostics/Pages/ApplicationInstructions.aspx
- Each LOI must include in the header of the narrative pages the text “GCGH-Dx Program” and “Topic Area (1, 2, 3, or 4).” LOIs can only address one topic area.
- Applicants addressing more than one Topic Area must submit a separate LOI for each Topic Area. Multiple LOIs from the same organization are permitted.

Even at the LOI step, however, it is important to read carefully the full guidelines for applicants given below to make certain that the applicant organization is fully capable of complying with all the requirements and terms of award.

Step 2: If invited based upon a successful LOI, submission of a full proposal to the Bill & Melinda Gates Foundation.

Instructions on the preparation of full proposals will be provided to selected applicants for Phase I. Note that:

- Due to expected high volumes, the Bill & Melinda Gates Foundation will not provide individual critiques or feedback on why LOIs were not selected;
- The foundation will use external reviewers to advise on the merit of proposals but final selection decisions will be made by the foundation

5.3 Application Schedule

<i>Key dates and deadlines</i>	<i>Event</i>
December 1, 2009	Letter of Inquiries accepted
February 16, 2010	Application deadline for LOI at 11:59 pm PST
April, 2010	Invitation for Submission for full proposals
June, 2010	Application deadline for full proposal

5.4 Evaluation Criteria

1. Significance/Topic Responsiveness. Is the proposal likely to result in or significantly advance a component technology that will add substantively to our ability to integrate a state-of-the-art point of care diagnostics platform?
2. Approach / Execution Plan. Are the conceptual framework, design, methods, and analyses innovative, adequately developed, well integrated, and appropriate to the aims of the proposal? Does the proposal acknowledge potential problem areas and consider alternative tactics? Is there a high likelihood of successful project completion? Are the proposed time line and interim milestones appropriate, feasible and technically sound?
3. Best Value. Proposals will be evaluated for the cost of the proposed effort relative to the complexity of the proposed work and the degree of risk and advancement proposed. Proposals that have execution plans which represent particularly thoughtful and efficient use of resources will be preferred over proposals representing comparable efforts that do not represent the same value for the investment.
4. Organizational and Investigator Capability. Is the research and development team appropriately trained, experienced and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)? Is there strong evidence of substantive organizational capability and commitment? Does the environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environments including partnerships with industry or employ useful collaborative arrangements? Is there adequate evidence of institutional support?

5.5 Eligibility Criteria

Applicant organizations must be individual non-profit organizations, for-profit companies or other recognized institutions that can successfully execute the activities in their respective technical area. Grantees awarded projects will be required to actively collaborate with the STAG in Phase I and eventually collaborate and engage in technology transfer with System Integrators in Phase II.

5.6 Allowable Costs

Grant funds may be used for the following costs: personnel, necessary travel, supplies, contracted services, sub-grants, and consultants. Partial or full support for equipment may be requested subject to the circumstances described below. Please provide budget estimates according to these categories.

- Assume that you will need to budget at least a half time of a technical expert to participate in the STAG.
- Equipment: Use of any equipment purchased with grant funds is limited by law to charitable purposes for the depreciable life of the equipment. Please note that for many non- U.S. entities, U.S. tax law considerations may affect whether the Bill & Melinda Gates Foundation will permit

purchase of equipment with a depreciable life that is greater than the grant period being requested. In such cases, leasing would be preferable.

- Indirect costs: The Bill & Melinda Gates Foundation provides a limited amount of indirect costs, if any, based on the nature of the applicant organization.
- Travel funds to participate in meetings twice a year for key members of the team.

5.7 Privacy Notice

To help The Bill & Melinda Gates Foundation staff in their evaluation and analysis of projects, all proposals, documents, communications, and associated materials submitted to the Bill & Melinda Gates Foundation (collectively, "Submission Materials") will become the property of the Bill & Melinda Gates Foundation and may be subject to confidential external review by independent subject matter experts and potential co-funders in addition to analysis by the Bill & Melinda Gates Foundation staff. Please carefully consider the information included in the Submission Materials. If you have any doubts about the wisdom of disclosure of confidential or proprietary information, the Bill & Melinda Gates Foundation recommends you consult with your legal counsel and take any steps you deem necessary to protect your intellectual property. You may wish to consider whether such information is critical for evaluating the submission, and whether more general, non-confidential information may be adequate as an alternative for these purposes.

We respect confidential information we receive. Nonetheless, notwithstanding your characterization of any information as being confidential, the Bill & Melinda Gates Foundation may publicly disclose all information contained in Submission Materials to the extent as may be required by law and as is necessary for potential co-funders and external reviewers, such as government entities, to evaluate them and the manner and scope of potential funding consistent with appropriate regulations and their internal guidelines and policies.

6.8 Warranty

By providing any Submission Materials, the sender warrants the Bill & Melinda Gates Foundation that they have the right to provide the information submitted.

Applicants with questions concerning the contents of their Submission Materials may contact the Bill & Melinda Gates Foundation at: grandchallenges@gatesfoundation.org

6.9 Intellectual Property

Since the output of this program may lead to innovative technologies and/or products that will result in improved diagnostics for those that need of them most in the developing world, the successful development of these high priority products may require substantial involvement and support of private

sector industries as sub-contractors, and may also involve collaborations with multiple organizations, including academic and/or non-profit research institutions. It is the intent of this program to support the formation of appropriate public-private partnerships that are essential to meet these urgent global health needs. Intellectual property (IP) rights and the management of IP rights are likely to play an important role in achieving the goals of this program. To this end, the foundation requires that, even at the LOI stage, all applicants seriously consider their willingness to submit a full proposal in compliance with the foundation's proposal guidelines, a portion of which asks for certain information and intentions regarding intellectual property and global access concerns. Specifically, the Bill & Melinda Gates Foundation requires that you agree to use good faith efforts to conduct and manage the research, technologies, information and innovations involved in the Project in a manner that enables (a) the knowledge gained during the Project to be promptly and broadly disseminated, and (b) the intended product(s) to be made available and accessible at reasonable cost to the developing countries of the world. The Foundation refers to this as "Global Access."

As part of the foundation's review and evaluation of each full proposal, due diligence will be conducted with respect to each participant's ability and commitment to manage intellectual property in a manner consistent with the stated scientific and charitable goals of the Bill & Melinda Gates Foundation. Due diligence activities may include inquiry into an applicant's:

- 1) Freedom to operate (FTO) and ability to freely use and acquire needed background technology;
- 2) Commitment to share data and technology with other participants to facilitate the development of a common set of technical and business standards and enable integration of component technologies into viable POC diagnostic platforms;
- 3) Commitment to promote the utilization, commercialization and availability of inventions for public benefit in developing countries; and
- 4) Business plan for the development and sustainable commercialization of the POC diagnostics and technologies developed as part of the GCGH-Dx Program.

In order to facilitate this due diligence process applicants are encouraged to provide information with respect to items 1-4 above in their submission materials.

Applicants and their collaborators, in cooperation with the STAG and other Component Builders, will be required to participate in the creation of a Global Access Strategy in an effort to codify their commitment to achieving the stated scientific and charitable goals of the Bill & Melinda Gates Foundation to promote the utilization, commercialization, and availability of inventions for public benefit in developing countries. The Global Access Strategy will include provisions for the management and use of intellectual property, know-how and technologies to facilitate collaboration among the STAG, Component Builders and System Integrators with the goal of developing and delivering viable POC diagnostic platforms consistent with the TPP.

Applicants are also expected to make new information and materials known to the research and medical communities in a timely manner through publications, web announcements, progress reports to the foundation, and other appropriate mechanisms. These concepts may be discussed at some length

with the applicants invited to submit full proposals, and will be addressed (to the extent appropriate) within each final grant agreement. The Global Access Strategy will also include provisions defining these concepts.

It is our intention that at least funding in year three of Phase I activities will be contingent upon the participation of an applicant in the creation of the Global Access Strategy and their agreement to be bound by its terms.

6 RESEARCH ASSURANCES

While not necessary for the LOI, as applicable to the individual project, the Bill & Melinda Gates Foundation will require that for each venue in which any part of the project is conducted (either by your organization or a subgrantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. The foundation will further require you to agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies' approvals are obtained.

6.1 Research Involving Human Subjects.

You agree that no funds will be expended to enroll human subjects in any research project subject to Institution Review Board (IRB) or independent ethics committee (IEC) approval until such approval has been obtained for each site.

6.2 Clinical Trials

We do not expect Phase I projects in this GCGH-Dx program to require clinical trials on human subjects; in the unlikely situation that you do, a condition of this grant is your agreement that the appropriate Institutional Review Boards ("IRBs") and ethical committees will review and approve the clinical protocols prior to trial initiation. You further agree to conduct clinical trials associated with the project under the generally accepted principles of "Good Clinical Practices" as defined by the International Conference on Harmonization (ICH) E-6 Standard, the United States Food and Drug Administration (FDA) or the European Agency for the Evaluation of Medicinal Products (EMA), as applicable. You acknowledge and agree that, as between you and the Foundation, you take and will have full responsibility for all compliance, data safety, monitoring, and audit requirements of the relevant regulatory agencies, both for yourself and all other sites included in the project, including those activities conducted through subgrants, subcontracts or other collaborative efforts. You acknowledge and agree that any activities by the Foundation as the grantor funding the Project,

including its review of the Proposal or suggested modifications to the Project, does not modify the provisions of this paragraph or constitute the basis for any claim by you against the Foundation.

6.3 Coverage for all Sites

You agree that for each venue in which any part of the Project is conducted (either by your organization or a subgrantee or subcontractor) all legal and regulatory approvals for the activities being conducted will be obtained in advance of commencing the regulated activity. You further specifically agree that no funds will be expended to enroll human subjects until the necessary regulatory and ethical bodies' approvals are obtained.

6.4 Regulated Activities

The coverage requirements set forth in the preceding paragraph include but are not limited to regulations relating to: research involving human subjects; clinical trials, including management of data confidentiality; research involving animals; research using substances or organisms classified as Select Agents by the U.S. Government; use or release of genetically modified organisms; research use of recombinant DNA; and/or use of any organism, substance or material considered to be a biohazard, including adherence to all applicable standards for transport of specimens, both locally and internationally, as appropriate. As applicable, regulated activities and their documentation are to be conducted under the applicable international, national, and local standards. Documentation of research results should be consistent with regulations and the need to establish corroborated dates of invention and reduction to practice with respect to inventions where this is relevant.

6.5 Institutional Review Board (IRB) Approval

You agree to obtain the review and approval of all final protocols by the appropriate IRBs and ethical committees prior to enrollment of the first human subject and when using human material. A similar provision applies to Institutional Animal Care and Use Committee approval of studies involving animals, and Institutional Biosafety Committee for biohazards and recombinant DNA. You agree to provide prompt notice to the Foundation if the facts and circumstances change regarding the approval status of the IRBs or ethical committees for any final protocol(s).

6.6 Provision of Care for Human Subjects Research

In keeping with "Good Clinical Practice" standards, you will disclose to subjects and the IRBs what care and/or referrals will be available through participation in the study. Institutional policies regarding what care will be provided to personnel who are injured as a result of their work on the Project should be similarly be developed, approved and implemented with notice to the employees.

6.7 Use of Animals in Research

You agree to be responsible for the humane care and treatment of animals in projects supported in part or whole by Foundation funds; and to adhere to the official guidelines for animal research applicable in the country and locality where the trial is being conducted. No grant funds may be expended on studies involving animals until all requisite approvals are in place, and notification to that effect has been provided to the Foundation. For purposes of this provision, an “animal” is defined as any live, vertebrate animal used or intended for use in research, research training, experimentation, biological testing or for related purposes. In the case of multi-national collaborations, the standards of each country may be followed, as long as (i) differences do not interfere with the design and analysis of the Project, and (ii) regulations in your institution and host country do not conflict with the management of the Project.

You agree to take responsibility for compliance of all subgrantees or subcontractors (if any) with the appropriate animal welfare laws, rules and regulations. You must report annually as a part of your progress report that the activities are being conducted in accordance with applicable laws in each respective venue (e.g., U.S. grantees must use the U.S. Public Health Service standards. Non-U.S. grantees may cite national laws or the CIOMS International Guiding Principles for Biomedical Research Involving Animals (see http://www.CIOMS.ch/frame_1985_texts_of_guidelines.htm) if there is not relevant national standard.

APPENDIX A: STAG WHITE PAPER

1.0 Goal

We want to create a new class of point-of-care (POC) diagnostics that will be broadly applicable in supporting our global health objectives and in particular will be easy to use, low cost and otherwise appropriate to ensure that these new tools will achieve significant impact and rapid uptake in resource poor settings. A POC diagnostic platform for Global Health has the ability to assess multiple pathogens and health conditions using a common set of technical, logistical, and medical decision-making paradigms. The results of the test should allow a minimally trained community health worker or other user to decide if a course of treatment is needed. A science and technology advisory group (STAG) will be created to advise the foundation on the particulars of our POC platform strategy, facilitate collaboration among the Grand Challenges in Global Health – Diagnostics (GCGH-Dx) grantees, and to set common technical and business standards for POC diagnostics platforms in developing world settings.

2.0 Background and Objectives

In order to bring about common diagnostic platforms suitable for low resource settings, it is important that they have the characteristics of being low cost, requiring minimal infrastructure to operate, short time-to-answer, minimal training to use, moderate to high performance, and simplified storage and distribution requirements. The recommitment to this Grand Challenge was designed to achieve the following objectives:

1. Develop a framework for collaboration by recommending a common set of technical and business standards for the development and integration of diagnostics components
2. Advance the state of the art in critical component technologies consistent with the business and technical standards developed under this program
3. Integrate best-in-class component technologies into diagnostic platforms under the framework of standards developed in this program

There will be three groups of players responsible for carrying out the main objectives. The main participants in Phase I will be Component Builders who will advance the state of the art in component technologies. In addition to Component Builders, the key participants in Phase II will be System Integrators who will take the best available component technologies (both developed during Phase I and from other potential partners) and integrate them into viable POC diagnostic platforms. The STAG will be responsible for drafting and recommending a common set of standards allowing the Component Builders and System Integrators to collaborate on novel platforms, in addition to advising on POC platform issues and facilitating collaboration. Analogous to the micro-electronics industry, we anticipate that such a framework of standards for diagnostic platforms could provide opportunities for continued innovations in specific components that could be integrated into an extended value chain of future platforms creating opportunities for improvements beyond the horizon of our investment. In addition, the standards would specify certain performance aspects that would simplify and harmonize logistics

and use. Creation of such standards is not only beneficial to the foundation's future effort in diagnostics research but also to the general diagnostics industry serving the developing world.

The design and limited proof-of-principle for a POC platform with a target product profile includes characteristics like:

- Quick time-to-answer,
- Simple readout,
- Low cost,
- Good sensitivity and specificity,
- Able to be used by minimally trained personnel,
- The ability to function above 30 °C and at high humidity,
- The ability to be stored for long periods of time without refrigeration,
- The ability to conduct the test without the need for local reagents/water and/or specialized laboratory equipment, and
- The ability to detect multiple pathogens or to distinguish between different pathogens and/or strains and subtypes.

The STAG is critical to the success of the GCGH-Dx program. In addition to advising the foundation on the particulars of our POC platform strategy, STAG will facilitate collaboration among the Diagnostics grantees, and will set common technical and business standards for diagnostics in developing world settings.

3.0 STAG Structure

The structure of the STAG is shown in Figure 1. Teams with separate but distinct functions will work together to carry out the most crucial functions of the STAG. These teams are described in the following sections.

3.1 STAG Executive Committee

The STAG Executive Committee will be formed with advisors and leaders from industry, academia, public-private partnerships, and other organizations engaged in global health work. As the POC platform standards take shape, these leaders will advise the foundation on the quality of the standards and how they will be received by the larger diagnostic community. They will serve as advocates to promote the agreed upon standards to the greater diagnostic community.

3.2 BMGF: foundation representation

This team will consist of stakeholders from various parts of the foundation. The exact membership will be determined as the GCGH-Dx program matures. We initially envision that the key members of this team will consist of experts from Global Health Discovery working in diagnostics and biomarkers. They will work to align the STAG's overall direction with the strategic needs of the foundation.

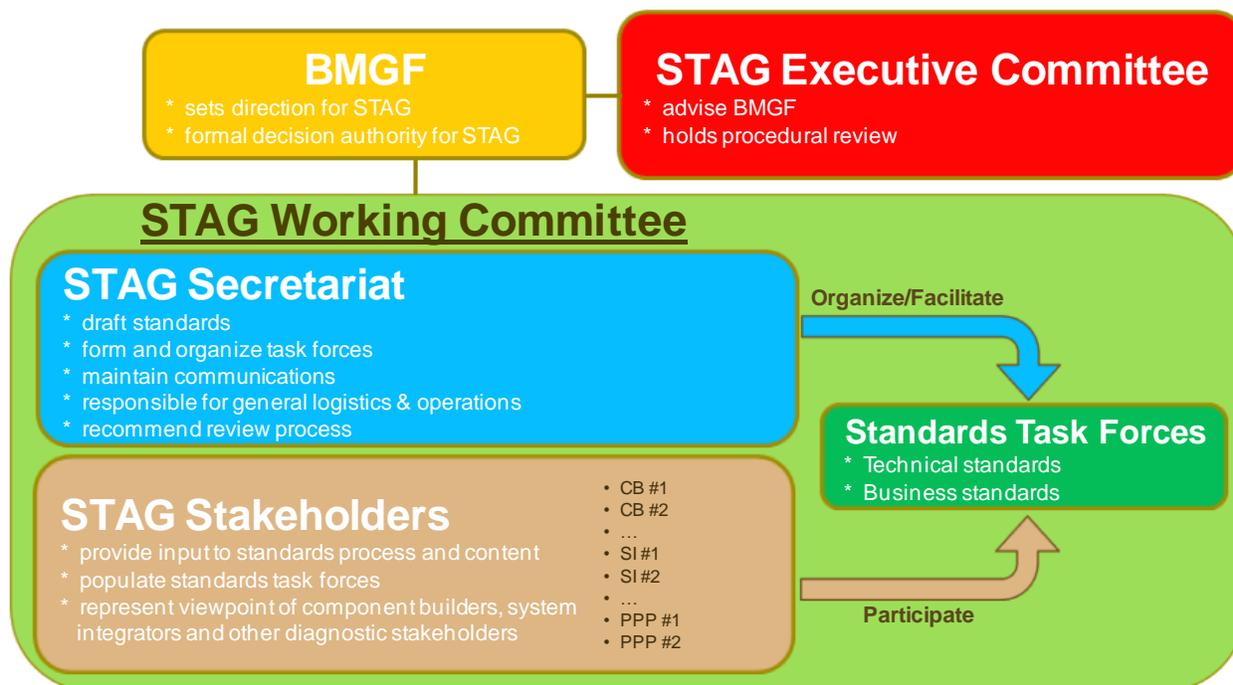


Figure 1. STAG Structure.

3.3 STAG Secretariat

In parallel to the funding of grants to individual Component Builders from this Grand Challenge in Global Health public request for proposal (RFP), we will seek proposals for a STAG secretariat that will coordinate the STAG Working Committee, the Stakeholders, the Executive Committee and with the BMGF. Their mission will be to coordinate the Component Builders’ activities in Phase I and make sure they align with the interests of Phase II System Integrators and the overall goals for POC platforms. The STAG Secretariat will take the lead in forming task forces that draft specific standards, facilitate communications, and encourage collaboration by ensuring smooth operation of the overall STAG.

3.4 STAG stakeholders

The STAG stakeholders will consist of participants from Phase I Component Builders and potential Phase II System Integrators. The Component Builders will each be allowed to send representative(s) to work in task forces and also to present their organization’s viewpoint. They will be asked to add an estimate for at least one half-time personnel to participate in the STAG as part of their Phase I grant proposal. Each potential System Integrator can also choose to send one volunteer to represent the viewpoints of diagnostic manufacturers. We also plan to include representatives from public private partnerships (PPPs) which have been long-time partners for developing diagnostic tools for global health diseases in developing world settings. Consideration will also be given to include other stakeholders, end-users, and health practitioners into the general STAG membership if the need exists.

3.5 STAG Working Committee

The STAG Working Committee will consist of various task forces formed to address each of the standards areas on a needed basis. The members and leaders for these task forces will be drawn from the STAG stakeholders. The secretariat may actively participate in the day-to-day operations of specific task forces, but will ultimately be responsible for consolidating the outputs from each task force into a set of written standards.

4 Developing Standards

A notional process for developing standards is represented by the diagram in Figure 2. One can start with developing world needs and some generalized notion about what specifications are needed for diagnostic platforms to fulfill those needs. The STAG Secretariat (blue team) will consolidate those ideas and form task forces to address those issues. The entire family of task forces together with staff from the STAG Secretariat makes up the STAG Working Committee (green team). An initial set of task forces can potentially be formed around the technical areas from the GCGH-Dx RFP. There should be standards in the areas of sample preparation, recognition and transduction, readout technologies, a cross sectional task force focused on technical integration, and task forces focusing on collaboration and business integration. Other more specialized task forces can be formed as needed. Although we don't envision any barriers to the stakeholders from joining any of these task forces, we expect that the participants will come from Component Builders within that technical area. Each time the task force drafts a set of standards, the Secretariat will ensure that it is disseminated to the entire Working Committee (green team) for review. A more formal procedural review will be held by foundation (gold team) and the Executive Committee (red team). A standard is formalized only if it passes all these stages of review and acceptance. We expect this process to be refined and updated by the Secretariat once it has been convened.

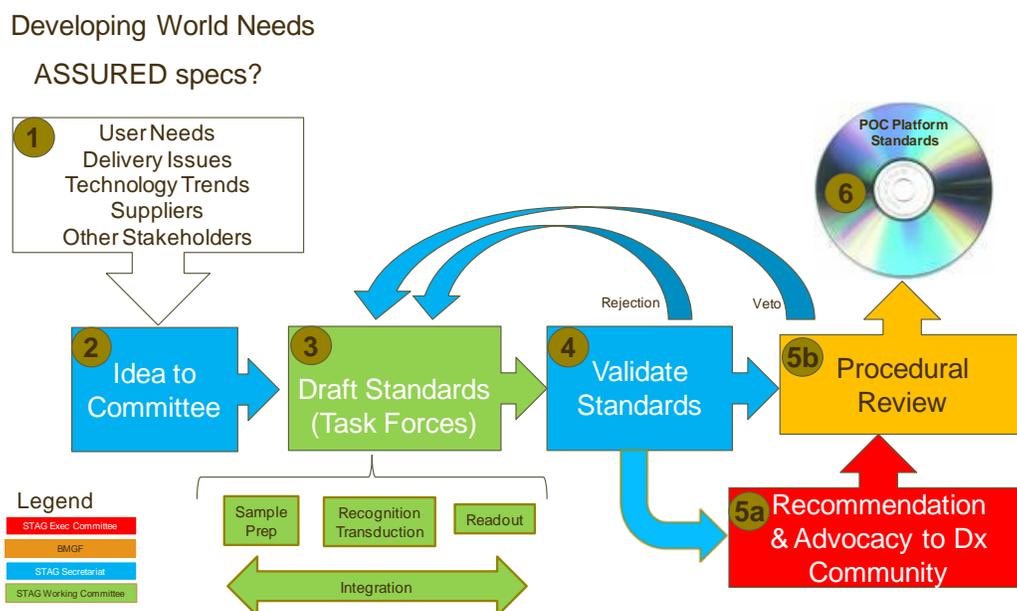


Figure 2. Process for developing standards.

5 Potential Standards Categories

The final standards document provides guidelines for general POC platform interface design and materials selection that can reduce redundant engineering effort and lead to improved design, manufacturability, operation and lowered costs. The goal is to enable devices from different vendors to interconnect via an open architecture and have common performance and usability features. The specification is intended as an enhanced capability to the state-of-the-art technologies incorporating a combination of electronics and fluidics. It will provide device researchers adequate room for product versatility and market differentiation without the burden of carrying obsolete interfaces, losing compatibility, and choice. Some of the top level standards categories are listed below. They generally refer to

- Performance – How does the device or system perform, and what limits does it need to operate within?
- Reliability – How long will the device or system achieve its stated purpose under the expected operating conditions?
- Quality – How well must the device or system be made so that it can achieve its stated purpose. An example is interfacial dimensional requirements
- Process – How is the device or system created, and what are the constraints on the fabrication process that limit device variation
- Test – Test, measurement, and methodological standards
- Design Requirements – Interfacial constraints, dimensional constraints, materials performance constraints, etc.
- Logistics
- Internal interfaces & system integration
- User friendliness, ease of use, lower training threshold
- Business standards, IP and information sharing

6 STAG ORGANIZATION

During the first quarter of 2010, we expect to identify a team or organization to carry out the responsibilities of the STAG Secretariat. The STAG Secretariat will put forward a cogent plan on how they expect to achieve the overall mission based on their experience in performing similar activities. Below are some of the elements that will be included in the detailed description of the Secretariat of the STAG:

- Group charter: the STAG Secretariat will need to draft and finalize a version of their charter, which will establish a common understanding regarding STAG membership and governance. A specific example of governance issue is that the STAG needs to clarify the process on what it means to “pass a standard.”
- Framework and plan for communications: communications between the major players in this GCGH-Dx should be transparent and timely. The STAG Secretariat needs to work with the

Stakeholders to agree on how much information will be communicated in a virtual fashion through email or website portal and how often the membership will meet.

- Standards development plan: the STAG Secretariat will be expected to layout the general framework for how to develop technical and business standards. They can form task forces to specialize on a subset of the standards if necessary. As the gap between the POC platform specifications and the component technologies future potential is understood, we expect a better defined and solidified task force structure to emerge.
- Analysis of fit for large scale manufacturing: the STAG Working Committees will need to perform an analysis of the component technologies and standards being advocated in Phase I of this GCGH-Dx program and determine whether they are amenable to large scale manufacturing processes that will be required for eventual delivery of the final product to large numbers of potential end-users in the developing world.
- Broad agreement on concepts and specifications: toward the end of Phase I, the STAG Secretariat should be leading the effort to finalize a set of standards that enable innovation and integration of component technologies into POC platforms for the developing world. There should be broad consensus from current and future participants of this GCGH-Dx program that these standards will enable breakthrough platforms not only for Phase II System Integrators, but also for other stakeholders in the extended diagnostics community serving the developing world.
- Project Plan: the STAG Secretariat will need to define a project plan that specifies what resources they need and the timing of the individual activities needed to accomplish its mission. This project plan will need to be updated on a quarterly basis.
- Clear Definition of the Deliverables from the STAG Secretariat: which must at a minimum include:
 - i) A specific set of Target Product Profiles (TPPs) for the POC platform;
 - ii) Architecture for the technical integration of components into a platform meeting the TPPs defined in i);
 - iii) A specific set of TPPs for each component in the defined architecture of ii). as well as other TPPs for elements of the systems where appropriate; and
 - iv) Clearly defined business and collaboration standards including an approach to the management of IP that ensures that the IP generated with these investments as well as any background technology needed is available to ensure that any POC platform developed under this program is broadly available to meet global health needs in the developing world while at the same maximizing the value of these innovations in the developed world.