Diabetes Screening in Low-Resource Settings: Developing Target Product Profiles for Gestational Diabetes, Type 2 Diabetes, and Potentially Type 1 Diabetes

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PATH has identified diabetes screening as an area in need of new approaches that are more suitable to low-resource settings (LRS).

In order to address the emerging and rapidly growing diabetes epidemic in LRS, there currently appear to be at least two distinct screening needs, (1) a point-of-care (POC) Type 2 diabetes mellitus (DM Type 2) assay that is low-cost, easy-to use, and requires no patient preparation and (2) an assay with similar characteristics that detects the smaller and more transient metabolic changes due to gestational diabetes mellitus (GDM). There may also be a need for a third distinct assay for Type 1 diabetes, although it appears possible that a Type 2 assay may serve as a Type 1 screening tool as well. However, we would like to focus discussions at the current time on DM Type 2 and GDM.

Towards Target Product Profiles (TPPs) for Diabetes Screening in LRS

A TPP is a statement of the essential attributes of a putative clinically and commercially successful product, which can form the basis for commercial evaluation and guide discovery and development activities. In this instance, it can also be used to evaluate the appropriateness of existing screening technologies for new (low-resource) settings and whether some adaptations might be required.

Opportunities for alternate screening and treatment monitoring approaches that are amenable to LRS may lie in a new generation of noninvasive or minimally invasive, rapid diabetes screening technologies that measure biomarkers of sustained hyperglycemia.

Although there is much overlap between the TPPs for DM Type 2 and GDM, there are also some important differences. Therefore, they are discussed separately in the following sections. No diagnostic device that fulfills all these requirements currently exists, or may ever exist. A real-life device for LRS will likely not be able to fulfill every single one of the requirements, but will rather be an attempt at compromise. Several companies, academic groups, and nonprofits are in the process of developing tools that are potential GDM screening candidates.

Brief summary of current standard approaches for diabetes screening, and associated problems

The following is a nonsystematic overview of approaches for and issues with diabetes screening, based on current WHO guidelines (http://www.who.int/diabetes/publications/en/screening_mnc03.pdf) and recent literature:

DM Type 2 screening—standard approaches:

Screening approaches for DM Type 2 include risk assessment questionnaires, biochemical tests, and combinations of the two. The biochemical tests currently available are blood glucose, urine glucose, blood HbA1c, and blood fructosamine measurements. Each screening test needs a designated and predetermined threshold or "cutpoint" that defines high risk. Screening tests are usually followed by diagnostic tests (fasting plasma glucose [FPG] and/or an oral glucose tolerance test [OGTT] using standard criteria) in order to make the diagnosis.

Problems with standard approaches:

- Questionnaires are low-cost but time consuming, have sensitivity in the 70-80% range, but low specificity (30-40%).
- Urine glucose has low sensitivity of 21-64% but greater than 98% specificity
- FPG has sensitivity of 40-65%, specificity greater than 90%, and requires fasting (typically two visits are needed, creating patient compliance and loss to follow-up issues)
- Random plasma glucose (RPG) testing has a sensitivity of 40-80% and specificity of 60-77%
- HbA1c testing needs an instrument/disposable, and is currently pricey on a per-test basis; the sensitivity is from 78-81% and specificity is 79-84%.

GDM screening—standard approaches:

GDM differs from DM Type 2 primarily in that it is a transient condition during pregnancy. The International Association of Diabetes and Pregnancy Study Groups proposed a single screening algorithm for GDM worldwide—the 75-g OGTT. This approach is now also endorsed by the American Diabetes Association. However, other algorithms remain in clinical use, including RPG, FPG, and questionnaire-based approaches.

GDM screening – problems with standard approaches:

- OGTT – Requires a baseline blood glucose test, a glucose challenge, and at least one (usually two) additional blood glucose tests for diagnosis. Under ideal conditions (in the

24-28th week of pregnancy), sensitivity is around 80% and specificity is around 80%. However, this test creates problems of nausea and vomiting, and the failure rate of the OGTT in screening for GDM is about 10%.

- FPG – Requires fasting and one blood glucose test. FPG has the potential to avoid nearly one-third of the cumbersome OGTTs at the expense of missing one-fifth of pregnant women with milder GDM.
- HbA1c – Literature varies widely on sensitivity, specificity, and appropriate thresholds for GDM. General consensus is that it is not sensitive enough to be useful at a reasonable specificity. It also needs an instrument/disposable, and is currently pricey on a per-test basis.

Ideal product characteristics of a DM Type 2 screening device

Increasing access to DM Type 2 screening for populations in LRS has to be the primary goal of any related product and algorithm research and development. Ideally, such devices could be used in a variety of settings, ranging from mobile or stationary screening campaigns to general primary care and incidental screening (where a patient visiting a caregiver for an unrelated condition is also screened for diabetes). Ideal devices might have some or all of the following characteristics:

- Is low cost (<$1, comparable to that of a glucose test strip)
- Can be administered ad hoc (without fasting or any other preparation by the patient) and provide a result within minutes
- Allows incidental screening of patients during caregiver visits for unrelated conditions.
- Requires no follow-up visits.
- Determines one or several parameters correlated to chronic hyperglycemia (i.e., parameters that represent a *longer*-term average of hyperglycemia are appropriate)
- Provide a definitive, actionable diagnosis of DM Type 2 or rule-out (sensitivity and specificity >90%)
- Is simple to use (preferably usable by minimally trained health workers)
- Requires only a finger stick or urine sample collection
- Requires no maintenance, calibration, temperature-controlled storage and use, or additional reagents
- Can be manufactured in existing facilities in developing countries and distributed using existing supply chains

Ideal product characteristics of a GDM screening device

Operationally, most characteristics listed for DM Type 2 apply also for GDM screening, with some modifications:

- The test determines one or several parameters correlated to gestational hyperglycemia (i.e., parameters that represent a *shorter*-term average of hyperglycemia are appropriate)
- Can be integrated with existing antenatal screening protocols, algorithms, and/or devices

Emerging devices and methods that may be candidates for diabetes screening in LRS

Current and emerging nonfasting DM Type 2 screening methods, and extension of their use to GDM screening:

A variety of novel methods for diabetes screening are being studied, and in some cases are already in use, including POC-compatible HbA1c readers, autofluorescence-based readers that detect advanced glycation endproducts (AGEs) in skin[1], and devices that measure sudomotor function (and by inference diabetes risk) by detecting deviations in the ionic balance of the sweat.[23]

A1c readers can be very inexpensive and POC-compatible but, so far, require expensive disposables that need to be refrigerated, as well as a (minimally) invasive finger stick sample. AGE readers and the sweat gland reader require no expensive disposables and are noninvasive. While the devices initially are more expensive than A1c readers, their cost can be amortized over time, resulting in likely very low per-test costs.

Table: Comparison of candidate DM Type 2 screening technologies

	Pros	Cons
POC HbA1c readers	• Low device cost • POC-compatible	• High disposable cost • Refrigeration required • Minimally invasive
AGE readers	• No disposable • Non-invasive • Low per-test cost	• High device cost • Earlier in the development pipeline • Need more evaluation for both GDM and DM Type 2 screening
Sudomotor function readers	• No disposable • Non-invasive • Low per-test cost	• High device cost • Earlier in the development pipeline • Need much more evaluation for both GDM and DM Type 2 screening

The primary use of these devices would appear to be for DM Type 2 screening, as the markers they measure typically represent averages of hyperglycemia over a long period of time.

However, given that most pregnant women in LRS typically go for their first (and sometimes only) appointment later than their high-resource setting counterparts, it would be likely that whatever changes are already present due to GDM are more pronounced and more easily measurable. Thus, classes of devices that can identify patients with diabetes risk without fasting, but for which there is no agreement on their usefulness for detection of GDM in high-resource settings, might nevertheless be useful for this purpose in LRS, and should be studied.

Even if AGE, sudomotor function, and A1c readers ultimately prove too insensitive to the relatively rapid diabetes-related changes during pregnancy, they may still be appropriate for monitoring both the mother and child for the onset of overt DM Type 2, given their elevated risk resulting from the GDM. In this context, it may be used more like a DM Type 2 screening tool, albeit at prescribed intervals and with a greater expectation of a positive result.

New biomarkers specifically for GDM screening:

As current DM Type 2 methods such as HbA1c can only identify slow changes in physiology due to exposure to elevated glucose levels, new, faster-responding biomarkers are needed. One promising possibility is in the area of determining the level of glycation of serum proteins with shorter half-life than glycated hemoglobin. The most promising candidate for this technique is glycated albumin (GAlb). GAlb, produced by a similar mechanism to A1C, is an emerging marker that may eventually become useful in GDM screening due to its shorter latency[4], but investigations are still in the research stage, and no consensus has emerged. GAlb remains in circulation approximately one-third as long as A1c, and thus integrates the effects of elevated glucose over approximately one month, long enough to average out the effects of recent nutritional intake, but short enough to allow identifying the changes within the gestational period. Human serum albumin has a clinical range of (3.4 to 5.4 g/dL, making it the most prevalent protein in serum. A fraction of it is glycated under normal and abnormal conditions (around 7-17% for normal individuals, and about 12-23% for diabetics[5]). The gold standard for GAlb quantification is high performance liquid chromatography (HPLC), with several enzyme-linked immunosorbent assays (ELISAs) available as well. HPLC is not suitable for POC diagnostics because it is very complex and expensive; ELISAs can be relative low cost per test, but require refrigeration and a laboratory. In order to determine if GAlb can be a useful marker to screen for GDM in LRS, PATH is working on an instrument-free rapid strip test to detect elevated GAlb. Rapid diagnostic strip tests typically can be stored at room temperature, cost less than $1 per test, and can be used by minimally-trained health workers.

Other markers that also have some potential for GDM screening include cytokines, chemokines, hormones, and transcriptional factors stimulated by the AGE/receptor for advanced glycation end products (RAGE) signaling pathway[6,7,8,9], soluble RAGE[10] (a circulating, nonsignaling isotype of the receptor that may function to buffer the signaling pathway against transient AGE spikes),

and even other common clinical laboratory "chemistries", if tested in multiplex with other markers and risk factors and evaluated in combination.[11] However, significant investment in additional study will be required before any of these can be considered feasible alternatives for GDM screening and monitoring.

(Re)visiting urinalysis for DM Type 2 and GDM screening in LRS:

A compelling possibility is that well-established, inexpensive urine dipstick tests for glucose and albumin, which have been displaced as diagnostics in wealthier settings, may be employed to make a significant impact in LRS.

Elevated urine glucose, while a relatively insensitive test for GDM and DM Type 2, is likely superior to exclusively biometric and/or questionnaire-based screening alone.[12] A positive result could indicate the need for follow-up with a more accepted assay. Alternatively, it might be possible to screen with a questionnaire and follow up with a high-specificity urine glucose test for confirmatory diagnosis in some LRS.

Another urine marker, microalbuminuria, is a well-known indicator of risk for the cardiovascular and renal sequelae of diabetes. This marker is elevated in GDM even when subsequent DM Type 2 does not manifest[13], and would also signal the need for follow-up. It is not clear that the currently available albumin dipsticks have the analytical sensitivity to be effective in this context, but further investigation would better define the need. A multiplex urine dipstick including tests for glucose, microalbumin, and nutritional indicators could be a powerful initial screening tool in an LRS antenatal clinic—enabling follow-up and treatment that would significantly increase the health of both mothers and their babies.

Integrated screening devices for multiple parameters that are relevant for antenatal care in LRS:

An alternative approach to creating a low-cost screening assay just for GDM is to create a multivalent platform that screens for a variety of parameters. While the platform may be more costly, added utility may provide sufficient benefits to justify the expense and potential complexity. Parameters that might be tested on such antenatal screening platforms are malaria; syphilis; anemia-related parameters such as ferritin and hematocrit; HIV; and a GDM marker such as GAlb. Platforms under evaluation at PATH include immunoassay-based methods, as well as a reagent-free, light scattering-based blood test that can, in principle, detect all these parameters.

Discussing TPPs as part of the Diabetes Expert Advisory Board Meeting

For the first meeting of the Diabetes Expert Advisory Board, we would like to discuss issues related to developing TPPs for DM Type 2 and GDM. Some of the questions that we would like to discuss include:

- Can existing diabetes screening products be rolled out largely as they are used in high-resource settings? Or are new algorithms with current products (e.g., urinalysis), or entirely new screening products required to adapt to LRS?
    - Is our characterization of current product attributes accurate? Are there any egregious errors or anything we neglected to mention?
- What benefits could new screening products for diabetes bring to LRS?
    - Do you agree with the two distinct screening needs we have identified up-front? Is there anything we neglected to mention?
    - Are there specific needs in terms of confirmatory diagnosis that we should also consider?
- For both DM Type 2 and GDM:
    - Are the general categories of product characteristics given above on page 3 appropriate? Which characteristics should be added, and are there any that can be removed? Which characteristics are highest-priority?
    - What should TPP targets be for:
        - sensitivity
        - specificity
        - turnaround time
        - throughput
        - per-test and instrument costs
        - complexity of use
        - service and calibration
    - What are your reactions and concerns regarding the candidate technologies we identify above? Do any candidate technologies seem especially promising in terms of:
        - serving as a single device that can screen for GDM and DM Types 1 and 2?
        - serving as a single device that could combine screening and diagnosis into one step?
        - applications for DM Type 2 treatment monitoring?

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absence of subsequent diabetes is associated with microalbuminuria: results from the Kidney Early Evaluation Program (KEEP). *Diabetes* Care. 2010;33(12):2586–2591.

For PATH Fund admin only: PATH Fund file #

PATH Fund Application

Instructions to applicants: Your proposal must be submitted using this form. Proposals may be no longer than 5 pages, inclusive of this application cover section. In addition, the proposal must be accompanied by a budget with labor breakdown, in Annbud or Propbud format. Submit application by e-mail to the PATH Fund Administrator (*jneptune@path.org*) and to Carla Ware ***cware@path.org*** **.**

Project title	Novel low-cost technical approaches for diabetes screening and treatment
Investment level	☐ 1: early stage activity essential to launching a new area of work or project ☒ 2: project activity that is an important stepping stone to large-scale project implementation)
Primary health focus area **(Choose only one)**	☐ Emerging and epidemic diseases ☐ Reproductive health (not abortion-related) ☒ Health technologies ☐ Vaccines and immunizations ☐ Maternal and child health
Implementing program	TS
Project RPM	Bernhard Weigl
Project PADM	Kathy Tietje
Brief project summary	Several new technologies with a large potential impact on rapidly growing populations at risk for diabetes in low-resource settings are now on the cusp of availability. They appear to be candidates not only for screening for diabetes risk, but also for guiding treatment with insulin and/or monitoring the effectiveness of lifestyle changes. The proposed project, a cross-cutting activity comprising TS, RH, and the Tanzania Country Program, aims to seek out and review these technologies, create a framework for evaluating them in the context of larger diabetes control programs, and initiate a small proof-of-principle field study with a leading candidate technology. Starting with this project, we believe that PATH can become well positioned to be an effective and credible partner in future larger LRS diabetes and chronic disease programs.

PATH's Strategy Framework 2010 - 2015

- *Accelerate interventions:* move new tools, technologies, and interventions as efficiently as possible through the innovation cycle from idea to broad and effective use.
- *Expand reach:* extend the capacity and coverage of our existing field programs to reach those of greatest need and, where appropriate, establish new field operations in strategic, high-priority countries.
- *Achieve scale:* reach more people with scaled-up, integrated sets of health interventions and clearly demonstrate the value of sustained political and financial commitment to global health.

What are the key ways in which this project is aligned with PATH's 2010-2015 strategy?

This proposal addresses an increasing health problem in low-resource settings (LRS), namely chronic diseases, and specifically diabetes prevention, screening, treatment, and control. It is based on innovation and partnering with industry, as well as cross-program collaboration. Specifically, new tools for diabetes screening and treatment are becoming available that, we believe, have great applicability in developing countries, but will not successfully be deployed there without engaging the developers at this stage and accelerating these interventions.

The PATH Diagnostics Group (PATH Dx) within TS has so far primarily focused on infectious disease areas and has been successful in introducing assays for, among others, HIV, malaria, STDs, and cervical cancer. As morbidity and mortality caused by chronic diseases start to surpass those caused by infectious diseases in some developing countries, we see addressing chronic diseases, and especially diabetes, as both an area of critical need as well as a significant growth opportunity for PATH Dx.

PATH Dx, through our project work and, more recently, as the lead organization of the NIH/NIBIB-funded Center for Point-of-Care Diagnostics for Global Health (GHDx Center), has developed core areas of expertise in diagnostics development, lab and field validation, technology transfer and support of manufacturing and quality systems, user needs assessment, and diagnostics developer and user training. We believe that our core competencies are very transferrable to chronic disease diagnostics and diabetes screening for LRS.

The Reproductive Health Global Program (RH) has, over the last year, explored opportunities for engagement in chronic disease programs. Two outcomes of this work were an issue of *Outlook* analyzing the relationship between chronic disease and reproductive health and an internal white paper summarizing the results of an extensive literature search and series of interviews with experts in chronic disease. In May, RH submitted, in consultation with PATH Dx, a proposal to the Centers for Disease Control and Prevention (CDC) that seeks to develop and implement evidence-based programs in Guatemala and Tanzania to prevent and control diabetes among women through low-cost risk-assessment tools using questionnaires and urine glucose testing screening and group-based behavioral interventions.

The RH proposal team and the team on the PATH Dx side agree that, while significant benefits may be available through self-assessment and urine testing, linked with lifestyle prevention approaches, ultimately there will be a large share of the at-risk population that will require screening and drug treatment monitoring based on highly cost-effective novel diagnostic devices. Several new technologies, now on the cusp of availability, appear to be candidates not only for screening of populations for diabetes risk, but also for guiding treatment with insulin and/or monitoring the effectiveness of lifestyle changes. The proposed project aims to seek out and review these technologies, create a framework for evaluating them in the context of larger diabetes control programs, and initiate a small proof-of-principle field study with a leading candidate technology.

This proposal comprises collaboration across three programs: TS, RH, and the Tanzania Country Program (with a strong potential for expansion to India Country Program through a GHDx Center supplement from NIBIB). The effort will be led by Bernhard Weigl, Ralph Schneideman, and Ken Hawkins of PATH Dx; Jen Drake and Vivien Tsu of RH; and Mohammed Makame in Tanzania. Input and guidance will be also be sought from Jane Hutchings and Jose Jeronimo, and from the VP, Global Programs as it pertains to the PATH-wide chronic disease interest.

PATH Dx has been in discussions with several groups developing candidate technologies for diabetes screening, including Veralight, Inc. (Albuquerque, NM), Diagnoptics (Groningen, The Netherlands), Bayer Diabetes (Tarrytown, NY), and Siemens, as well as diabetes testing experts such as Tom Schulte, formerly of Pelikan Technologies, and Gerald Kost of UC Davis, all of whom have expressed a desire to partner with PATH on diabetes research. We expect others to be added to this list.

The proposed work will review emerging technologies that are potentially suitable for diabetes screening and diabetes treatment and prevention monitoring in LRS. So far, all technologies that have been reviewed are targeted towards high-resource settings, and have been evaluated primarily or only in the US and Europe. While many features of the proposed products appear to be a good fit for developing country healthcare, some are not. As those technologies are developed further, there is a unique current opportunity to influence their development by providing information, incentives, and an evaluation framework to the developers such that the devices may become ultimately useable and acceptable in developing country contexts.

Why is the PATH Fund a critical source of funding for this proposal?

While we see several exciting funding opportunities for LRS diabetes-related programs, PATH does not yet have the ability to actively compete for those funds. The PATH diagnostics development and evaluation framework, the programmatic abilities of RH, and the PATH country programs all are very credible and critical components of any diabetes proposal, but we still lack hard diabetes device and disease expertise. The proposed project will allow us to jump-start this work, and, supplemented by additional funds that may become available through NIBIB in the near term, will create an evaluation framework that will make us an extremely attractive partner for diabetes device developers and screening and prevention programs.

How do you plan to share your work with the broader PATH community?

This work will already be a cross-cutting collaboration between two global programs, one (and hopefully later, two) country offices, and ELT involvement, and as such, we expect the information to diffuse fairly rapidly across PATH programs. Nevertheless, we will also conduct at least one brown bag, and an Outlook article or similar publication to present both the results of this project as well as our plans for expansion into larger diabetes programs.

I. Introduction—background and rationale

In 2010, diabetes prevalence worldwide was estimated at 6.6 percent among people ages 20 to 79.[1] As the overall burden of infectious diseases decreases in developing countries—due in large part to effective public health programs implemented over the past several decades—the burden of chronic diseases is growing.[2] By 2030, the worldwide prevalence is projected to be 7.8 percent, an 18-percent increase over the 2010 rate, largely due to greater food availability and increased consumption of sugar and fats. Between 2007 and 2025, the number of people living with diabetes globally will increase from 246 to 380 million, and the majority will live in developing countries.[1]

Diabetes imposes a considerable burden in terms of premature mortality, morbidity, and health care costs. The International Diabetes Federation estimates that 4 million deaths were caused by diabetes in 2010 among people 20-79 years old.[1] This estimated number of premature deaths is similar in magnitude to deaths in this age group from several infectious diseases. The death rate for men with diabetes is almost twice that of men without it, while for women it is 2.5 times higher than that of women without diabetes. Diabetes is a major risk factor for cardiovascular disease (CVD), which causes up to 65 percent of all deaths of people with diabetes in developed countries.[3] Life expectancy for people with diabetes has been estimated to be up to 10 years shorter than for people without diabetes.[4] The direct health care costs of diabetes range from 2.5 percent to 15.0 percent of the annual health care budgets in developing countries. But the indirect costs are even higher, and, because diabetes is projected to increase most among people in their productive years (ages 20 to 64) over the next 30 years, the future indirect costs will be even higher.[3] Efforts to prevent type 2 diabetes involve lifestyle interventions—changes in diet and increased physical activity among people at high risk—and medications. Other interventions include screening to detect diabetes in its early stages, and managing the disease to reduce its complications. Current interventions common in developed countries would not be cost-effective or

feasible in many LRS, including specific high-cost drugs, cholesterol and/or intensive glucose control, and laboratory-based screening for undiagnosed diabetes. The new generation of devices to be evaluated in this proposal has the potential to change that, allowing effective treatment and monitoring of the effectiveness of preventive measures, even in LRS.

II. Project goal and objectives

Several novel methods for screening for diabetes and pre-diabetes with potential application in LRS are currently in late stage R&D. Those methods include at least two different spectroscopic, non-invasive methods to test skin for the presence of glycated proteins, as well as new lower cost methods for HbA1c measurement in finger-stick blood. Those methods could both replace, and improve upon the established method of fasting glucose tolerance testing (GTT) which is complex to administer, and, in itself, only useful for screening but not for treatment monitoring and prediction of diabetes-related complications (while the newer methods are).

The goal of this PATH Fund application is to create institutional knowledge, collaborations, a framework for evaluation of diabetes-related testing technologies, and a small pilot evaluation field study. While this project will focus on at-risk population diabetes screening and treatment monitoring, lessons learned can also be applied to other areas such as gestational diabetes screening and treatment. The project goal will be supported by five objectives:

Objective 1: Establish relationships with US and international diabetes experts and opinion leaders and create an informal expert group to advise on options for diabetes screening in different LRS contexts, including general population and pregnant women (gestational diabetes) screening.

Objective 2: Establish formal relationships with companies that develop novel diabetes screening technologies, including Veralight, Diagnoptics, Beyer (A1cNOW), Novo-Nordisk, and Siemens (DCA Vantage).

Objective 3: Create a landscape analysis document comparing and evaluating the candidate technologies options and approaches.

Objective 4: Conduct a small pilot evaluation study in a LRS (Tanzania) with a leading screening technology identified in Objective 1. Current main candidates are the Veralight and Diagnoptics noninvasive screening techniques, to be compared in the study to fasting glucose tolerance testing.

Objective 5: In collaboration with the expert group, outline a clinical evaluation framework and a list of introduction opportunities for the leading candidates in one or two representative LRS contexts and seek funding for this work.

III. Future funding potential

Existing grant application: Global Collaboration with NGOs: A focus on diabetes among women in Guatemala and Tanzania (submitted to CDC May 2010, decision expected September 2010).

Proposals under consideration or preparation:

- Bridges Program, 3rd round, International Diabetes Federation.
- Health Innovation Portfolio, HIP1 proposal.
- GHDx Supplement (to expand proposed work to India), a proposal to NIBIB.

Further suitable funders will be approached in the future for larger programmatic efforts.

III. Implementation plan describing major project activities (with timeline)

The implementation plan consists of key activities under each project objective.

Objective 1 Activities:

Form a cross-program advisory committee comprising representatives from TS, RH, ELT, and the Tanzania country office to assist the project with selecting the international experts.

Establish an expert group comprising technical advisors as well as potential collaborators on future larger programmatic diabetes-related projects. The initial focus will be on experts based in the US, Europe, Tanzania, and India, with expansion as the project develops.

Convene expert group in conjunction with major diabetes meeting. Potential conferences include the Diabetes Technologies Conference—ATTD 2010, the ADA annual meeting, and the EASD Annual Meeting. Later, the expert group will be convened via web/phone conference.

Objective 2 Activities:

Identify companies and research groups active in diabetes screening technologies with potential for LRS use.

Approach candidate partners and perform due diligence on technology and business capacity.

Establish formal relationships (with CDA and MOU) between selected groups and PATH.

Objective 3 Activities:

Create initial landscape document describing viable technology options for evaluation studies based on information obtained from groups on whom due dilligence was performed.

Present findings for review to advisory committee and expert group.

Integrate advisory panel recommendations in initial pilot study.

Objective 4 Activities:

Plan small pilot evaluation study with leading candidate technology in Tanzania.

Obtain IRB approval – expectation of minimal risk if non-invasive screening technology is used with patients who undergo fasting glucose testing already as clinically indicated.

Conduct sudy in Tanzania: Approximately 30 patients with normal and elevated risk for diabetes will be screened with candidate technology and compared to fasting glucose tolerance. Expected duration of study is one week or less.

Evaluate results and present findings for review to advisory committee.

Objective 5 Activities:

Plan further and larger evaluation activities within programmatic framework: Consult advisory committee and screen funding opportunites.

Develop draft protocol for larger follow-on study.

On an ongoing basis, take advantage of smaller funding opportunies as the present themselves to supplement PATHfund activiites.

Approach potential funders of larger study.

Timeline:

Key Activities By Objective	Q4 2010	Q1 2011	Q2 2011	Q3 2011	Q4 2011
Objective 1 Activities:					
Form a cross-program advisory committee	x				
Establish an expert group	x				
Convene expert group	x	x	x	x	x
Objective 2 Activities:					
Create initial landscape document	x				
Partner due diligence		x	x		
Establish formal relationships with partners		x	x		
Objective 3 Activities:					
Create initial technology landscape document			x		
Present findings for review to expert committee			x		
Advisory panel recommendations for pilot study				x	
Objective 4 Activities:					
Plan pilot evaluation study		x	x		
Obtain IRB approval			x		
Conduct study in Tanzania				x	
Evaluate results and present findings for review				x	
Objective 5 Activities:					
Plan further and larger evaluation			x	x	x
Develop draft protocol for follow-on study				x	
Take advantage of smaller funding opportunies to supplement PATHfund activiites.		x	x	x	x
Approach funders for larger study					x

IV. Outline of expected project outputs (tangible deliverables) and outcomes (broader program/health achievements) by activity

This project will deliver:

- A standing advisory committee comprising diabetes experts from academia and industry, with strong developing country representation.
- A landscape document on emerging diabetes screening and treatment monitoring technologies that are suitable for LRS.
- Report on outcomes from a pilot evaluation study.
- A draft protocol and plan for more comprehensive evaluation and introduction activities and cost-effectiveness research.

V. Monitoring and evaluation plan

The project will be successful if we complete the activities described in section IV, which are summarized in the critical outputs and outcomes below.

Results	Targeted Achievement
Outputs	
Advisory panel and expert group established (Y/N)	December, 2010
Partner due diligence completed (Y/N)	February, 2011
Study planned and conducted (Y/N)	September, 2011
Outcomes	
Feasibility of device-based diabetes screening in LRS investigated (Y/N)	October, 2011
Feasibility of device-based treatment and prevention monitoring under discussion (Y/N)	October, 2011
Findings and recommendations utilized to inform PATH positioning in diabetes-related diagnostics development and evaluation and programmatic activities (Y/N)	October, 2011

VI. Conclusion

This set of proposed activities will play a critical role in establishing PATH as an active agent in diagnostic and programmatic interventions for diabetes in LRS. It will build on interests and capacities in several programs within PATH, while also bringing in outside technical expertise and creating partnering opportunities with commercial and academic innovators. It capitalizes on the availability of several new technologies and on the existing resources of the PATH Diagnostic Group, which is well positioned to move into this new area.

VII. Budget Justification

The budget covers the personnel of Seattle team members working across TS, RH, and Tanzania. Bernhard Weigl, Vivien Tsu, and Mohammed Makame will perform Objective 1 activities; Bernhard Weigl, Jennifer Drake, Ralph Schneideman, and Kenneth Hawkins will perform Objective 2 activities; Bernhard Weigl, Vivien Tsu, Jennifer Drake, and Kenneth Hawkins will perform Objective 3 activities; Bernhard Weigl, Jennifer Drake, Mohammed Makame and Juma Mahayu will perform Objective 4 activities; Bernhard Weigl and Kathleen Tietje will perform Objective 5 activities. In addition, Kathleen Tietje and Alan Barclay will provide overall project management and administrative support, and Juma Mahayu will provide project administrative support in Tanzania.

Travel funds are requested to establish relationships with domestic and international collaborators and convene a diabetes expert group in conjunction with a major diabetes meeting. In addition, travel funds to Tanzania are requested to conduct noninvasive diabetes screening as described in the Project Objectives.

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