RESULTS FOR DEVELOPMENT INSTITUTE

Prizes for Global Health Technologies:

An Assessment with a Case Study on TB Diagnostics

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This is a consultation draft: conclusions may evolve. Please post comments to our website (http://healthresearchpolicy.org/) or send them to the authors at pw2101@columbia.edu and apalriwala@resultsfordevelopment.org.

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Acknowledgments

To be added

Executive Summary

Prizes are enjoying a resurgence. More and larger prize contests are being launched and prizes of all kinds are attracting attention from scholars, policy-makers, governments, and funders. In health, several groups have proposed incentive prizes— large cash rewards for achievement of specified objectives—as a way to spur development of needed new health technologies (drugs, vaccines, diagnostics) for the diseases of the developing world, products that have been largely neglected by a pharmaceutical industry focused on lucrative markets in high-income countries. There is little experience with prizes for health product development, however, and many questions remain about the feasibility of this approach. This study addresses some of these questions, including the relevance of prizes for different kinds of technologies; the willingness of product developers to pursue a prize; the merits of prizes for final products ("end" prizes) as well as important milestones in product development; and the best way to promote affordable access to products developed through prizes.

The study has two main parts: a general analysis of the strengths and weaknesses of prizes as a way to drive product development and access in the developing world and a detailed case study of recent prize proposals for point-of-care TB diagnostics. In addition, it offers a preliminary analysis of prizes for other health products.

Prizes, like advance market commitments (and the patent system), promote investment in specified products by increasing the reward for success, in contrast to grants and other so-called "push" mechanisms that reduce the cost or risk to product developers. An important advantage of prizes is that sponsors do not have to choose among candidate products or product developers: they need to only define with sufficient precision the desired product (or product development milestone) and then leave the door open to all comers. Prizes can thus bring new minds and new ideas to difficult problems and are particularly attractive when the way forward is not clear and substantial innovation is required. Since prize sponsors pay only if their conditions are met, R&D funding through prizes can be considered a form of "results-based financing".

An important disadvantage of prizes relative to grants and contracts is that only researchers and product developers who can bear the risk and raise the necessary funds for R&D upfront can participate. This may exclude valuable contributors.

A prize for a neglected disease drug, vaccine, or diagnostic test will have failed if the new product doesn't reach the people who need it. One way to promote access is to make the prize reward contingent on licensure of relevant intellectual property (IP) to all interested manufacturers. This strategy could be a powerful way to ensure sustainable supply at an affordable price, but only if generic production is feasible, markets are sufficient to attract suppliers, and prize specifications steer developers toward appropriate technologies. Moreover, licensing provisions must be acceptable to product developers if a voluntary prize mechanism is to succeed. Other ways to promote access are to rely on cost provisions in the prize specifications or to require winners to supply the product at an agreed price or at an agreed mark-up from cost. These approaches may not be as effective as generic production in driving down prices and ensuring supply over the long run but may be more practical in many cases.

Tuberculosis (TB) claims almost two million lives ever year and progress in controlling the disease in developing countries has been slow, especially where HIV prevalence is high, in large part because of inadequate drugs, vaccines, and diagnostics. In particular, there is broad consensus that an improved diagnostic test—one that would be more sensitive and accessible than sputum smear microscopy, the current standard in most poor countries—could save many lives and slow transmission. The primary obstacles to development of the needed point-of-care tests are technological: the two most promising paths are blocked, respectively, by lack of biomarkers and lack of a suitable platform for use in remote areas. The X Prize Foundation and a coalition of four countries, Bolivia, Barbados, Bangladesh, and Suriname ("BBBS"), supported by Knowledge Ecology International and Médecins Sans Frontières (MSF), have independently proposed prizes for improved TB tests. Both are end prizes for tests that meet a set of specifications in field trials. Neither is yet funded or launched.

The X Prize proposal offers $5-20 million for winning products, depending on performance in several dimensions, while the BBBS proposal offers a $100 million grand prize to the first winning product plus smaller prizes along the way. We conclude from interviews with diagnostic firms and from our own analysis that the X Prize purse, while it might cover R&D costs, is probably too small given the risks to spur widespread industry investment. There may be a substantial market for a point-of-care TB test; thus the prize need not provide the sole return on investment. Yet $5-10 million is small compared to the expected market, so would probably not change the commercial calculations of firms. The amount proposed by BBBS is almost certainly sufficient to interest a wide range of firms, but such a large prize might not be the most efficient use of scarce resources, given the potentially large market.

The two proposals differ as well in their approach to access. BBBS would require that winning product developers license all IP necessary for competitive supply, in the field of use, to a patent pool; they must also meet a manufacturing cost provision or market penetration test. We conclude that licensing provisions for diagnostics would deter some firms from participating; one key to making this approach work is to find an acceptable and enforceable way to handle IP related to technological platforms that can be used for multiple tests. The X Prize proposal requires only that contestants submit a manufacturing plan with some cost information—we believe that this provision is unnecessarily weak, as firms consulted for this study had no objection to cost ceilings.

The two proposals include other features that would increase their appeal to product developers, included subsidized clinical trials and, in the case of X Prize, access to specimen banks and a promise to help aggregate demand. X Prize's demonstrated capacity to attract media attention could also appeal to industry.

Would a TB diagnostics prize change the behavior of firms and speed development of urgently needed new tests? Discussions with firms, based largely on hypothetical scenarios, cannot provide a definitive answer. But we believe that a prize of the right size and design could make a difference. The class of firms most likely to respond to this kind of incentive are established biotechnology companies, which have more flexibility to pursue secondary applications of their technologies than start-ups, are attracted by revenue opportunities too small to interest the biggest firms, and are more willing to consider new business models. Small firms are also more likely to provide the type of

breakthrough innovation needed and might see a TB prize contest as an opportunity to validate their technologies. But these firms, which have a high cost of capital and may not be able to take a product all the way through clinical trials, would be more interested in a milestone than an end prize. Since the primary obstacles to a point-of-care TB test are technological and the market could probably pull promising candidates through later development, a milestone prize might be the most appropriate design for this product.

Some large diagnostic firms are already investing in TB tests and might find the publicity associated with a global health prize contest attractive, but they are less willing than small firms to consider prizes a viable commercial alternative to market revenues.

More generally, our discussions suggest that milestone prizes are more familiar to most firms. End prizes designed to substitute for inadequate markets constitute a more radical departure from established ways of doing business and our interviews suggest that the idea is not always well understood. In theory, prizes that are sufficiently large to offer a return on investment comparable to that promised by alternative uses of resources should be able to compete successfully for R&D investment. Since commercially unattractive markets are characteristic of neglected disease products—this is, after all, the main reason they are neglected—end prizes should continue to be developed as potential solutions. But milestone prizes may be an easier—and quicker—way to test important features of the prize concept and familiarize industry with this new mechanism. Milestone and end prizes are not incompatible, of course, and some groups are considering incentive structures that include rewards at more than one stage.

To what extent do our conclusions from TB diagnostics hold for other diagnostics and for other drugs and vaccines? We believe that much of our analysis could apply quite broadly. But several features of products and product markets influence the value and design of prizes. First, the potentially considerable market for an improved TB test means that a milestone prize may be sufficient; this will not be the case for many neglected disease products with much smaller markets, which will require additional subsidy in the form of end prizes or push funding to reach patients. Second, prizes for drugs or vaccines would probably have to be much larger than prizes for diagnostics because of the greater R&D costs and longer development timelines. Third, licensing and competitive supply as a strategy for sustainable access is most suited to drugs, for which generic regulatory pathways are well established and product composition patents are the main barrier to competitive supply.

When are prizes a better approach than other R&D financing mechanisms, including grants and subsidies through product development partnerships? Our study did not focus on this question, but our analysis suggests that prizes are probably most useful where two conditions are met. First, the way forward is not clear and new ideas are needed to overcome scientific or technological barriers; second, the kinds of innovators whose participation is most required are likely to be able to find funding to pursue a prize. Where these conditions are not met, for example when the necessary R&D is relatively straightforward, conventional push approaches are probably more appropriate.

I. Introduction

New drugs, vaccines, and diagnostic tests that meet the needs of the developing world could save millions of lives. But despite the enormous potential benefits of these new health technologies, which could include vaccines against malaria, drugs for late-stage Chagas disease, and faster and more sensitive tests for tuberculosis, only a small fraction of global investment in health R&D is devoted to them[1]. Although there are often many obstacles to development of particular products, the fundamental cause of this imbalance is the poverty of those who would benefit from them and of their governments, which translates into small and uncertain markets and lack of incentive for investment by the private pharmaceutical industry, which is responsible for most health technology development and manufacturing.

Governments and philanthropic foundations have attempted to substitute for private-sector investment in these products through grants to university researchers and to product development partnerships, among other channels[2]. A variety of alternative approaches to accelerating neglected disease R&D have been proposed, however, and several have been implemented in recent years.[3] The Center for Global Health R&D Policy Assessment, a project of the Results for Development Institute, is carrying out in-depth studies of several of these new ideas, with the aim of helping potential donors, policy-makers, and others to decide whether and in which circumstances these new approaches could be useful.[4]

Prizes, which have been used for centuries to reward achievement and stimulate innovation (see next section), are enjoying a resurgence lately, and governments, foundations, and the private sector are exploring their potential in a variety of contexts, including global health.[5] Advocates have proposed that large cash prizes could spur the development of needed health technologies—drugs, vaccines, and diagnostics—by bringing new ideas to difficult problems, focusing R&D effort on public health needs, and providing a return to commercial investment in products with small or uncertain markets.

These ideas are attractive, but there has been very little experience so far with prizes as an incentive for pharmaceutical R&D, especially for the expensive later stages of product development.

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[1] Add references to GFRH 90/10 reports.

[2] The George Institute for International Health, 2009. Neglected Disease Research & Development: New Times, New Trends, G-Finder 2009, available at http://www.policycures.org/downloads/G-FINDER_survey_of_global_R&D_funding_for_Neglected_diseases_2009.pdf (accessed 11/15/2010).

[3] Hecht, Robert, Paul Wilson, and Amrita Palriwala. 2009. Improving health R&D financing for developing countries: A menu of innovative policy options. *Health Affairs* 28 (4) (July 1): 974-85.

[4] For more information on the Center for Global Health R&D Policy Assessment visit http://healthresearchpolicy.org/.

[5] Innovation prizes: And the winner is… | the economist [cited 11/5/2010 2010]. Available from http://www.economist.com/node/16740639 (accessed 11/5/2010).

This report analyzes the potential of prizes for global health R&D, asking in what contexts—for what kinds of products and for which kinds of R&D—they might accelerate R&D, and analyzing how they should be structured to achieve the desired ends. As a case study, we will consider prizes for TB diagnostics, as several groups are developing proposals in this area. We believe that many our findings from this in-depth example are relevant to other diagnostics, drugs, and vaccines, although with important caveats.

There are, of course, many kinds of prizes. This study assesses what are sometimes called incentive or inducement prizes, cash awards for the achievement of specified aims, as opposed to recognition prizes such as the Nobel that reward past achievement. More specifically, we focus on prizes for specific new products or for substantial R&D milestones on the path to these products. We do not consider either small inducement prizes for solution of specific technical or scientific problems or proposals for very large prize funds covering a broad range of products. These multiproduct prize funds proposals are intellectually compelling but involve complex additional issues. These ideas may be considered in a subsequent R4D assessment.

Our assessment looks to answer several questions, in detail for the TB diagnostics prize proposals and in more general terms for prizes for other health products.

- Are the specifications for the product or milestone clear, achievable, and sufficiently ambitious? Would a product that satisfied them meet needs in the fields?
- Would the proposed mechanism engage innovators and spur investment in the necessary R&D? Is the reward sufficiently large to shift industry priorities? Which kinds of firms are most likely to be attracted by the prize?
- Does the proposal include workable mechanisms for ensuring that a product that won the prize would be reach those who need it? What provisions does it make for sustainable supply at an affordable price?
- More generally, to which types of products and which stages or R&D are prizes best suited and which aspects of prize design are most important in determining success?

We have addressed these questions through review of the published literature, extensive interviews with prize proponents and experts, TB and diagnostics specialists, and executives and investors from the diagnostics industry. Annex 1 lists the people interviewed for the study.

In Chapter II of the report, we suggest a conceptual framework for weighing the potential benefits of prizes and address some important aspects of prize design; in Chapter III we present our analysis of the TB diagnostics prize proposals. In Chapter IV, we consider the value of prizes for other technologies and outline some advantages and disadvantages of prizes relative to other R&D incentives. In the final chapter we present some broad conclusions.

II. General framework

There is a considerable theoretical literature on prizes and similar inducements to innovation.[6] Although we cannot provide a thorough review of this work here, we present in this chapter an overview of the main potential advantages and disadvantages of prizes as a tool for driving innovation in global health, as well as an analysis of several important elements of prize design. This general framework will inform our detailed assessment of TB diagnostic proposals in Chapter III and our preliminary look at the potential of prizes for other technologies in Chapter IV.

We begin this chapter with a summary of some of the developments which led to the recent interest in prizes as a way to spur development of needed health technologies for the developing world.

A. Background

Innovation prizes have a long history. The prize offered by the British government in 1774 for a determination of longitude at sea (the "Longitude Prize") is perhaps the best-known example,[7] but governments, foundations, and individuals have offered numerous prizes for the achievement of pre-specified objectives in areas as diverse as agriculture, mathematics, aviation, and medicine[8]. Many of these prizes were successful and led to important new technologies.

With the growth of government funding for research and increasing reliance on the patent system, the use of prizes to drive innovation declined in the 20th century[9]. But prizes are back in fashion: a recent report from McKinsey & Co found 60 prizes of $100,000 or more launched since 2000; although this list includes so-called "recognition prizes" honoring past achievement, inducement prizes account for most of this new money for prizes.[10]

There have been few prizes for neglected disease health technologies. In 1994, the Rockefeller Foundation offered a prize of US$1 million for the development of a simple, rapid point-of-care test for gonorrhea and Chlamydia infection.[11] This award was never

[6] Specific references to be added. See also the prizes bibliography developed by Knowledge Ecology International, available at http://keionline.org/content/view/82/1.
[7] Sobel, Dava. 1998. The illustrated longitude: The true story of the lone genius who solved the greatest scientific problem of his time Walker & Company.
[8] Selected innovation prizes and reward programs, KEI Research Note 2008:1, Knowledge Ecology International, available at http://www.keionline.org/misc-docs/research_notes/kei_rn_2008_1.pdf (accessed 11/15/2010); Masters, W. A and Delbecq, B., Accelerating Innovation with Prize Rewards: History and Typology of Technology Prizes and a New Contest Design for Innovation in African Agriculture, IFPRI Discussion Paper 00835, December 2008, available at http://www.ifpri.org/sites/default/files/publications/ifpridp00835.pdf (accessed 11/15/2010).
[9] Masters, op. cit.
[10] "And the winner is ..." capturing the promise of philanthropic prizes. Mckinsey 2009.
[11] Berkley, S. 1994. Diagnostic tests for sexually transmitted diseases: A challenge. Lancet 343 (8899) (Mar 19): 685-6.; Mabey, David, Rosanna W. Peeling, and Mark D. Perkins. 2001. Rapid and simple point of care diagnostics for STIs. Sexually Transmitted Infections 77 (6): 397.

claimed, however, perhaps because the technical requirements were too stringent and the amount too small.[12]

The more recent interest in prizes for global health stems from at least four sources. First, the Center for Global Development's proposal for advance market commitments (AMCs) for new vaccines for the developing world, which arose out of earlier academic work on prizes and advance purchase commitments and led to the current pneumococcal vaccine AMC, drew attention to the idea of large rewards for successful product development as an alternative to grants and other conventional forms of support for neglected disease R&D.[13]

Second, large prize funds covering a broad range of products have been proposed as an alternative to patent-protected monopolies as the primary incentive to commercial medical innovation. These very ambitious proposals, put forward by James Love of Knowledge Ecology International and his collaborators and also by Thomas Pogge and Aidan Hollis as the Health Impact Fund, are focused as much on ensuring access to new products at affordable prices as on stimulating new innovation.[14] The concept of an all-encompassing prize fund for medical innovation was embodied in a bill submitted to the US Congress by Senator Sanders of Vermont in 2007.[15] Prizes and prize funds were also discussed by the WHO Intergovernmental Working Group on Public Health, Innovation, and Intellectual Property. The resulting World Health Assembly Resolution endorsed exploring prizes among other incentive mechanisms, in the context of "de-linking" the prices of health products from the cost of R&D.[16]

Third, the success of InnoCentive, an organization specializing in the design and management of prizes for solutions to specific scientific and technological challenges, has attracted the attention of the neglected disease R&D community[17]. Several Product Development Partnerships (PDPs) have used InnoCentive to launch prize contests.[18] These prizes have generally been small, however, and have typically been aimed at the solution of particular technological problems, not actual product development. For example, the International AIDS Vaccine Inititative (IAVI) posted a $150K challenge on InnoCentive for the design and a sample of an important viral protein in a particular conformation.[19] Although there were more than 300 responses to the challenge, none met the requirements. IAVI is currently considering launching a second challenge: a larger, tiered milestone prize for development of biomarkers.

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[12] M. Tam, formerly of the Rockefeller Foundation, pers. comm.
[13] Center for Global Development, Making Markets for Vaccines, available at http://www.cgdev.org/section/initiatives/_archive/vaccinedevelopment (accessed 08 November 2010). See also GAVI's website on the AMC, which provides links to many documents (http://www.vaccineamc.org).
[14] Love, James and Hubbard, Tim, "The Big Idea: Prizes to Stimulate R&D for New Medicines," Chicago-Kent Law Review Vol. 82 No. 3, November 2007; Pogge, Thomas, and Hollis Aiden. 2008. The health impact fund: Making new medicines accessible for all. Incentives for Global Health.
[15] Add reference to Sanders bill S.2210- Medical Innovation Prize Act of 2007
[16] Add reference to WHO Global Strategy (WHA61.21)
[17] For more information, visit Innocentive website at www2.innocentive.com.
[18] Add more information on contests posted by TB Alliance, IAVI, and DNDi.
[19] **"**The International AIDS Vaccine Initiative Posts $150,000 Challenge On InnoCentive In Search Of New Approaches To AIDS Vaccine Design,**"** Medical News Today, available at http://www.medicalnewstoday.com/articles/133522.php (accessed 11/15/2010).

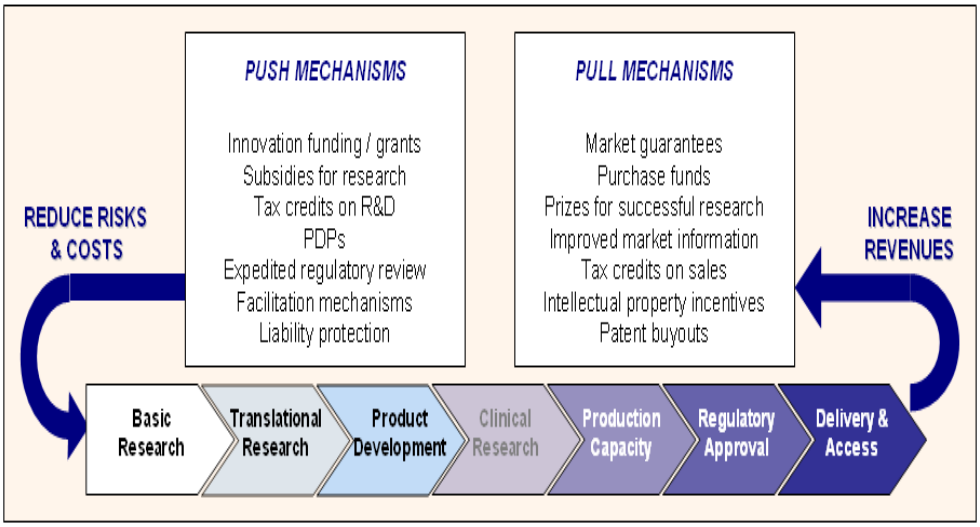
Finally, the success of the Ansari X Prize for private space flight, perhaps the most publicized recent prize contest, has greatly raised the profile of prizes among policy-makers and the general public[20]. Since the space prize, X Prize has moved into new areas, including biotechnology and medicine, and is considering launching a prize for TB diagnostics[21]. We assess this proposal in Chapter III.

These prize concepts differ greatly in scale, design, and intent—Section C of this chapter addresses some of these differences. But they have converged to make prizes a hot topic among policy experts and funders interested in new health technologies for the developing world. Although the AMC, the big multiproduct prize funds, and InnoCentive are beyond the scope of the current assessment, which focuses on prizes for particular products or R&D milestones, these ideas inform our analysis in many places.

B. Advantages of prizes

Prizes are an example of a "pull" mechanism for motivating R&D. Incentives of this kind make investment in development of a particular product more attractive by increasing the reward for success, in contrast to "push" mechanisms that work instead by reducing the risk or cost of R&D, for example through grants or tax breaks. Other examples of pull incentives are advance purchase or market commitments and the Priority Review Voucher, which is essentially a prize with the voucher as the reward instead of a cash payment.

Figure 2.1: Push and Pull Mechanisms for Health Research and Development (R&D)



Source: International AIDS Vaccine Initiative

[20] For more information on the Ansari X Prize, visit http://space.xprize.org/ansari-x-prize.
[21] "X PRIZE Foundation to Help Fight Tuberculosis Worldwide with Gates Foundation Support," 16 October 2008, X Prize Foundation, available at http://www.xprize.org/foundation/press-release/x-prize-foundation-to-help-fight-tuberculosis-worldwide-with-gates-foundati (accessed 11/5/2010).

Prizes share two major theoretical advantages with other pull incentives. First, unlike grant funders, who pay whether or not the funded research leads to something useful, prize sponsors pay only for success. (In practice things may not be so clear-cut: sponsors must pay if the product specifications or milestones spelled out in the contest guidelines are met, which may not always mean that the original objectives were achieved – see below.) Another way of expressing this is that product developers rather than funders bear the risk of failure. For funders this can be an important selling point.[22]

This advantage of pull incentives is more nuanced than it first appears. Because sponsors must make a prize big enough to compensate product developers for the risk of failure, a prize will cost more than a grant covering one research approach or candidate product. But since many such efforts will fail, the total cost to sponsors of funding enough "shots on goal" to ensure success may be similar to the cost of a prize (if developers' assessment of risk—and the sponsor's guess at this assessment—are accurate). This basic equivalence is often misunderstood by advocates of one approach or the other. In the real world, of course, the cost-effectiveness of push and pull mechanisms may well differ for a number of reasons.

A related advantage of pull mechanisms is an alignment of incentives between sponsors and product developers. Since developers will be paid only if they meet the prize specifications, they are strongly motivated to do so and sponsors don't have to "police effort". Grant recipients, on the other hand, may be motivated more by the need to perpetuate grant funding than to reach the final objective, and funders must constantly check that their money is being well spent.

Second, prize sponsors only have to specify the desired end – the product or R&D milestone – not the path to this end. In other words, they don't have to "pick winners", either among competing research approaches or product candidates or among researchers and product developers. Grant funders, of course, must choose whom to fund by evaluating potential grantees and proposed approaches. This advantage of pull mechanisms is particularly pronounced when the way forward is not clear to the sponsor or where the best solution to a problem could come from unknown or unexpected sources. (Economists call this an information asymmetry.) Prizes in this way constitute a more open model for innovation than push funding, in that in theory any researcher can participate and hope to win the reward. The "cloud-sourcing" models of web-based prize mechanisms like InnoCentive take full advantage of this openness, drawing on the expertise and creativity of thousands of potential "solvers"[23].

These advantages of prizes apply as well to advance purchase or market commitments, in which the reward for product development takes the form of subsidized or guaranteed product sales. Prizes have an additional advantage relative to these mechanisms, however: they separate or "de-link" reward for innovation from product prices. In other words, they separate markets for R&D from markets for products.[24] Since R&D is

[22] Curiously, this advantage of prizes can in some circumstances create a budgetary headache for funders. Sponsors pay only if the prize is won, but money set aside for the award may be difficult to reallocate or even lost if the prize is not claimed.

[23] Lakhani, Karim, InnoCentive.com (A), Harvard Business School, October 2009.

[24] Love, James and Hubbard, Tim, "The Big Idea: Prizes to Stimulate R&D for New Medicines," *Chicago-Kent Law Review* Vol. 82 No. 3, November 2007.

expensive and risky, product developers relying on product sales to repay R&D costs must charge more than the cost of producing the product, sometimes much more; this distorts markets and can be an important barrier to access. Love and others have proposed that access to new products could be maximized by paying for R&D through prizes and then allowing prices to fall close to cost through generic competition. This and other approaches to ensuring access are discussed further in Part E of this Chapter and in the TB diagnostics case study.

Another potentially very important advantage of prizes is the ability to attract attention to neglected problems or needs, from a broad public as well as from those who might offer solutions. This attention can lead to new ideas and new effort beyond those associated directly with pursuit of the reward, and perhaps new funding from other sources as well. For prize contestants, it can translate into recognition, interest in their technologies, and good public relations, all which make participation more attractive and may cause them to invest more than could be justified by the prize itself. Although this benefit of prizes is difficult to quantify, it is often cited by prize enthusiasts and figures prominently in the X Prize model, among others. It is worth noting, however, that this "publicity bonus" would presumably be diluted by widespread use of prizes: dozens or hundreds of simultaneous prize contests could not hope to garner as much attention as the Ansari X Prize, especially as the novelty of prizes wore off.

A more subtle form of the publicity advantage is the ability of prizes to reshape problems or redefine success in a useful way. Even if a prize does not attract new researchers to a field, it can redirect their efforts or cause them to think about a problem in a new way; if the prize specifications are well chosen, this could put the field on the path to success. For example, the Prize4Life Foundation, which uses prizes to further the search for a cure for Amyotrophic Lateral Sclerosis (ALS or Lou Gerhig's Disease), hopes to change the way ALS research is done by promoting more rigorous use of animal models and by focusing attention on the need for better markers of disease progression.[25]

Some other potential advantages of prizes are discussed in the McKinsey report.

Potential risks and challenges

Prizes have potential risks and disadvantages as well, in addition to those mentioned above. Three are particularly important. First, prizes (and pull mechanisms in general) can only work well if the desired result can be defined with clarity and precision and its features captured in practical product or milestone specifications. Bad specifications could discourage R&D altogether, lead researchers in an unproductive direction, limit the range of solutions pursued, or require sponsors to reward development of a useless product. We illustrate some of these risks with specific examples in the case study on TB diagnostics. The challenge of setting good prize specifications—as well as the difficulty of setting the prize amount—is particularly great when research is at an early stage.

Another major risk is that prizes, by pitting researchers against each other, could hinder the collaboration and sharing of information among researchers that PDPs and others have worked so hard to encourage. Prizes can also *foster* collaboration, as researchers

[25] For more information, visit Prixe4Life website at www.prize4life.org.

work together in pursuit of the reward, and the design of prizes can be adapted to require or encourage sharing of results, but the mechanism is inherently competitive.[26] To the extent that prizes or other pull mechanisms make investment in a certain areas of R&D attractive where it was not before, it is only natural that firms and other researchers who hope to capture some of this new value will be less willing to share what they know with potential rivals.

The competitive dynamic created by prizes is also potentially wasteful in that it can lead to duplication of effort. To the extent that contestants pursue distinct, viable approaches to a solution, the money required to attract many participants may be well spent; but having several developers with equivalent capacities investing in very similar product candidates is probably wasteful. In other words, the benefit of attracting multiple contestants depends on the diversity of their skills and approaches.

The most important disadvantage of prizes compared to grants and other forms of push funding is that it limits participation to researchers and product developers who can find the resources to fund the necessary R&D upfront. Although if the prize is attractive enough, investors may be willing to finance pursuit of the reward, in practice some researchers with promising ideas will be excluded. The seriousness of this drawback depends on the kinds of innovators needed to solve a particular problem and on their capacity to raise the necessary funds.

It should be clear from this discussion that no general conclusion about the value of prizes compared to other ways of funding and motivating R&D is possible: the merits of a prize approach will depend on particular circumstances. But these general considerations provide a useful guide to identifying the cases in which prizes are most promising. We return to this discussion in Chapter IV, after analyzing the case of TB diagnostics.

C. Prize models and design issues

Current models for health product prizes (both proposed and already launched) vary considerably. At the most basic level, these models differ in their objectives—the problems that they hope to solve—in ways that correspond loosely to the different potential advantages of prizes listed in the previous section. Since these basic differences in objectives are not always clearly articulated or understood, we will illustrate the point with some examples (see Figure 2.2).

Some prizes aim primarily to solve the problem of inadequate markets for important products, for example health technologies that are needed most by the poor, by alternative sources of return sufficiently large to substitute for the missing markets[27]. The Pneumococcal vaccine AMC, although not strictly a prize, falls into this class.

[26] For example, InnoCentive has considered introducing features to encourage collaboration within its prize contests. See Lakhani, Karim, InnoCentive.com (A), Harvard Business School, October 2009.

[27] Diseases that affect few people may also offer inadequate markets for drug developers—some of the subsidies and other incentives in the Orphan Drug Act therefore resemble measures proposed for diseases

The proposed big prize funds, including the Health Impact Fund, although they would also correct for small markets, are focused at least as much on another problem: the barrier to access imposed by high prices for new, patented medicines. These proposals would remove this barrier by making the prize award conditional on licensure of generic production.

Prize4Life and InnoCentive are intended instead to overcome early-stage scientific and technological obstacles by promoting and channeling new innovation. These interventions could be useful even when there might be substantial markets for the desired products, as there would be for a successful treatment for ALS.

The X Prize model, for its part, places great emphasis on the ability of prizes to attract attention, transform thinking about whole fields, and inspire. In general, X Prize believes that its prizes should not substitute for markets but instead should *unlock* them, in part by driving development of new technologies for which new markets will naturally materialize and in part by drawing attention to market opportunities that may not have been fully appreciated. These more visionary objectives are difficult to analyze in straightforward economic terms, but they may be powerful nonetheless.

In many circumstances, more than one of these objectives may be relevant. But it is important to be clear about what a prize hopes to achieve and to make sure that the design of the incentive is appropriate for the chosen objectives.

Figure 2.2: Examples of prize models and objectives

Prize Model	Objective	Approach
AMC ADVANCE MARKET COMMITMENTS for vaccines	Augment or substitute for inadequate markets for new vaccines in poor countries	Create an artificial, donor-subsidized market for new vaccines that meet agreed specifications
Medical Innovation Prize Act of 2007	Align medical innovation to public health need; promote access by bring prices close to costs	Reward new products according to health benefit; enable generic production from regulatory approval
PRIZE4LIFE	Overcome scientific barriers to new treatments for ALS; make R&D faster and more efficient	Use milestone prizes to stimulate early-stage innovation and to make trials easier
X PRIZE FOUNDATION	"Unlock" a market for point-of-care TB tests in developing countries	Use a prize to overcome technological barriers and attract attention to the field

of the developing world. The difference, of course, is that a decision to invest less in diseases that impose relatively little burden is not necessarily inconsistent with public health priorities.

Many different prize structures are possible—a full consideration of the relevant issues is beyond the scope of this study. But we will address briefly two design questions.

Winner-take-all versus multiple winners

The most familiar kind of prize is winner-take-all, with the entire prize purse going either to the first candidate to meet the specifications or to the best candidate presented within a specified period. These designs have the advantages of simplicity and ease of communication. But they also make the contest riskier for potential contestants, which may deter some from participating[28]. A single-winner design may also make it less likely that multiple products with different characteristics reach the market. In many cases, it may be better to reward several competitors, by giving prizes to all candidates that meet the specifications before an agreed deadline or the first ones up to a set number to do so.

A further advantage of rewarding multiple winners is that by keeping more firms involved it may help to build a sustainable ecology of global health innovation and product development.

An interesting alternative is to divide the prize purse among contestants according to the estimated benefits of their invention. The prize funds proposed by Love and his co-workers and by the Health Impact Fund would take this approach, relating the size of prizes for new health technologies to the incremental health benefits that they produce in actual use. Similarly, Masters proposes a prize competition for agriculture innovation for developing countries in which the purse would be divided among innovators according to the increases in yield resulting from their inventions.[29]

The main disadvantage of prize designs that reward multiple innovators is that they cost more.

Milestone vs final product prizes

Another important distinction is between prizes for final products ("end" prizes)—in the case of health technologies, products that have demonstrated their value in clinical trials and are ready for large-scale manufacture—and prizes for the achievement of significant R&D milestones along the way to a product. For health products, possible milestones might be proof of principle in an animal model or (in the case of diagnostics) in rigorous laboratory evaluation, or preliminary demonstration of efficacy in a small clinical trial. A prize contest could include awards at several stages, including for final products.

One of the main advantages of milestone prizes, either alone or in conjunction with end prizes, is that they're less costly and risky for contestants, since less investment in R&D is required and the risks of later-stage development are avoided. Milestones can also be reached sooner, which is important if the cost of capital is high. These advantages could be particularly attractive to small firms, which often need to show results quickly and may not have the capacity or resources to carry products all the way through clinical

[28] Cason, Timothy N., Masters, William A & Roman M. Sheremata. "Entry into winner-take-all and proportional-prize contests: An experimental study". *Journal of Public Economics 94* (2010) 604-611.
[29] Masters, William A. "Research prizes: a new kind of incentive for innovation in African agriculture. *International Journal of Biotechnology 2005* Vol. 7 No. 1/2/3/ pp. 195-211.

trials and manufacture. Finally, milestone payments are familiar to small firms, as they're often included in product development partnerships with other firms. Milestone prizes may be less attractive to big firms, whose expertise is typically in later stages of product development.

But the choice of milestone versus end prizes also depends on the objective of the incentive. If the main goal is to overcome a technological barrier or to attract new ideas, a prize for a substantial step toward the desired product may be the best choice, since it is in early stages of R&D that a breakthrough is needed. This is particularly true if the market for the product would be sufficient to pull a promising candidate through later stages of development without additional incentives. If the main purpose of a prize is to augment or substitute for too-small markets, however, or to put in place new mechanisms for product manufacture and access, an end prize is appropriate.

Milestone prizes raise distinct issues, including how to determine the size of the award, how handle intellectual property to maximize on-going innovation, and how to ensure a smooth hand-over to other product developers if the prize-winner is not willing or able to take the product to market.

D. Prize size

In the broadest terms, prizes should be large enough to motivate a sufficient number of product developers to invest in the required R&D but not larger than the expected benefit of the new product. If this isn't possible, another approach to funding product development should be considered (or the new technology simply isn't worth the cost of developing). But a number of other considerations may be relevant. For example, the prize may need to be big enough to attract media or public attention, if this is important to the prize model.

We will not discuss how to estimate the potential benefit of a new technology— rather we focus on how large an incentive must be to change the behavior of researchers or product developers. In considering this issue, it's important to keep in mind that product developers will have different thresholds for participation. This means that a bigger prize will in general mean more competitors, which in turns means a greater chance of success and possibly success sooner. So while there may be a minimum reward size, below which a prize will not stimulate new activity, increasing the size above this threshold may bring important benefits.

Purely commercial considerations

The most basic situation to consider is that of a for-profit product developer considering pursuing a prize on purely commercial grounds, with the prize reward the only pay-off for its investment. In most situations, of course, a number of other factors will enter into the decision; some of these are considered below. In this context, a firm would weigh the expected investment (the cost of the R&D) against the potential reward (the amount of the prize), taking into account four additional considerations:

- Technological risk: the chance that it will not be able to develop the specified product or reach the milestone. Most product development efforts fail.

- Competitive risk: the chance that other product developers will win the prize.
- Cost of capital: the interest or rate of return that a firm must pay on the funds used for R&D.
- Opportunity cost: the potential return from investing scarce resources, including staff, in other projects.

In other words, the risk-adjusted reward must not only exceed the expected costs, but provide a return on the invested capital that compensates for the cost of raising it or (if investment capital is limited) provides a higher return than alternative uses of this capital. In technical terms, these considerations are captured in net present value (NPV) or internal rate of return (IRR) calculations. In large companies working with well-established technological platforms,[30] costs and risks can be estimated with some confidence; for start-ups developing new technologies, these calculations necessarily rely to a large extent on educated guesswork and experience.

A critical parameter in these calculations is the cost of capital or the required rate of return (these quantities are in some sense two sides of the same coin: from a firm's perspective, the minimum rate of return that its investors will accept before contributing additional funds represents the cost of capital). The higher the cost of capital, the larger a prize will have to be to represent a viable commercial opportunity. High cost of capital also makes the time to pay-out critically important. Firms of different classes face different costs of capital. Start-up firms, which rely on venture capital, have a very high cost of capital, as these investors look for a very high return to compensate for the very high risks associated with new firms and new technologies. Large firms, on the other hand, can raise money at much lower rates on stock markets or from commercial banks. These firms may also be able to support R&D from their own revenues, as long as the expected rate of return from the available projects is greater than what they could obtain with other uses of this capital (the opportunity cost). Although in principle, firms with more promising projects than they can carry out with their existing resources should be able to raise more money and hire more people; in the short run, however, these resources are limited and firms must choose the most promising initiatives.

Most of these considerations are similar to those that govern choices about any R&D project. Technological risk in the case of a prize differs only in that success or failure is determined by the prize specifications (and whatever mechanism is established to judge whether these have been met) rather than by an internal target product profile or the decision of a regulatory body. But the competitive risks that potential participants in a prize contest are distinct from those that companies face in regular markets, and these risks depend on prize structure. Whereas in considering whether to enter a market, firms must decide what share of a market they will be able to capture, given timing, product characteristics, and marketing strength, in pursuing a prize they may face an all-or-nothing outcome. This characteristic of prizes—and the risk to firms—can be mitigated by prize designs that reward multiple winners. Whether this design is more attractive to a

[30] In general terms, a "platform" is the technology used in a diagnostic test, for example an amplification and detection technology to detect pathogen-specific nucleic acid sequences or a lateral-flow format to detect antigens. More specifically, the term can apply to the actual machine used to run the test, which in many cases can be used or adapted to run many different tests, for example in conjunction with disposable cartridges specific for particular tests.

potential participant depends of course on how it judges its chances against its competitors.

Top-down versus bottom-up approaches to estimating necessary prize size

One approach to estimating how large a prize has to be employs the kind of detailed analysis outlined here, using estimates of R&D costs and risks to simulate the calculations of potential contestants. Although this is the way that firms will assess whether to pursue a prize, this kind of information is often not available to prize designers. Another approach looks instead at the kinds of market opportunities that have typically stimulated investment by firms in a particular industry and assumes that firms would respond to a prize if it offered a similar commercial prospect. Indeed, firms and investors have rules of thumb about thresholds in market size that represent attractive opportunities. Our assessment will make use of both approaches in assessing prize size.

Other considerations

In most circumstances, the prize itself will not be the only return on investment that firms will concern. At least four other types of benefit can be important.

- **Markets for the product.** Although in general markets for the kinds of products considered here are assumed to be small – this is in many cases why a prize or other subsidy to R&D is considered necessary – they may be significant nonetheless. Some products may have donor-subsidized markets in the poorest countries or private-sector markets in middle-income countries; some may have small markets in high-income countries. In these cases, a prize only has to be big enough to fill the gap between the market that firms expect and the total reward that would be sufficient to make developing the product attractive. Note that a firm may be able to capture a share of these markets even its product does not win the prize. An important consideration is whether the product specifications set for the prize would be appropriate for other markets.[31]
- **Market positioning or strategic considerations.** In some cases, even in the absence of a prize, a firm may choose to invest in a product with relatively small market potential in order to fill out a product line or to stake out a position in key market. This kind of strategic position is particularly important to large firms with many products.
- **Validation of new technologies.** In many cases the technology used in a prize competition may have other more lucrative applications. For example, a platform developed for a new TB test could be used to test for other diseases that are more important in the US and Europe. A prize competition may offer a firm, especially a start-up, an opportunity to validate a new technology, which it could then use to purse larger commercial markets.
- **Public relations and recognition.** A prize may bring positive attention from investors, potential customers, and the general public. For big firms, the positive PR

[31] This will often not be the case. For example, the prize proposals for TB diagnostics emphasize the need for a new test that can be used at peripheral levels of the health systems in poor countries. Although there is a demand for TB testing in developed countries, there is little need for such a "point-of-care" test.

that may come from involvement in a neglected disease initiative could be quite valuable, while for new firms, recognition may attract money and talent.

While it's possible to estimate the size of potential markets for products and take this into account in setting the size of a prize, it's difficult to place a value on the other three considerations. They may, however, be quite important in some contexts.

This analysis assumes that potential participants in a prize contest assess costs and risks realistically. Some research shows, however, that contestants often over-estimate their chances of success, which leads them to invest more in pursuit of the prize than a rational calculation would suggest[32]. If this is true, prizes can be smaller and still attract the same amount of R&D effort. This phenomenon may explain in part the often-cited observation that the teams competing for the Ansari X Prize for private space flight spent 10 times more than the total prize purse[33], although another important factor was probably that contestants factored in important benefits to participation beyond the prize itself, including media attention and validation of their technologies. The two considerations together allow prize sponsors to "leverage" their investment in the prize.

E. Access issues and treatment of intellectual property

The ultimate goal of a prize for a neglected disease technology is to reduce disease through the widespread use of a new product. An important risk is that a product will meet the specified criteria and win the prize but never be used, because no one agrees to supply it, because it is unaffordable, or because it is unacceptable in some way to the people it was intended for. The third possibility can be forestalled by careful consultation with prospective users, but ensuring supply at an affordable price and uptake requires additional elements in the prize design. Three main approaches have been proposed for promoting access to products developed through prizes.

Cost or price ceilings. One approach is to require that the winning contestant demonstrate in some way that the cost of manufacturing its product is below a pre-specified amount. Manufacturing cost then becomes, in essence, another technical specification. The cost ceiling would be set a level that would make the product affordable, either to patients themselves, to governments in affected countries, or perhaps to donors willing to subsidize purchase of the product. As with other specifications, this ceiling must be realistic or product developers will not participate.

This approach has two disadvantages. The first is that manufacturing cost is sometimes difficult to define and determine independently of information provided by the manufacturer, which may make conformity with this requirement hard to verify – this is apparently the reason the X Prize Foundation did not include a cost ceiling in their TB diagnosis prize proposal (see Chapter III). A second disadvantage is that having a product that's relatively cheap to make doesn't by itself guarantee that anyone will make it—the developer may not be capable of manufacturing at scale or may not find the market attractive. This risk can be mitigated by including in the prize terms an actual

[32] Reference to be added. One possibility is Cooper, A. C., C.Y. Woo and W.C. Dunkelberg (1988) 'Entrepreneurs' Perceived Chances for Success,' Journal of Business Venturing, Vol. 3, pp. 97-108

[33] See X Prize description of the Ansari prize at http://space.xprize.org/ansari-x-prize.

supply commitment—an obligation to provide certain quantities of a winning product over a specified period at a specified prize—although this may deter some product developers and does not ensure sustainable supply over the long term. Moreover, this approach creates no incentive for manufacturers to make sure their product is used and has the hoped-for impact, only to meet the supply terms.

A related but weaker approach, often used by grant funders of neglected disease R&D, is to require supply at "cost-plus", a nominal mark-up over cost. Although this requirement eliminates most risks for manufacturers, it shares with cost ceilings the problem of verification and does nothing to steer R&D toward products that can be produced at an acceptable cost.

Licensing requirements. A very different approach to access is to require that the winning product developer turn over relevant intellectual property to the organization running the prize contest or grant non-exclusive licenses, either to a licensing pool or directly to interested third parties. In theory this would allow generic manufacture of the new product. Since experience with generic drugs, especially HIV drugs, has shown that the competition resulting from generic manufacture drives down prices, this could be a way to achieve sustainable supply at low prices without having to delve into and verify manufacturer's claims about costs. In addition, generic manufacturers, often based in India or China, may have substantially lower costs than originator firms based in the US or Europe.

This strategy should work well for drugs with high-volume markets (for AIDS, TB, and malaria, for example). But it may not work as well in some other cases. One problem is manufacturing costs: while most (but not all drugs) can be produced cheaply, this is not always the case with vaccines or diagnostics. Unless the licensing provision is accompanied by cost ceilings, the prize sponsor could end up with a product that cannot be produced at an affordable price even by generic manufacturers, and which, moreover, no one will want to supply because there is no market at a profit-making price. A second problem is that in some cases access to relevant patents is not enough to allow manufacturers to make a product. For many vaccines and some diagnostics, "know-how" is necessary too. The prize agreement can require transfer of this additional knowledge as well, but it is not clear how successful this kind of technology transfer would be when the transferring party is unwilling or at best disinterested. There may be regulatory hurdles as well, especially in the case of vaccines, for which no formal generic regulatory pathway exists. A third drawback to this approach is that in some cases, for example drugs for sleeping sickness, the market may be too small to interest even one supplier, let alone the multiple suppliers required to drive down prices through competition. In these cases, a purchase subsidy may be needed, which would of course largely defeat the purpose of generic competition, although the advantage of de-linking prices from R&D costs would remain.

The concept of mandatory licensing has been controversial in industry—many firms are leery of any initiative that might weaken sacrosanct intellectual property protections. Licensing provisions associated with a prize competition would of course be voluntary in the larger sense, as firms could choose whether to participate, and from an economic perspective, it should be possible to evaluate a licensing requirement in strictly business terms. If licensing means giving up exclusive control of potentially lucrative markets, the

prize will have to be correspondingly larger to compensate firms for what they're losing. On the other hand, if the lost markets would not be profitable, firms should be willing to license without much additional compensation. This calculation depends critically on the restrictions placed on the licensing requirement. In most cases, the licenses would be restricted to the particular application, use of the IP in producing a malaria drug for example, leaving the firm an exclusive right to exploit the invention for other uses. The license might also be restricted geographically, allowing licensees rights in low- or low- and middle-income countries but not the US and Europe, or only in high-burden countries. In cases where a product might have significant markets in high-income countries this distinction is crucial, but access to middle-income countries is becoming increasingly contentious and may be an obstacle to this approach.

From the perspective of firms, there are other concerns beyond the loss of exclusive rights to particular markets for the prize-winning product. Some firms may fear that products produced by licensees may leak into high-income markets, although there's not much evidence that this has been a problem. A more complicated concern is that granting licenses for technological platforms or manufacturing know-how with broad application may compromise the firm's most valuable asset and give competitors a leg up in other product areas. Even if license terms in principle don't allow use of the IP for other products, this may be difficult to control.

Market penetration requirement. A third approach to promoting access is to make part or all of the prize award contingent on a certain level of uptake. Such a condition would not only ensure supply, at least until the requirement is fulfilled, but would make it in the manufacturer's interest to develop an affordable and attractive product and to help with introduction and distribution. Such a requirement would deter innovators who lack the expertise in the relevant markets, however.

A prize with a market penetration test is closely related to an AMC, and AMC advocates argue that by making the reward to product developers conditional on sales in the relevant markets, AMCs solve the access problem while rewarding innovation and paying for R&D.

As this discussion illustrates, there is no perfect way to guarantee that a product developed through a prize contest reaches those who need it. In fact, some might argue that prizes should not be expected to solve the access problem, which is best addressed by other means. But at a minimum, prizes should be designing in such a way that a winning product is likely to be affordable, since R&D decisions have important consequences for manufacturing cost.

These issues are discussed in the context of TB diagnostics in Chapter III.

III. Prizes for TB diagnostics

In 2009, the governments of Bangladesh, Barbados, Bolivia, and Suriname ("BBBS") submitted to the WHO Expert Working Group on R&D financing and coordination a proposal for a prize fund for the development of low-cost, rapid, diagnostic tests for TB[34]. This proposal, which is based to a large extent on ideas developed by Knowledge Ecology International (KEI) and Médicins Sans Frontières (MSF), is to date the only public prize proposal in this area. However, the X Prize Foundation, which has developed and managed prize competitions in a number of other technology areas, has developed its own TB diagnostics prize proposal with financial support from the Gates Foundation. Although this proposal is not yet public, X Prize granted us permission to share a summary of this proposal with interviewees and gave us confidential access to more detailed documents on their prize design and plans. Finally, MSF is continuing work on a TB diagnostics prize and may eventually announce its own proposals. None of these initiatives has yet been funded or launched.

We have devoted considerable attention to these initiatives because these are the most developed prize proposals for global health R&D that we were able to identify and gain access to.[35] The potential of prizes, as well as their design, will vary with product type, market circumstances, and stage of R&D. It is therefore important to go beyond generalities to the details of a particular case in order to illustrate the many factors that could determine success or failure; TB diagnostics offer the most developed example currently available. Moreover, diagnostics in general offer several advantages relative to drugs and vaccines as a testing ground for the prize concept. R&D costs are lower and product development timelines shorter than for drugs and vaccines, meaning that a prize can be smaller; diagnostic technology is evolving rapidly, presenting opportunities for radical innovation; and the ability to bring a new product to market is less concentrated in a small number of firms (see Chapter IV).

Our case study on TB diagnostics will focus primarily on the X Prize proposal, which is more detailed and thus provides more specific material for analysis, but we will address the BBBS proposal as well where it differs from the X Prize design in important ways.

After a brief overview of TB diagnostics and the diagnostics industry (Section A), we will outline the main features of the prize proposals (Section B) and present our analysis (Section C). This analysis is based on the theoretical considerations discussed in Chapter II and extensive interviews with the prize proposal developers, TB diagnostic experts, and current and former executives of large and small diagnostics firms and well as venture capital investors (see Annex for a list of people interviewed for this study). In our assessment of the TB diagnostic proposals, we cover product scope and technical

[34] Full proposal available at http://www.who.int/phi/Bangladesh_Barbados_Bolivia_Suriname_TBPrize.pdf (accessed 11/5/2010)

[35] BioVentures for Global Health, an NGO working to engage the biotechnology industry in global health, is developing proposals for pay-for-success incentives in several areas, including diagnostics. Although these proposals were not ready in time to be included formally in our study, we provide a brief overview of this work in Section IV.

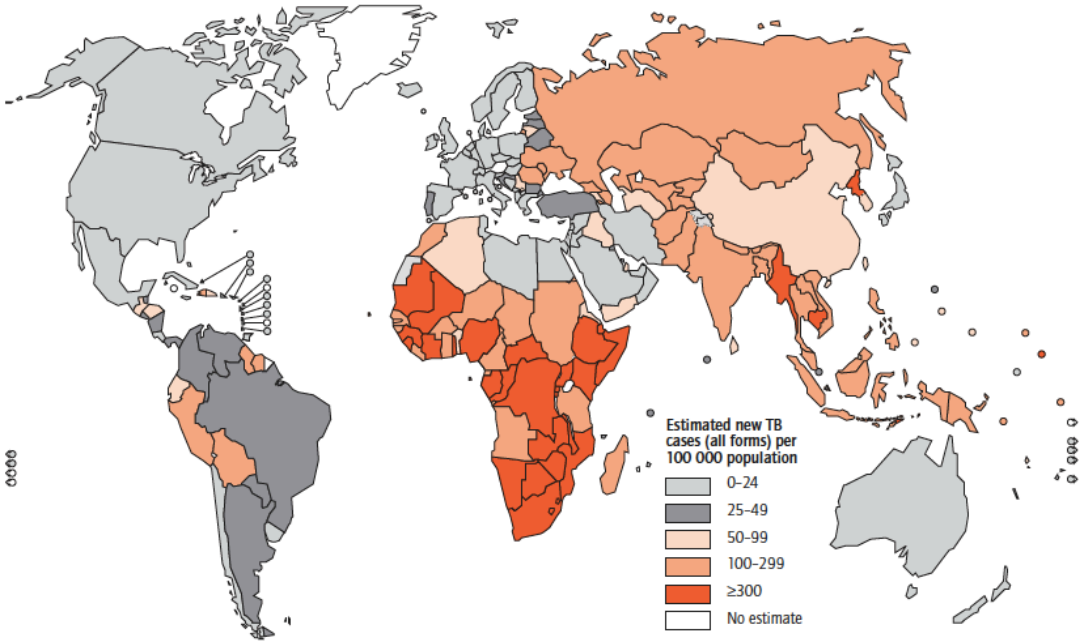
specifications, prize amount and related determinants of participation in prizes, other prize features and alternative prize designs, access provisions and treatment of intellectual property, and finally, present our conclusions to the case study.

A. Background

Tuberculosis in the developing world and the benefits of better diagnostics
Tuberculosis, a disease largely eliminated from high-income countries decades ago, remains an enormous problem in many parts of the world. About 1.7 million people died of TB in 2008, more than of any other infectious disease except AIDS; almost 10 million more developed the disease[36]. Despite broad consensus on a strategy and increased funding, progress in controlling the epidemic has been slow: although per capita incidence rates may have begun to decline, the annual number of new cases continues to increase.

Many factors have contributed to TB's resurgence, including above all the HIV epidemic, which has dramatically worsened TB rates in areas of high prevalence and now contributes to almost a third of TB deaths. But there is broad agreement that current tools for fighting TB are inadequate. New drugs are needed to shorten treatment and treat cases that are resistant to the standard drugs, and an effective vaccine to replace BCG could make an enormous difference. In addition, however, better diagnostic tests are urgently needed.

Figure 3.1: Estimated TB incidence rates, 2008



Source: WHO 2009 TB Update

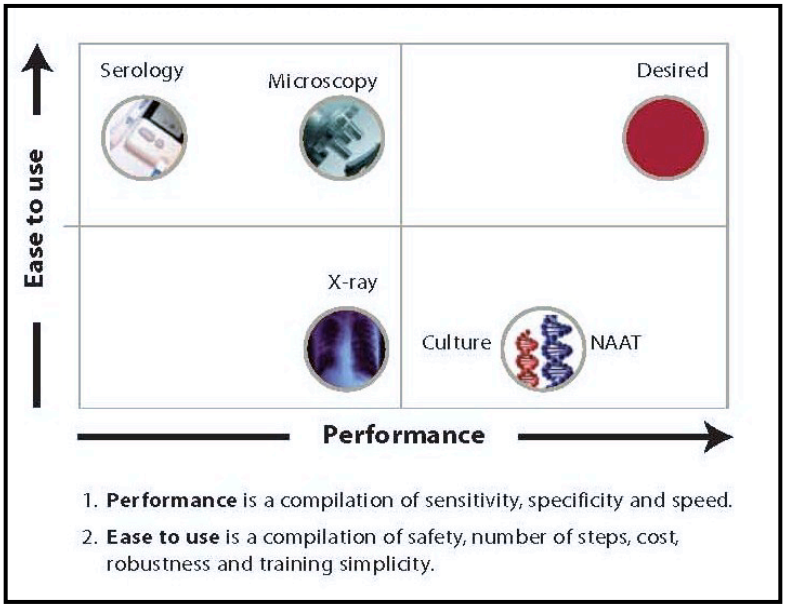
[36] WHO (2009): Global tuberculosis control: a short update to the 2009 report.

In most developing countries, tuberculosis is diagnosed in the same way it has been for almost 100 years: by looking for TB bacteria in sputum samples, using microscopes and simple stains. While this method, known as sputum smear microscopy (SSM) is fairly cheap and highly specific (it does a good job of distinguishing TB from other infectious agents), it has a number of crucial drawbacks. It is relatively insensitive, successfully detecting TB in only about half of infected patients, it performs poorly in children (who often cannot provide sputum) and in patients with HIV, and it cannot determine drug susceptibility.[37] Perhaps most importantly, SSM requires at least a simple laboratory with a microscope and a trained technician and typically takes several days to return a result, in part because two or three samples collected on separate days must be examined. In rural settings, where patients may have to travel long distances to seek diagnosis and treatment, this delay often means that patients with TB do not return for test results and do not begin treatment.

According to a model of TB diagnosis and treatment in high-burden regions, a new test that was more sensitive, could be used in remote areas where people have little access to health infrastructure, and returned results quickly could prevent as much as 36% of deaths, saving 100's of thousands of lives every year.[38] Most of these gains would come from expanding access to testing and reducing loss to follow up. Another modeling study that considered the long-term effect of new tools on TB incidence also found a substantial impact of new diagnostic tests that could reach more people and provide results quickly.[39] New tests to fill other needs – detection of drug resistance, determination of likelihood of reactivation of latent TB, monitoring of treatment – would also bring significant public health benefits.[40]

[37] WHO, Diagnostics for Tuberculosis: Global Demand and Market Potential, 2006. See in particular p. 35 and p. 81. From a public health perspective, sputum smear microscopy does better than its overall sensitivity would suggest, as the cases that it can detect contribute disproportionately to transmission.
[38] Keeler, Emmett, Mark D. Perkins, Peter Small, Christy Hanson, Steven Reed, Jane Cunningham, Julia E. Aledort, et al. 2006. Reducing the global burden of tuberculosis: The contribution of improved diagnostics. *Nature* (November 2006). Also see FIND website (http://www.finddiagnostics.org/programs/tb/need.html).
[39] Abu-Raddada, Laith J., Lorenzo Sabatellia, Jerusha T. Achterberga, Jonathan D. Sugimotoa, Jr Longini Ira M., Christopher Dyee, and M. Elizabeth Hallorana. 2009. Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. *Proceedings of the National Academy of Sciences* 106 (August 18, 2009): 13980.
[40] Wallis, Robert S., Madhukar Pai, Dick Menzies, T. Mark Doherty, Gerhard Walzl, Mark D. Perkins, and Alimuddin Zumla. 2010. Biomarkers and diagnostics for tuberculosis: Progress, needs, and translation into practice. *The Lancet* 375 (9729) (05-28): 1920-37, http://www.thelancet.com/journals/lancet.

Figure 3.2: Advantages and limitations of current technologies for TB diagnosis



Source: WHO, Diagnostics for Tuberculosis: Global Demand and Market Potential, 2006

There is thus a clear need for improved TB diagnostics and substantial consensus that what's most needed is a rapid, point-of-care test, one that can be used in lower levels of the health system or in the community and gives results while the patient waits. In general, a point-of-care (POC) diagnostic test is defined as one that can be used close to where treatment will be provided rather than in a laboratory at a higher level of the health system, but what this should mean in detail for TB tests is not entirely clear. Priorities for POC tests are discussed in more detail below, in the section on technical specifications in the prize proposals.

Although sputum smear microscopy and to a lesser extent X-ray and solid and liquid sputum culture, which also have important deficiencies, remain the mainstays of TB diagnosis in low- and middle-income countries, several new technologies are under development and several are used in high-income countries. None of the products currently on the market is yet suitable for use as POC diagnostic in poor countries, however, as all require some degree of laboratory infrastructure and most are quite expensive.[41]

The Gates Foundation and other donors have supported the development of improved diagnostics for important infectious diseases primarily through the Foundation for Innovative New Diagnostics (FIND), a Geneva-based product development partnership. FIND has in its portfolio several candidate TB diagnostic technologies, ranging from incremental improvements to SSM and culture to radically new approaches. FIND is currently testing a sophisticated device from Cepheid that would provide rapid, sensitive,

[41] Wallis, R. et al., Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice, The Lancet, Vol. 375, Issue 9729: 1920-1937, 29 May 2010.

and specific diagnosis of active TB together with information on drug susceptibility[42]. But Cepheid's machine is expensive and is not suited for the most peripheral levels of the health system[43]. FIND's pipeline includes work on technologies that could result in a POC test, but none of these projects is close to market.

Obstacles to development of improved TB diagnostics for developing countries

There is little doubt that lack of need in high-income countries and lack of ability to pay in low- and middle income countries have historically made TB diagnostics commercially unattractive to product developers. This lack of market was compounded by the divergent needs of rich and poor countries in TB diagnostics and by issues with reimbursement systems in the US and elsewhere that made POC diagnostics in general commercially unattractive in most cases. But as discussed below, the potential market for a POC TB test in developing countries may actually be quite large now, and industry perceptions may be changing. Thus lack of market may no longer be as important an obstacle as it has been. Even if markets in poor countries may be bigger than previously thought, though, these markets pose other challenges to diagnostics firms, including fragmentation and unfamiliarity.

One challenge for firms considering entering developing country markets for diagnostic tests is the lack of a clear regulatory process. While the WHO has established a pre-qualification process for diagnostic tests analogous to the processes that have provided useful guidance on product quality for vaccines and some drugs, no tests have yet completed the process[44]. In many developing countries, the regulatory process remains quite informal and, to the extent products are subject to government approval at all, no clear standards exist and authorities typically rely on data from a variety of source. In fact, many substandard or even useless tests, including for TB and malaria, are on the market in developing countries, according to several diagnostic experts consulted for this study. Such an environment can pose a threat to firms considering investment in products for the developing world. The alternative of seeking FDA approval or European Union approval is costly and time-consuming.

Beyond commercial considerations, the development of a useful, affordable POC TB diagnostic requires overcoming significant technological barriers, including the identification of appropriate biomarkers and the development of a platform that can detect them in difficult environments, where there may be no refrigeration, no reliable running water or electricity, and where highly trained staff is scarce. These problems can probably be solved, but doing so will require substantial investment, much more than the development of a new assay based on known biomarkers and an existing detection platform. Several diagnostic industry experts interviewed for this study identified

[42] Cepheid press release on FIND website (http://www.finddiagnostics.org/media/press/090324.html); personal communication with M. Perkins of FIND. For results of field trial of the Cepheid machine, see Boehme, Catharina C. et al, "Rapid molecular detection of tuberculosis and rifampin resistance," New England Journal of Medicine, Vol. 363, pp. 1005-1015, September 2010.

[43] Morris, Kelly, "Xpert TB diagnostic highlights gap in point-of-care pipeline," Lancet Infectious Diseases, Vol 10 November 2010.

[44] For more information, visit http://www.who.int/diagnostics_laboratory/evaluations/en/.

technological barriers, in particular the lack of appropriate biomarkers, as the greatest obstacle to development of a POC TB test for developing countries.

The lack of broadly available samples on which to test candidate diagnostics is another important obstacle. Development and testing of a new diagnostic can require thousands of samples, and few if any firms have access to sufficient samples from prospective TB patients.

The *in-vitro* diagnostics market and industry

The market for *in-vitro* diagnostics (IVD), which includes all tests performed outside the body, was estimated to be more than $28 billion in 2004.[45] Recent projections show the market expanding at an average rate of 6% per year to $56 billion by 2012[46]. IVD companies are specialized in one or multiple technologies ranging over laboratory instrumentation, data and information management, microbiology or molecular diagnostics.

Although the IVD market consists of hundreds of firms, increasing consolidation over the last five to ten years led to over two-thirds of the market being concentrated in the hands of ten large companies by 2006[47]. Some of these firms (Roche, Abbot, Chiron) also produce drugs or vaccines, while others specialize in diagnostics and medical devices.

Small firms or start-ups are also important players in the diagnostics industry, and are responsible for much of recent innovation in the industry. These firms rely, at least initially, on venture capital to support R&D and generally do not have large-scale manufacturing capacity. As in the pharmaceutical industry, it is common for new technologies developed by small firms to be acquired and commercialized by the larger, established companies. The diagnostic industry in emerging economies, particularly India and China, in growing in sophistication, and these firms are capable of manufacturing many types of tests at low cost.

Point-of-care (POC) testing is broadly defined "any testing performed outside of the traditional laboratory and conducted close to the site of patient care"[48]. Estimated to be $11 billion in 2007, the POC segment of the IVD market is forecast to reach more than $18 billion in 2012.[49] Yet several industry experts stated that challenges with receiving sufficient reimbursement through the U.S. Medicare system and the lack of incentives for doctors to use POC tests have dampened innovation in this area. Recently, the POC market has also suffered from the economic recession as the lack of venture capital and other investment funding has slowed the development of emerging technologies.

[45] WHO, Diagnostics for Tuberculosis: Global Demand and Market Potential, 2006.
[46] Park, Richard, The Year in IVDS, IVD Technology, 2010, available at http://www.ivdtechnology.com/article/year-ivds-9 (accessed 11/05/2010
[47] WHO, Diagnostics for Tuberculosis: Global Demand and Market Potential, 2006.
[48] Ibid.
[49] Ben-Haim, Atalya. The POC Market for Diagnostics of Diabetes, Maternal and Child Health, Tuberculosis, Malaria and Diarrhoeal Diseases in India and the World, ICTPH, December 2008 (Edited by Arijit Sarkar and Namrata Sharma).

The market for TB diagnostics

Total global expenditure on TB diagnostic testing is estimated at about $1 billion/year, more than twice the market for TB therapeutics.[50] But developed countries, despite their low TB burden, account for almost 70% of this spending, the bulk of which is on labor rather than reagents, while the rest of the world, where most TB cases occur, spends much less. Of the $300M or so that the WHO estimates is spent in low- and middle-income countries on about 150M tests, sputum smear microscopy and X-Ray account for 80%[51]. Only very small amounts are spent on commercial culture or PCR-based systems.

Only three of the 10 top IVD companies have TB diagnostics devices or tests in their portfolios.[52] Becton Dickinson, which provides a system for obtaining more rapid results from liquid culture, is the market leader. Biomerieux also has a culture diagnostic system, while Roche has developed a nucleic acid amplification product for TB. Many products using microbiological, nucleic acid, protein detection, or immunoassay technologies are in the pipeline, but few if any of these products would be truly point-of-care in a developing country setting.

Although markets for diagnostic tests in devices in developing countries have traditionally been seen as small despite the great need and potentially high volume, two trends may change this perception. First, rapid economic growth in some middle-income countries, particularly India and China, has spurred rapid growth in markets for pharmaceutical products, especially in the private sector, and created the expectation that these so-called emerging markets will be responsible for much of future growth in global demand for these products. Most of this demand will be for products directed against the same diseases that plague rich countries, such as cardiovascular disease, cancer, and diabetes, but there could be a significant market as well for diseases like tuberculosis where they remain a serious problem, as in India.

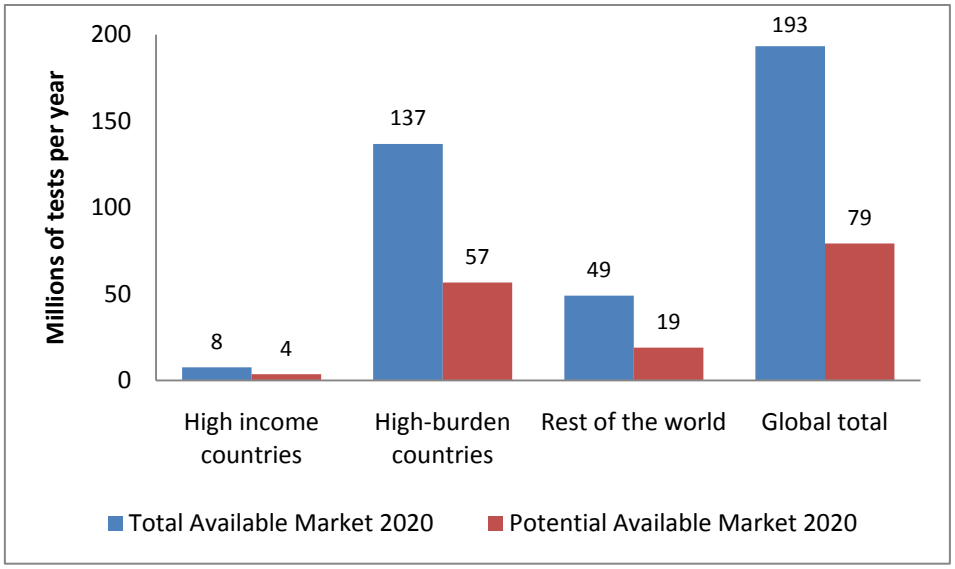
The second factor changing perceptions of developing country markets for diagnostics (as well as drugs and vaccines) is the demonstrated willingness of donors to pay non-trivial prices for global health technologies needed by high-burden low-income countries, especially for the AIDS, TB, and malaria. Many countries in Africa, for example, are paying about $5 for CD4 tests (not counting the cost of the machines), using resources from the Global Fund and PEPFAR[53]. This experience has changed the perception that to reach people in low-income countries, diagnostic tests have to cost $1 or less.

Growing markets in the emerging economies, coupled with the apparent willingness of donors to pay several dollars a test for important diagnostics in low-income countries, could make diagnostics for TB and some other previously neglected diseases attractive to industry. Volumes could be very high: a 2006 WHO report estimated the "total available

[50] Tuberculosis diagnosis: Attractive market with a global demand [cited 11/1/2010 2010]. Available from http://www.frost.com/prod/servlet/market-insight-top.pag?Src=RSS&docid=107170469 (accessed 11/1/2010).
[51] WHO, Diagnostics for Tuberculosis: Global Demand and Market Potential, 2006.
[52] Ibid.
[53] M. Murtagh, Clinton Health Access Initiative, pers comm

market" for a POC TB diagnostic at 193 million tests/year in 2020[54]. This study estimates, however, that only 40% of this total, or about 80M tests, could be captured by 2020. The majority of this demand would be in high-burden countries.

Figure 3.3: Estimates of Total Available Market and Potential Available Market for Point-of-Care TB Tests in 2020



Source: Adapted from World Health Organization: Diagnostics for Tuberculosis: Global Demand and Market Potential, 2006.

Although the WHO report does not venture a guess at the prices that developers of a POC test would be able to charge in various markets, this analysis clearly suggests that at prices of more than $1 per test the potential market for a POC TB test could be considerable.

B. TB diagnostic prize proposals

The X Prize proposal

The X Prize Foundation, a nonprofit organization devoted to the development and management of prize contests, has launched prize competitions for private space flight and exploration (Ansari X Prize and Google Lunar X Prize), automobile fuel efficiency (Progressive Automotive X Prize), and rapid DNA sequencing (Archon Genomics X Prize). X Prize contests for prizes of more than $10 million typically last for 3-8 years[55]. The space flight prize was won in 2004 and the fuel efficiency prize was awarded in September 2010.

[54] WHO, Diagnostics for Tuberculosis: Global Demand and Market Potential, 2006.
[55] X Prize also conducts competitions called X Prize Challenges that address significant technological barriers and are smaller in prize purse, scale, and duration.

X Prize seeks external sponsors to fund the prize competitions that it develops and manages.

The X Prize philosophy differs from that of some other prize proponents, in that it does not see prizes as a substitute for markets. The foundation's aim instead is to "unlock" latent or potential markets by motivating innovators to take critical first steps that pave the way for further breakthroughs, and eventually, open up substantial commercial opportunities. An implication of this model is that the prizes themselves need not be the only or even the primary reward to participants. In addition to access to newly opened markets, X Prize considers publicity and recognition to be important benefits of participation in their prize competitions, and they devote substantial resources to attracting media attention.

The TB diagnostics prize. X Prize Foundation has designed a $20M prize competition to create a set of rapid, accurate, point-of care TB diagnostics for use in peripheral settings in developing countries. Participating teams can win up to four prize purses of $5M each if their products are shown in clinical trials to meet all of a set of minimum technical criteria[56] (see Box 3.4) and to perform better than any other qualifying product in one or more of four specific areas. Prizes will be awarded for diagnostics that achieve the highest accuracy, fastest time to result, highest sensitivity in HIV patients, or best detection of TB drug resistance. The first two purses will be awarded if at least one team meets the minimum technical specifications. But the latter two purses are bonus prizes, in that they would not be awarded unless a product reached the 60% minimum set for performance in these two areas.

The competition will be open to all types of organizations globally; X Prize expects that many contestants, including small and large diagnostic firms, will choose to form and register as teams. It is divided into two phases, a laboratory evaluation phase that can take two to four years and a one-year joint clinical study that will test the leading teams' products in two high-burden TB countries (see Figure 3.5). To enter the contest, interested contestants have to pay a registration fee of $15,000 or more. The first phase begins with the signing of a Master Team Agreement spelling out the prize guidelines in detail and giving contestants a legal claim on the prize. Teams will submit data from in-house tests of their devices to an independent research organization contracted by X Prize, which will independently evaluate the devices in its own laboratory (about 100 or so would need to be provided) and validate the team submissions. On the basis of the laboratory evaluations and team submissions, a panel of judges will choose 5-7 teams to participate in the clinical studies, suggested to be in South Africa and India. Leading teams will have to be able to provide thousands of devices for these trials. Winners would be announced after the one-year trial and six months of analysis.

[56] These specifications are intended to satisfy the "ASSURED" criteria (Affordable, Sensitive, Specific, User-friendly, Rapid Robust, Equipment-free, and Delivered) developed by the WHO Sexually Transmitted Diseases Diagnostics Initiative (http://www.who.int/std_diagnostics/about_SDI/priorities.htm).

Box 3.4: X Prize minimum technical criteria

- **A**ccessible/Affordable: Can be manufactured to scale and supplied to purchase aggregator in a cost-plus model
- **S**ensitive >80% accuracy for TB diagnosis
- **S**pecific >95% accuracy for diagnosis of non-TB patients
- **U**ser Friendly: Meet FDA's CLIA Assessment for device usability with a score of ≤12
- **R**apid: Total time from sample preparation to result: ≤100-minutes/test
- **E**quipment Free: Self-contained with no cold chain, electrical, water supply or climate control needs
- **D**eliverable: Weight <10 kg; Size: <30x30x30cm; Storage Life: ≥12 months, at ≥35 degrees C, 70% humidity, including transport stress (e.g. 48 hours at 50 degrees C)

Minimum criteria for bonus prizes

- At least 60% sensitivity in HIV+ patients
- At least 60% success in detecting drug resistance

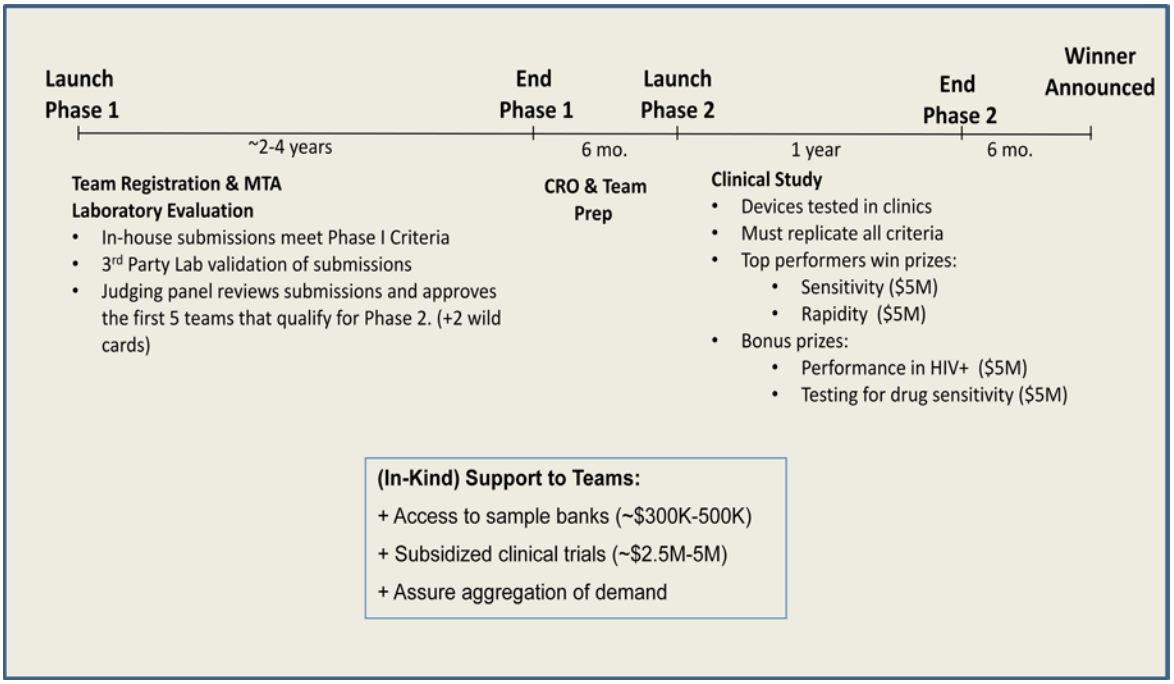
Source: Adapted from X Prize Foundation

During the prize competition, the X Prize Foundation will offer competing teams free access to specimen banks (such as for sputum, urine, and blood); X Prize estimates that the cost of providing samples could be as much as $300K to $500K. In addition, X Prize will pay for the culminating clinical studies, which are estimated to cost $2.5M to $5M.

The X Prize proposal would allow contestants to retain all intellectual property developed during the competition and includes no licensing provision. Moreover, winning teams are not required supply their products at a specified price or to demonstrate that they can be produced at an affordable cost. But in order to participate in the clinical trial, teams must submit a business plan that explains how the product would be manufactured and describes the status of agreements with a "reputable manufacturer" and includes some information on production costs.

X Prize is currently seeking a sponsor for the TB diagnostics prize. Although it considers the design process to be complete, X Prize is open to changes, both in response to the preferences of sponsors and in negotiations with potential competitors preceding the signing of the Master Team Agreement.

Figure 3.5: X Prize Competition Timeline



Source: Adapted from X Prize Foundation

The BBBS proposal

The proposal submitted by the four countries to the WHO Expert Working Group shares a number of features with the X Prize proposal, including the goal of stimulating the development of a point-of-care TB test for use in peripheral settings in developing countries, a two-stage evaluation of candidate products, and subsidy of clinical trial costs by the prize fund[57]. But there are important differences between the two proposals.

- A much larger prize: a $100M "grand prize" for the first contestant to meet the technical criteria, plus a series of small prizes of various types.
- An affordability and access standard, which could be either a pre-specified price ceiling or a market penetration test.
- A requirement that the winner grant licenses on reasonable terms for all patents and know-how needed for competitive supply of the product to a licensing pool.
- Technical specifications: although these are yet to be set, the proposal implies that they would include performance in HIV+ patients. While the X prize proposal would award one of the four prizes for high performance in this group of patients, it does not include it among the minimum criteria to be met by any winning product.
- Governance: The prize competition would be housed at WHO and governed by a committee comprising international organizations, TB NGOs, and a representative of

[57] BBBS proposal available at http://www.who.int/phi/Bangladesh_Barbados_Bolivia_Suriname_TBPrize.pdf (accessed 11/5/2010)

TB patients. In contrast, the X Prize would be governed by the X Prize Foundation with the help of expert committees.

- Source of funds: The proposal suggests that the prize fund be endowed by governments, including a contribution from developing countries, as well as private donors. X Prize contests are typically funded by private individuals, although the US government is contributing to at least one contest and X Prize is open to other kinds of sponsors, which could include the Gates Foundation and endemic-country governments.

The BBBS proposal also includes several additional awards and incentives, including small inducement prizes for the solution of technical challenges, biannual "best contribution" prizes, and a provision awarding 10% of the grand prize to researchers who contribute to the success of the winners and made their results freely available to all. In addition, it provides a subsidy to encourage participation of firms in emerging countries.

MSF's work on prizes for TB diagnostics

The Médecins Sans Frontières (MSF) Campaign for Access to Essential Medicines has made improved TB diagnostics for low-income countries a priority and has been an early advocate of a prize approach.[58] MSF has held several meetings to define the minimum requirements for a POC test, focusing on the need for better performance in children and HIV-positive patients. The Access Campaign was involved in development of the BBBS proposal and may put forward proposals of its own. MSF is considering both an end prize similar to the BBBS proposal and a milestone prize focused on discovery of new biomarker.[59]

Analysis of product scope and specifications

Scope and objectives. The first question to ask is whether these proposals have correctly identified the most urgent needs for TB diagnostics. Both proposals focus on point-of-care tests. While some TB experts consulted for this study suggested the importance of a point-of-care test might be overstated and that centralized, high-volume diagnostic laboratories should remain a big part of a diagnostic strategy—South Africa and India are investing heavily in central labs—most agreed that a rapid and accurate TB test that can be used in peripheral settings was a high priority and would have a big impact.

Some interviewees suggested it might be possible to achieve the objectives of increasing access and cutting loss to follow-up by other means. These could include using mobile phones to inform patients about their test results or mobile laboratories to reach patients in more remote areas[60]. These ideas highlight the importance of focusing on ultimate goals and illustrate how any set of technical criteria inevitably incorporates assumptions about how the goals should be reached.

[58] http://www.msfaccess.org/main/tuberculosis/diagnosing-children-with-tb-a-terrible-neglect/
[59] M. Childs, MSF Access Campaign, pers. comm. Can update to EC presentation.
[60] In fact, David Persing of Cepheid suggested that mobile laboratories would be the best way to bring the benefits of his company's GeneXpert technology, which is unlikely to be used in facilities below the district hospital level, to communities.

In addition to rapidity and accuracy, many have cited a need for greater effectiveness in detecting TB in HIV+ patients and children and TB drug resistance. While the design of the X Prize proposal gives priority to accuracy, rapidity, and point-of-care criteria, it does include prizes for performance in HIV+ patients and detection of resistance. The BBBS proposal does not yet include technical criteria, but the statement of the problem suggests that it would probably give high priority to improved performance in HIV+ people, who make up a large fraction of TB patients in many high-burden countries. MSF also believes that ability to detect TB in HIV-positive patients should be a central priority.[61]

Minimum technical specifications. According to our interviews with TB experts, there is broad consensus that a POC TB test should be more sensitive and at least as specific as sputum smear microscopy. The X Prize minimum technical specifications of 80% sensitivity and 95% specificity are in line with these general expectations for accuracy and 98% specificity. The appropriate standard also depends on how a POC test would be used. Specificity, which determines the rate of false positive results, is particularly important if the test would be used to initiate treatment without a confirmatory test, as TB treatment is long and arduous—sputum smear microscopy is 97-98% specific. In contrast especially specificity, can be lower if the POC test is going to be used only for screening, to guide referral of patients to health facilities where more definitive testing is available. In this case, however, sensitivity should be as high as possible to avoid missing cases.

A test that returns results while the patient waits, perhaps within three hours in most settings, is critical to reaping the benefits of point-of-care testing, and the X Prize minimum specification of total time from sample preparation to result within 100 minutes seemed reasonable to the experts we consulted.

Some experts felt that the X Prize criterion of an 'equipment-free' test that does not require cold chain, electricity, water supply, or climate control was unrealistic and might be unnecessarily restrictive. A test that can be used in peripheral settings should not need cold chain; however, it is likely that some promising technologies would require limited equipment, for example rechargeable battery power or water.

In summary, the X Prize technical criteria are broadly consistent with published work on needs in TB diagnostics[62] and most experts that we consulted felt that they were reasonable, sufficiently ambitious to ensure that a new test would have substantial impact, yet attainable.

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[61] A set of draft specifications developed at a meeting convened by MSF in 2009 proposed that a new POC test should be able to detect 60-80% of culture-positive, smear-negative pulmonary cases, regardless of HIV status. See the meeting report "Defining Specifications for a TB Point-of-Care Test: Meeting Report," March 17-18, 2009, Paris, France, available at http://www.msfaccess.org/TB_POC_Parismeeting/fileadmin/user_upload/diseases/tuberculosis/TB%20POC%20full%20meeting%20final.pdf (accessed 11/15/2010). Substitute recent Lemaire paper/

[62] Pai, M., J. Minion, H. Sohn, A. Zwerling, and M. D. Perkins. 2009. Novel and improved technologies for tuberculosis diagnosis: Progress and challenges. *Clinics in Chest Medicine* 30 (4) (Dec): 701,16, viii; WHO, Diagnostics for Tuberculosis: Global Demand and Market Potential, 2006.

Two authorities on diagnostics expressed the view, however, that the criteria as written were not sufficiently detailed to be used to measure performance in a clinical trial and determine winners, especially if very different technologies making use of different sample types were being assessed (see below). More detailed guidelines could be added at a later stage, but it should be noted that the difficulty of capturing general criteria in a sufficiently detailed and rigorous prize guidelines represents a risk to any diagnostic prize proposal.

X Prize Foundation views their technical specifications as evolving until the final prize is launched and expressed a willingness to take these concerns into account.

Implications for prize approach. There is always a risk that technical specifications for a prize could rule out certain technologies that might meet the ultimate objectives for which prize contest was created. In the case of the X Prize TB proposal, this point has already been illustrated by the suggestion that creative delivery strategies could make a POC test unnecessary (see above). But such an outcome could also arise as a result for a more technical reason.

X Prize proposes that the accuracy of candidate products would be assessed against the current gold standard, liquid or solid culture of sputum samples—it is difficult to imagine how this could be done otherwise. But while sputum culture is very accurate in diagnosing pulmonary tuberculosis, the most common presentation, it does not work well in the case of extra-pulmonary tuberculosis, another important clinical problem. In recognition of this constraint, X Prize acknowledges that their criteria only cover pulmonary disease—it is not clear whether other means would be used to determine performance in HIV+ people.

But the choice of a gold standard against which to measure contestants has implications not only for determining the winner of the prize for diagnosis in HIV+ patients, but also for assessment of technologies using samples other than sputum. A test using urine, for instance, might work equally well in people with TB in or outside the lungs. In an area with high HIV prevalence, such a test might detect a greater fraction of TB cases overall than a test relying on sputum, but still fall below the 80% minimum for sensitivity, as measured by sputum culture. There's probably no easy solution to this problem, as there's no accepted gold standard for diagnosis of TB outside the lungs (or in children, who don't produce sputum easily). But it could well bias the contest against some more innovative technologies, and it illustrates the ways in which the need to be able to measure performance can have implications for prize contests.

Prize amount

The X Prize proposal offers four prizes of $5 million each, which would be awarded for the products that achieved the highest ratings in particular dimensions (sensitivity, sensitivity in HIV+ patients, detection of drug resistance, and time to result) while scoring above the specified thresholds for all so-called minimum criteria. A team could win several or even all four prizes. But since it is unlikely that a particular technology would excel in all these areas, a potential competitor would probably assume a pay-out of

$5-10 million.[63] Would this amount be sufficient to attract researchers and product developers to enter the competition and invest significant resources in winning the prize?

We conclude from our analysis and from interviews with diagnostic industry executives and venture capitalists that for most firms this amount is probably not enough by itself to drive investment in a new R&D project on purely commercial grounds. In general terms, this conclusion rests both on the fact that $5-10 million is below the thresholds reported by firms and investors for attractive market opportunities, and on back-of-the-envelope analysis of costs, risks, and desired rates of return. But it is useful to consider the circumstances of diagnostic firms of different types.

New start-ups. One way that a prize could drive new R&D would be by stimulating the formation of new companies with the prize as their primary commercial objective. But venture capitalists must typically invest $10-30M in diagnostic start-ups over several rounds, substantially more if the goal is to bring a product all the way to market.[64] Venture capitalists only make these large investments if they promise a very high potential return—as much five to ten-fold—as most ventures fail. Thus they look for initiatives that promise a one-time pay-out of $100M or market revenues of at least $20 M/year. These returns are clearly far more than the X Prize purse. Moreover, investors look to get a return on their investment in three years or so: since the X Prize competition would take 5-7 years, the amount of the prize would have to be even greater.

Start-up or small firms with other primary products or intended markets. A more realistic goal for a prize would be to persuade a small firm that is developing a technology for an application other than TB diagnostics to invest in applying this platform to TB. In this case, the prize would not have to cover the entire cost of establishing the company and developing the technology. The prize would still have to cover the risk-adjusted additional investment. The cost of the R&D required to develop a new TB test is difficult to estimate, as it depends on whether the necessary platform is already in hand and appropriate biomarkers are available. Developing a new test for an established platform could cost as little as $1 million, while developing a new platform would require at least $25 million and possibly much more. POC platforms impose additional engineering constraints and therefore can be more expensive to develop. Most small diagnostic firms work with a single platform and would only pursue the TB prize if they believed that this platform might allow them to meet the contest criteria. In this case, if appropriate biomarkers become available, R&D costs could be relatively modest and the $5-10 X Prize amount might in some circumstances be attractive.

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[63] The technologies required to meet the different objectives would probably have to be different. Drug resistance in particular will be difficult to detect with most plausible point-of-care technologies. Nucleic acid amplification technologies such as that used in the Cepheid machine can detect major forms of drug resistance quite rapidly; it is unlikely, however, that these technologies could meet X Prize's equipment-free and ease-of-use requirements. Lateral flow and similar technologies, which look for proteins or antibodies, are the easiest to make POC but are not currently able to detect drug resistance.

[64] This and other figures presented in this section are derived from about a dozen interviews with diagnostic entrepreneurs and venture capitalists. Although descriptions of the economics of diagnostic start-ups varied in detail, there was considerable consensus on the general outline presented here.

A prize is probably a better fit for more established firms than start-ups, because they have more capacity to pursue more than one objective at the same time—investors in start-ups may worry about diversion of time and resources from the primary objective. More established firms, especially those that have gone public and have products on the market, will also have a lower cost of capital than venture capital-dependent start-ups.

Large firms. Large diagnostic firms have a quite different set of circumstances. On one hand, they have a much lower cost of capital than small firms and have diversified product lines employing multiple technological platforms. As with small firms, they may be able to develop a new test for an existing platform relatively cheaply, if biomarkers are available. But their market thresholds are in general much higher, as much as $50-100M/year, especially if substantial investment is required. In most cases a prize of $5-10M is too small to get their attention on purely commercial grounds, although considerations other than the prize reward itself may be particularly important for this class of firms (see below).

Table 3.6: Factors influencing prize participation, by type of firm

Type of Firm	Technological competence	Revenue threshold for conventional markets	Total prize amount	Prize structure	Other benefits
New start-ups	Developing relevant platform or biomarkers	$20M/year	$5-10M too small	Strong preference for milestone	Recognition, technology validation
Established small to mid-size firms	Have relevant platform or biomarker	$20M/year, maybe less if costs low	$5-10M might be attractive in some situations	Strong preference for milestone	Recognition
Large firms	Have relevant platform	$50-$100M/year	$5-10M too small to be commercially interesting	Perhaps prefer end prize if PR stronger	Positive publicity from global health initiative

We conclude from this analysis that a $5-10 million prize might in some cases be enough to cover the costs of developing a new TB test, but for most firms would not be sufficient to compensate for the associated risks, both technical and competitive, and the cost of capital. Moreover, the amount is not large enough to justify investment in a new enterprise or a major new project at an established company, although it might suffice if all that was required was to add a test, using established biomarkers, to an existing platform. As this analysis illustrates, the necessary prize size should not be thought of as a simple threshold: in general a larger prize has the potential to attract firms of more types and to stimulate more ambitious, expensive R&D.

But firms deciding whether to invest in a POC diagnostic test would consider not only the prize offered by the X Prize Foundation, but potential markets for the product. The two sources of return together would be weighed against R&D costs and risks. X Prize believes that the market for a potential POC TB test might in fact be very large, as much

as $1-3 billion/year[65]. We believe on the basis of our consultations that this estimate is probably too high, but that the market for a POC TB test could indeed be quite substantial. Our consultations suggest that this view is shared by industry.

The large potential market for a new TB test means that a prize does not have to be as big as it would otherwise have to be to attract competitors. However, if the market is anywhere near as large as X Prize estimates, the obvious question is not whether the proposed prize purse is large enough, but why a prize should be necessary at all. If firms believe that a POC TB test is feasible with the technology they have at hand, a market of even $100M/year, a blockbuster in the diagnostic industry, should provide more than enough incentive and a prize of $5-10M would add little to the potential return to investment.

If this reasoning is correct, why hasn't a POC test been developed? There are several possible explanations for this paradox. One is that firms have only recently come to appreciate that TB diagnostics for the developing world represent a potentially lucrative opportunity. In fact, several interviewees suggested that industry's interest has been growing. If this is the case, investment in new TB tests may increase whether or not a prize is offered. A second explanation is that firms agree that a substantial market might materialize, but see this market as uncertain, unfamiliar, and difficult to enter. Many large diagnostic firms know little about markets in developing countries—although the so-called emerging economies are an growing focus of attention—and many are daunted by the prospect of winning regulatory approval and negotiating contracts with a large number of unfamiliar governments.

It is possible that a modest prize, in conjunction with the potential large but uncertain market, could tip the balance for some firms that were already considering developing a POC TB test. The prize itself might be a less important attraction than some of other forms of support that the X Prize proposal offers (access to samples and subsidized clinical trials) and the promise to work with international agencies to aggregate demand (see below). Such a scenario would align well with the X Prize Foundation's primary objective for a prize: to 'unlock" by drawing attention to unappreciated opportunities and inspiring innovation.

Another possible explanation, however, is that firms may be deterred by technological difficulty, rather than by inadequate market prospects. This view was expressed by several interviewees associated with large diagnostic companies, one of whom revealed that the interviewee's firm had made a considerable investment in developing a point of care TB diagnostic suited for developing countries. This effort had so far been unsuccessful because of the lack of appropriate biomarkers.

In conclusion, the reward offered in the X Prize proposal would probably be too small in most cases to drive new investment in TB tests by many diagnostic firms, although it could be sufficient for a firm that believes it could build a qualifying test on an established platform, using existing biomarkers. The potential for a large market for a

[65] The X Prize estimate assumes 200M tests/year at a prize of $5-10/test. The 200M figure comes from the 2006 WHO market study, which puts the "total available market" for a POC test at 193M. This study estimates, however, that only 40% of this total, or about 80M tests, could be captured by 2020.

POC TB test means that many firms may already be considering entering this field—a $5-10 million prize is so small relative to the potential market that it would only make a difference on the margin. The other elements of the X Prize proposal could make it attractive.

A prize of $100 M, as suggested by the BBBS proposal, would almost certainly be big enough to attract investment by a range of diagnostic firms. But a prize purse of this size would be much more difficult to raise. OECD governments or large foundations would almost certainly have to be involved, as anticipated by the proposal developers, as this amount would be beyond the reach of all but a few individuals and most endemic country governments.

Other determinants of participation

The preceding section considers whether the prize amounts suggested by X Prize and BBBS proposals would be sufficient to motivate firms of different types to make new investments in TB diagnostics. But, as discussed in Chapter II, other considerations may be quite important in determining whether firms participate in a prize contest. Our interviews confirmed that for small firms, the recognition for a new technology that winning a prize could bring could be quite valuable, although in general this would probably make a difference only at the margin. For some of the big diagnostics firms, the good publicity associated with a high-profile initiative devoted to global health could be quite attractive, and might persuade a firm to participate even if the expected rate of return were well below what it would expect from a purely commercial venture. In fact, one leading firm stated that the public relations considerations would probably be the main reason for participating in a TB diagnostics prize contest. But this was not a unanimous view: some executives told us that it is not as important to diagnostics firms to be seen as contributing to global health as it might be to pharma companies, who have suffered from more negative publicity in recent years. Working on products like TB diagnostics that promise great public health benefits would probably be attractive to scientists and other staff at most companies, and thus good for morale.

More broadly, our interviews revealed that many industry executives simply do not see prizes as a viable alternative to commercial markets. This resistance seemed to be based less on prize amount than on a perception that prizes were a "crapshoot", that they involved risks or uncertainties that were somehow of a different order than those that firms face in normal markets. This perception may stem in part from the assumption that any prize would be winner-take-all, or that winners would not be determined in an orderly, legitimate way that would allow firms to judge their chances relative to competitors. It was not possible, given the time available for these interviews, to assess whether these perceptions could change with more information and greater familiarity with the prize concept[66]. Moreover, almost all industry executives interviewed tended to weigh even quite large prizes against other measures that might allow them to invest in "global health" projects rather than against "commercial" projects aimed at markets in the

[66] This reaction to the prize concept may stem in part from the word "prizes" itself: this is why some proponents of pull incentives, including BioVentures for Global Health, prefer other terms. Another explanation is probably that they are hearing about prizes in the context of global health priorities.

US or Europe.[67] This attitude may not prevent these firms from participating in prize contests, but it may be a significant barrier to prize models intended primarily to substitute for inadequate markets, rather than to promote innovation, attract attention, or bring other benefits to participants.

Reluctance to consider the radical departure from conventional business models that a prize would represent was particularly pronounced among larger firms. This probably reflects in part greater conservatism and in part an understanding that the ability to evaluate and exploit markets—built on regulatory expertise and manufacturing, marketing and distribution capacity—is a core strength of their businesses. Smaller firms seemed more able to consider prize awards as viable alternatives to other revenue sources, perhaps in part because their business models may already include the possibility of milestone payments or even outright sale of the company to larger firms.

Other features of the prize proposals

Beyond the prize amount, there are additional features to the prize proposals we assessed – access to sample banks, subsidized clinical trials, and aggregation of demand – which could be quite valuable to firms and influence decisions on participation. Some of these features can be considered a form of push funding and complement the prize pull mechanism. Some of these additional measures could also help to remove significant non-financial barriers for firms.

Access to sample banks. The X Prize proposal would offer firms access to sputum, urine, or blood samples from high-burden regions through a sample bank. These samples can be very difficult to access and could pose an important obstacle for firms, particularly start-ups and smaller firms, in their development of TB diagnostics. We learned from one of the big diagnostic firms in the U.S. that they have made significant investments to import sputum samples from Mexico and other countries.

The provision of samples or other key reagents can be seen as a way to reduce the up-front costs of pursing a prize and thus lowering the barriers to entry. As another example, Prize4Life provided the expensive genetically engineered mice need by participants in its ASL treatment contest.

Subsidized clinical trials. Both the BBBS proposal and the X Prize proposal include subsidies for the clinical trials. The X Prize Foundation offers to pay for a one-year joint clinical trial for the top five teams that progress to the clinical study phase – their current proposal suggests that these trials would be conducted in South Africa and India. The cost of the joint clinical trial is estimated to be $2.5 to $5M. Similarly, the BBBS TB prize fund would bear the fixed costs of the clinical studies although contestants would bear the incremental costs to testing an additional product. The BBBS proposal gives a much lower estimate of the cost of these trials: $500,000 plus $50,000 for each product.

Running a joint clinical trial has three potential advantages: 1) more accurate comparison of competing products; and 2) overall cost savings since the trials aren't repeated for each

[67] This difference in how prizes are perceived by proponents—and economists—and by industry can be seen in the history of the vaccine AMC as well. While the group that originally proposed the AMC intended that firms see it as a commercially viable alternative to rich-world markets, vaccine firms have tended to cast their participation as part of their global access work.

individual product: 3) cost savings and other advantages to participating firms, which may not have expertise in conducting clinical trials in developing countries. A disadvantage is that contestants who reach this stage of development first would have to wait until competing products are ready to be tested.

In our interviews, firms agreed that clinical trials are a substantial cost and difficult to conduct in-country, especially where they currently do not have a presence. In addition, well-designed clinical trials could serve as an important step to toward regulatory approval in the countries where the trial was conducted and elsewhere.

Aggregation of demand. The X Prize Foundation proposes to help aggregate demand for TB diagnostics in developing countries, working with organizations such as the Global Drug Facility which already buys TB drugs for developing countries or the Global Fund. Firms that we consulted agreed that pooled procurement would help to realize the market potential for TB tests. Making progress in this area may be challenging for X Prize, however, since the organization has no experience with global health and global health institutions.

There is little doubt, then, that these ancillary benefits would be attractive features of a TB diagnostic prize. More generally, both X Prize and Prize4Life believe that reducing costs and risks to firms with measures of this kind be can in some circumstances be as important as the prize award itself. But if this is the case, why is a prize necessary at all, since these forms of assistance could be offered on their own or in conjunction with push funding? However, it is important to analyze the obstacles to product development and the potential advantages of the prize incentive vis a vis these features more holistically. A prize mechanism may still be the best way forward, but the case must rest on advantages intrinsic to prizes, for example the need to attract innovation from unidentified sources. This discussion illustrates the challenges of evaluating incentive proposals that represent a bundle of distinct elements.

Other features of the BBBS proposal. This proposal includes several elements in addition to the $100M "grand prize" for a new TB diagnostic that meets the technical specifications. These include small prizes for solution of technical challenges, annual "best contribution" prizes, a developing country researcher set-aside, and an incentive for collaboration and openness. We did not specifically assess these ideas, but they are reasonable responses to some of the potential drawbacks of simple winner-take-all prize designs.

Alternative designs: milestone prizes

Neither the X Prize nor the BBBS proposal currently offers milestone prizes, although the BBBS proposal would include "technical challenge" prizes for solution of technological problems and "best contribution" prizes for progress short of the final product. The X Prize Foundation would be open to including milestone awards in a revised design.

Small firms interviewed for this study were unanimous in preferring a milestone prize to a final product prize, for the reasons discussed in Chapter II: shorter time to pay-off, reduced risk, and better fit with company capacity. Small firms are also more familiar with the milestone payment concept, which is common in development partnerships between firms. Since the existing proposals did not include these elements, we were not

able to explore the details of a milestone-based structure, but firms indicated that a prize of $1-2 million for an appropriate laboratory milestone might be attractive. Some interviewees with large diagnostic firms also indicated that a milestone structure would be more attractive than an end prize by itself; it was not clear whether they would prefer a structure that included both milestone and final product prizes or milestone prizes only.

The preference for milestone prizes was one of the most consistent findings from our discussions with firms, suggesting that developers of diagnostic prizes should seriously consider this kind of design. It's important to remember, however, that milestone prizes have potential significant disadvantages as well, including the need for mechanisms to ensure that product development is completed, the risk of limiting the range of solutions, and the additional challenges of managing intellectual property.[68] Prize contests focused on milestones, which tend to be more technical in nature and less compelling to the general public, might also be less of a good fit for organizations like X Prize, which consider the ability to generate widespread publicity an important part of their model.[69]

Implications for access

The X Prize and BBBS proposals take very different approaches to promoting access to prize-winning products. The BBBS proposal would rely primarily on generic competition to ensure supply at an affordable price, requiring the prize winner to grant to a licensing pool "reasonable and non-discriminatory licenses to all patents and know-how needed for competitive supply of the technologies, in the relevant field of use"[70]. The X Prize proposal, in contrast, includes no IP provisions, allowing competing teams to retain exclusive rights to their products.

X Prize would require teams to submit business or manufacturing plans including the status of agreements with a 'reputable manufacturer' and some rough cost information on scale of production. But X Prize considers an 'affordable' cost criterion a disincentive to potential competing firms and believes that it would be difficult to define a cost ceiling and objectively audit a cost estimate[71]. On the other hand, the BBBS proposal considers access provisions a significant element of the prize design. It requires contestants to demonstrate that a product can be manufactured to scale at 'affordable prices on a sustainable basis' either by meeting an established price ceiling or a market penetration test[72].

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[68] Ideally, the inventions that enable a milestone to be reached would be available to other product developers to maximize the chance of success, especially if the winner of the milestone prize is unwilling or unable to continue development. But requiring this sharing may deter some potential participants.

[69] X Prize told us that a TB diagnostics prize focused on a milestone would probably be considered an "X Challenge", a less expensive and lower-profile class of contest, rather than an X Prize.

[70] It should be noted that the BBBS proposal would also offer an alternative if open licensing of the technology and competitive generic supply is not feasible, whereby the winner would have to provide sufficient assurances that the products will be manufactured in sufficient quantities and acceptable quality, at affordable prices.

[71] X Prize Foundation considered including a cost provision for consumables only.

[72] The BBBS proposal identifies several ways that competing firms could provide evidence to meet a market penetration test, for example, by requiring that the diagnostic device be manufactured, distributed and used by a large enough population or that it be manufactured and sold by one or more third parties without subsidies from the prize applicant.

IP provisions. Our interviews with venture capitalists and product developers revealed a mixed view on the issue of licensing requirements associated with incentives for development of products for developing countries. While some interviewees expressed a blanket opposition to any IP provisions in R&D financing mechanisms, others would consider a restrictive licensing approach whereby they would grant licenses for certain markets or regions (e.g. low and middle income countries) and for specific applications (e.g. TB diagnosis), at low cost if these markets were small or at higher cost if real opportunities were foregone. The Meningitis Vaccine Project (MVP) used a similar licensing arrangement between the NIH, PATH, and Serum Institute of India to develop and supply a new conjugate vaccine against Meningitis A[73] to GAVI-eligible countries. In addition, the recently established Medicines Patent Pool, supported by UNITAID, proposes that participating drug companies grant licenses specifically for generic production of pediatric ARTs in low and middle income markets.

Such a licensing structure could have important public health benefits if it is possible for 'generic' firms in emerging countries such as India and China to manufacture TB tests cheaply without having access to know-how. Several industry experts that we consulted thought that this would be possible. If substantial proprietary know-how is also required to make production by low-cost suppliers possible, reliance on competitive supply becomes more complicated.

However, nearly all firms we interviewed expressed concern about sharing IP for technological platforms, as this information could be very valuable for future product development and could be diverted to other uses. For example, one large diagnostic company told us that they decided not to participate in the CD4 initiative[74], a milestone-based push funding initiative to develop low-cost CD4 tests for resource-poor settings, because it required participants to grant access to all IP, including for platforms, if the originating firm is unable or unwilling supply the product. That said, funding from the CD4 initiative was awarded to 6 applicants, including two diagnostic companies, implying that the IP provisions were not insuperable obstacles to all firms. One solution to the problem of platform IP, suggested by a former executive at a large diagnostic company, is to withhold IP on a critical component and require firms that license the remaining patents to procure this component from an approved source, thus allowing the patent-holder to track how the platform is being used. The problem of platform IP would have to be solved to make a licensing approach feasible for diagnostics.

Cost provisions. All firms consulted were willing to work with a cost ceiling for manufacturing to scale and did not view such a provision as a deterrent to participation. The interviewees pointed out that some kind of price target is already a fundamental part of target product profiles for all markets. Moreover, most experts told us that it is in general possible to estimate production costs with reasonably accuracy, at least when there is some experience with the basic technology. While further investigation is required to determine an appropriate price ceiling for a POC TB test, one possible

[73] Brooke S, CM Harner-Jay, H Lasher and E Jacoby. 2007. How Public–Private Partnerships Handle Intellectual Property: The PATH Experience. In Intellectual Property Management in Health and Agricultural Innovation: A Handbook of Best Practices (eds. A Krattiger, RT Mahoney, L Nelsen, et al.). MIHR: Oxford, U.K., and PIPRA: Davis, U.S.A

[74] For more information, visit the CD4 Initiative website at http://www3.imperial.ac.uk/cd4.

standard of comparison to consider is the price range of current CD4 diagnostics available in Africa, near $5-10 a test for reagents.

We conclude that the access provisions currently included in the X Prize proposal are unnecessarily vague and could result in a winning product that cannot be scaled up at affordable cost. A cost ceiling of some kind is clearly acceptable to industry (if a level can be agreed). Although we acknowledge the difficulty of verifying claims about cost, we believe these challenges can be overcome. The licensing provisions proposed by BBBS are clearly more contentious, and would probably deter some firms on principle. But our consultations suggest that if these provisions were carefully designed they could be accepted by many product developers. The critical point is that if firms are to give up exclusive rights in potentially profitable markets such as India, China, or Brazil, the prize amount will have to be correspondingly larger to compensate for this loss.

Whether an approach that relies on licensing and generic competition or on cost ceilings is the best for a particular technology depends on a number of factors, including the feasibility of generic production, the attractiveness of the market to generic producers, and the ability to restrict the use of licensed technology to the product in question.

C. Conclusions on prizes for TB diagnostics

We conclude from this analysis that a prize could help to accelerate development of the improved TB tests badly needed in high-burden countries.

It is difficult to gauge the extent to which a TB diagnostic prize would persuade firms that are not already working in this area to invest in new R&D. There is no doubt that the prize model is unfamiliar to industry and that some firms, especially large ones, would be unwilling to consider such a different business model. Other firms, especially small ones, would have trouble finding the necessary resources upfront.[75] But we believe that a well-designed and sufficiently large prize would stimulate new investment and focus it on the specific needs of high-burden countries. Some large firms would be attracted by the good publicity associated with participation in the contest, and small firms might see it as an opportunity to validate and gain recognition for their technologies.

We believe that a prize focused on a substantial milestone in test development, for example demonstration that the specified criteria were met in a rigorous laboratory evaluation, might be more useful than an end prize for a fully developed and tested product. This conclusion, which might not apply to other products, rests on two arguments:

First, the potential market for a POC TB test for developing countries appears to be quite substantial, given the demonstrated recent willingness of donors to subsidize the purchase of critical new diagnostics. The diagnostics industry seems to recognize the commercial potential of this market. Thus a prize may not be necessary to drive later stages of test development.

[75] We did not explore in detail the impact of a prize on academic researchers. Although many would surely be inspired by a prize, their participation would depend on their ability to obtain funding for their research, either from grants or through partnerships with industry. University research is critical to development of all new health technologies, but it is not clear that prizes should directly target academic scientists.

Second, the major barrier to development of the needed point-of-care test is technological: on one hand the lack of antigen or antibody biomarkers suitable for conventional, inexpensive POC platforms and, on the other, the lack of a platform that would make nucleic acid-based tests truly point-of-care. Thus the main goal of a prize should be to encourage innovation by bringing in new ideas and new types of innovators. These innovators—small firms and university researchers—are more likely to be able to participate in a milestone prize contest.

We believe that the $5-20M prize purse proposed by X Prize is probably too small to change the decisions of most firms. Although it might be enough to cover the costs of R&D, it is insufficient to cover risks and to compete with alternative use of resources. X Prize argues that its prizes are not intended to substitute for markets; but if there is already a large market for POC TB tests, a $5-10M prizes would do little to change commercial calculations. A prize of this size, or even somewhat smaller, would probably be more than sufficient for a milestone award, however. The $100M prize proposed by BBBS would almost certainly be big enough to attract substantial commercial interest and but would be difficult to raise and might not be the most efficient use of scarce resources, given a potentially large market. Table 3.7 provides an assessment of both proposals.

In addition, we believe that in-kind support such as access to specimen banks and clinical trials organized by the prize sponsor would also encourage participation in a prize, as these measures could help address important barriers to entry.

A prize for TB diagnostics must include mechanisms to ensure that a winning product would be affordable (however that is defined). In our view, a prize should include a manufacturing cost ceiling among the criteria. In addition, requiring that winners grant non-exclusive licenses for relevant intellectual property, restricted by geography and field-of-use, could be a good way to drive down prices and ensure sustainable supply. Such a requirement would undoubtedly deter some firms from participating, however, and a satisfactory solution to the problem of access to platform technologies would have to be found to make this approach work for diagnostics.

Our case study of prizes for TB diagnostics illustrates the importance of careful analysis of context, including challenges to product development and market prospects, to understanding whether a prize would help to accelerate development of a particular product. Prize design must in turn be tailored to address the specific obstacles to product development and access.

Table 3.7: Assessment of TB diagnostics proposals

	X Prize	**BBBS**
Technical specifications	Reasonable, fairly ambitious	na
Prize amount	$5-10M too small for most firms	$100M sufficient for firms, but much more challenging to raise
Prize structure	Most firms prefer milestone structure to shorten time to pay-off and mitigate risks	Most firms prefer milestone structure to shorten time to pay-off and mitigate risks
PR and recognition	Publicity is an X Prize focus and attractive	na
Other features	Access to specimen banks, subsidized clinical trials, aggregation of demand attractive	Subsidized clinical trials attractive
Access provisions	Too vague; should include cost criterion	Cost or market penetration criteria useful; IP licensing could be contentious, especially for platforms

IV. Prizes for other global health technologies

In the previous chapter we analyzed in detail the potential of prizes for point-of-care TB diagnostics. To what extent do our conclusions from this analysis apply to prizes for other diagnostics needed in low- and middle-income countries and, more broadly, to prizes for drugs and vaccines? The answer, not surprisingly, is that it depends: we believe that each case must be analyzed separately, as the value of prizes relative to other instruments depends on the specific circumstances. But it should be possible to delineate some of the features of particular technologies that are most important to understanding whether a prize would be useful.

In this chapter we describe briefly some current prize contests or proposals in other health areas. We then examine how relevant features of other needed global health technologies might differ from the example of TB tests and what implications these differences might have for prizes.

A. Other prizes and prize proposals

Although more work has been done on prizes for TB tests than for any other global health product, prizes have been proposed or are being developed for other needed health technologies.

Other BBBS proposals

The four countries that submitted the proposal for the TB diagnostics prize fund to the WHO working group also put forward two other prize proposals. One outlines a prize fund for new Chagas drugs, vaccines, and diagnostics[76]. Although this proposal shares many features of the TB diagnostics proposal, it is substantially more ambitious and it incorporates several of the innovative elements of the comprehensive multiproduct prize funds proposed by KEI and others. In particular, rather than awarding a large prize of fixed size to the first product to meet a set of technical specifications, it would reward all new licensed medicines and vaccines for Chagas according to their incremental impact on health outcomes, with product receiving payments for up to 12 years. To be eligible, product developers would have to license all necessary patents and know-how to a new Chagas patent pool. New diagnostics would also be eligible for rewards, although the details of how this would work are not specified (as it might be more difficult to estimate the incremental health benefit of new tests).

Another BBBS proposal links prizes and patent pools to donor funding for the purchase of medicines, for example through the Global Fund[77]. It suggests that donors contribute a fraction, perhaps 10%, of their spending on drugs for developing countries to a new prize

[76] BBBS Chagas Prize Fund submission to WHO EWG available at http://www.who.int/phi/Bangladesh_Barbados_Bolivia_Suriname_ChagasPrize.pdf.
[77] BBBS donor prize submission to WHO EWG available at http://www.who.int/phi/Bangladesh_Barbados_Bolivia_Suriname_DonorPrize.pdf.

fund that would be used to reward new medicines for the included diseases. These rewards would again be linked to the incremental health benefit of the new products, and would go only to product developers who agreed to submit the relevant intellectual property to a patent pool. In theory, donors (and developing countries not receiving donor subsidies) would benefit from the lower prices that would come with generic production of the new medicines.

Finally, Bolivia, Suriname, and Bangladesh submitted a proposal for prize funds at the national level for new cancer treatments, highlighting the growing importance of non-communicable diseases in developing countries and extending the prize fund concept into the more controversial domain of products with primary markets in high-income countries[78].

BioVentures for Global Health (BVGH)
BVGH is developing one or more proposals for pay-for-success incentives for health technologies needed in developing countries.[79] Although this work is not yet public, BVGH has shared some features of the emerging proposals with us.

- The incentives will be milestone-based, with rewards at one or more development milestone and perhaps also for the end product.
- The primary target of the incentives will be biotechnology firms.
- One proposal will focus on diagnostics. The targeted product may be a platform capable of diagnosing several diseases, for example a test that could distinguish several common causes of childhood fevers. Another proposal may be for new Chagas drugs.

Prize4Life
As mentioned in Chapter II, Prize4Life is using prizes to accelerate development of new treatment for Amyotrophic Lateral Sclerosis. They have conducted two prize contests, one for new biomarkers of disease progression and one for new treatments that demonstrate efficacy in a specified animal model[80]. Although the focus on a disease with a large market in the US puts it beyond the scope of this study, the Prize4Life initiative is an interesting example of the use of prizes to overcome scientific and technological obstacles to development of new health technologies. It also illustrates the way that prizes can focus attention on critical needs, in this case markers of progression and rigorous animal models, that may not be receiving sufficient attention.

B. Prizes for other diagnostic tests

We believe that much of our analysis of prizes for TB diagnostics would apply to other diagnostics for the developing world. Our findings on the costs, expectations, and attitudes toward incentives held by diagnostic firms of various kinds should be broadly

[78] BBS cancer prize fund submission to WHO EWG available at http://www.who.int/phi/Bangladesh_Bolivia_Suriname_CancerPrize.pdf.
[79] BVGH prefers not to use the term “prizes”.
[80] For more information, visit Prize4Life website (http://www.prize4life.org/page/prizes)

applicable. Three features of TB diagnostics may differentiate this product from many others, however. The first is the relatively large potential market for a successful point-of-care TB test. Although this market is far from certain—especially given the more pessimistic outlook for donor funding for global health—many firms seem to find such a product commercially attractive. Important new diagnostics for HIV, for example a point-of-care CD4 test, might also have enough of a market to interest industry. But tests for many other diseases might have much less attractive markets, either because they would have to be very cheap to displace existing tests, because the needed volume would be much smaller, or because there would be no meaningful private market and no donor channel for substantial subsidy. Diagnostics for sleeping sickness might be an example of a badly needed product with a very small market.

The main implications of small market size for prizes is that the prize either has to be for the end product and large enough to substitute for the missing market, or, if the prize is for a milestone, be coupled to another mechanism (push funding or a purchase commitment) to bring the product the rest of the way to market. Where substantial markets exist, milestone prizes may make the most sense, since the market should suffice to pull a promising product through to licensure once technological and other barriers are removed. Access provisions of some kind are still needed, however, since a product intended primarily for private sector or donor-subsidized markets in developing countries must still reach others who need it.

The second important feature of point-of-care TB diagnostics for prize design is technological difficulty. On one hand, the magnitude of the challenge means that the prize may have to be quite large to compensate for the risk—and even a large prize may not be enough to persuade some firms who don't believe that their technologies can solve the problem. On the other hand, the need for new ideas and perhaps new innovators makes problems like these a good fit for prizes, especially early-stage prizes. Other needed tests are almost certainly easier to develop: the lack of interest by industry in the diseases of developing countries means that there is almost certainly low-hanging fruit to be found, and that the necessary tests can in many cases be developed on the basis of existing technological platforms, using known or relatively easily discovered biomarkers. In these cases, prizes of relatively modest size might have an effect, but more conventional approaches might work just as well or better. The Meningitis A conjugate vaccine developed by PATH's Meningitis Vaccine Project is an example from outside the diagnostics field of an important product whose development required no scientific or technological breakthrough and which could be pushed to a successful conclusion (with affordable access guaranteed) through a relatively simple partnership structure with foundation funding.

The third distinguishing feature of TB diagnostics is, ironically, that the urgent need for better tests is now quite broadly appreciated, thanks in part to the efforts of MSF. As a consequence, the value of a prize in mobilizing attention and resources and in bringing the problem to the attention of potential solvers is less than it might have been a decade ago, and less than it would be for another needed diagnostic, for example for Chagas.

C. Prizes for drugs and vaccines

The considerations discussed in the previous chapter apply to prizes for drugs and vaccines as well: market size, technological difficulty and the need for breakthrough innovation, and level of awareness matter in the same way. But drugs, vaccines, and diagnostics differ in important ways that have implications for prizes. We cannot attempt a systematic analysis here, but will outline a few potential important differences.

Most importantly, drug and vaccine development is considerably more expensive and time-consuming than in vitro diagnostic development, largely because of the long and expensive clinical trials required to demonstrate safety and efficacy. An often-cited study estimated the average risk-adjusted cost of developing a new drug at $800M;[81] although some have argued that this figure is inflated, it is clear that R&D costs can be ten-fold greater for drugs and vaccines than for diagnostics. This means that prizes for drugs or vaccines, or at least end-prizes for these products, would in general have to be much larger than for diagnostics, probably at least in the many $100's of millions if not billions. The long time it takes to bring a new drug or vaccine to market—typically a decade or more—increases the challenge, especially if the prize is aimed at innovators with a high cost of capital. While diagnostic prizes could be funded by a wide range of sponsors, including individuals, one consequence of the high cost of drug and vaccine prizes is to limit the range of potential sponsors to governments and large foundations and to make governance issues more important.

It's important to keep in mind that these challenges apply not just to prizes but to other incentives of drug and vaccine development: if the real costs are greater, any mechanisms for accelerating development of these products will be more expensive. But the relatively low cost and short development timelines make diagnostics an attractive testing ground for prizes.

The industries are also different. The vaccine industry in particular is highly concentrated, with five multinational firms accounting for 85% of global sales in 2008. Not only sales but also the capacity to bring new products through trials and the demanding regulatory process is concentrated in a few firms, although a number of companies in the emerging economies can manufacture all but the most sophisticated vaccine and have growing innovative capacity. This means that an end prize aimed at development of a new vaccine, especially a challenging one, would probably have to be designed to interest the handful of multinational vaccine firms. But these firms may be the least likely to consider such a departure from their usual way of doing business, even if they find the publicity associated with participating in an neglected disease initiative appealing. Moreover, if it is clear that the needed innovation must come from one of a small number of firms, a prize might not be the most efficient way to purchase this innovation. Milestone prizes aimed at university laboratories or smaller companies might be a useful alternative, with the possibility of handing over to a developing country manufacturer.

[81] DiMasi, Joseph et al., The price of innovation: new estimates of drug development costs, Journal of Health Economics 22 (2003) 151–185.

Some other differences relate to intellectual property and to the prospects for generic production. For drugs, the regulatory approval process for generic products is well established. Given the sophistication of generic manufacturers, in most cases it should be possible for multiple manufacturers to produce and win regulatory approval for their versions of a licensed drug, as long as patent and other IP barriers are removed. This means that the strategy of linking prizes to licensing and generic production could work, as long the requirement doesn't deter participation and the markets are sufficient to support generic suppliers. Moreover, the problem of platforms with multiple uses is much less relevant to drugs than to diagnostics. But it may be that drug companies would be more resistant to any IP licensing requirement, precisely because patents in many cases represent the only barrier to generic production and are thus perceived as indispensable to the industry's business model. For vaccines, as for diagnostics, there is no formal generic regulatory pathway—each new manufacturer must independently demonstrate safety and efficacy, since no two vaccines can be considered identical—although in practice "follow-on" vaccines often have an easier and cheaper path to market. Know-how, especially in manufacturing, is also much more important for vaccines than for drugs. Together these two considerations mean that a licensing and generic production approach to promoting access is much more challenging for vaccines.

D. Prizes compared to other incentives

To be added

V. Overall conclusions

Incentive prizes are an intriguing alternative to grants and other forms of push funding as a way to spur the development of needed health technologies for developing countries. Their greatest potential advantage is that they do not require the sponsor to choose either the most promising path to the desired product or particular product developers. They are thus most likely to be useful when the way forward is not clear and new ideas—and new innovators—are needed. It follows that prizes are probably not the most efficient mechanism when the needed R&D is relatively straightforward.

An important disadvantage of prizes (and other pull mechanisms) is that they exclude researchers and product developers who are not able to fund the necessary R&D upfront.

Prizes could be used both to overcome scientific or technological obstacles or, like AMCs, to augment or substitute for commercially unattractive markets. But the two uses of prizes focus on different kinds of participants and require different designs.

Milestone prizes, either free-standing or as a part of a structure that includes final product prizes as well, are particularly attractive in circumstances where the primary obstacles to development of the needed product are at early stages. Prizes of this kind are attractive to biotechnology companies, which have a shorter time horizon than large firms. But milestone prizes must be accompanied by mechanisms to ensure that candidate products are taken all the way to market and will be available to those who need them at an affordable price.

Final product or end prizes would be most appropriate where the primarily obstacle is lack of market, as will often but not always be the case for the products needed by the poor. Prizes of this kind also offer an opportunity to de-link product prices from R&D costs through IP licensing and generic manufacturing. In situations where generic production is feasible—and other elements of the prize have guided developers toward low-cost technologies—this approach could be a way to promote sustainable supply at affordable prices. But the viability of end prizes depends on their attractiveness to the typically large firms with the capacity to bring new products all the way to market.

In the case of TB diagnostics, we believe a prize could help to overcome the challenges to the point-of-care test needed in many high-burden countries. Since the primary obstacles are technological (notably the lack of biomarkers suitable for conventional point-of-care platforms) and since the market for a good test is probably sufficient to attract developers and suppliers once the obstacles are removed, we believe that a milestone prize might be sufficient, although milestone rewards could be coupled to a final product prize.

Firms consulted for this project had a mixed reaction to the idea of prizes. Many biotechnology firms suggested that a sufficiently large prize, especially for a milestone that they could reach on their own, could be an attractive alternative to other kinds of return on R&D investment. Established firms were more likely to be able to pursue a prize than start-ups. Large firms, with their business models centered on production, distribution, and pursuit of market share, were in general less willing to consider prizes as

an alternative return on investment, suggesting that even large prizes might have trouble changing the priorities of these firms. Some large firms might be drawn to make modest investments in prize contests by the positive publicity. Not surprisingly, most firms expressed a preference for upfront and risk-free funding in the form of grants over prizes. Some but not all firms said that IP licensing requirements could deter them from pursuing a prize.

There are limits to how much can be learned from industry consultations, however. In the absence of a concrete initiative with money behind it, many firms have not devoted much time to the concept and may not completely understand what is being proposed. Moreover, it is impossible in a realistic number of interviews to cover the full range of types of firms, especially when the goal of a prize may be to attract participants who are new to a field. Although these conversations are necessary, and can provide crucial insights into the needs and priorities of firms of various types, ultimately the only way to know who would participate will be to launch a prize. We believe that some questions will only be answered by experimentation, and that the case for prizes for global health technologies is strong enough to justify investing in one or more carefully chosen initiatives. The great need for better TB tests, together with the modest R&D costs and relatively short development timelines of diagnostics, could make TB diagnostics a good testing ground for prizes.

Annex: Participants in interviews

Organization	Name	Title
Aberdare Ventures	Paul Klingenstein	Managing Partner
AdvaMed Advanced Medical Technology Association	Ralph Ives	Executive Vice President
AdvaMed Advanced Medical Technology Association	Sarah Smiley	Vice President of Strategy
Ahimsa Partners	Jean Francois de Lavison	President
Alloy Ventures	J. Leighton Read	Partner and Board Member of BVGH
Aviir	Doug Harrington	Chief Executive Officer
Bayer Diagnostics	Rolf Classon	Former CEO
Becton Dickinson	Gloria Young	Vice President of Global HIV/AIDs Initiative
Becton Dickinson	Krista Thompson	Vice President/General Manager Global Health
BioVentures for Global Health	Andrew Robertson	Chief Policy Officer
BioVentures for Global Health	Elizabeth Aden	Consultant
Catalysis Foundation	Richard Thayer	Chief Executive Officer
CD4 Initiative	Hans-Georg Batz	Director
Cepheid	David Persing	Executive Vice President and Chief Medical and Technology Officer
Cepheid	Ellen Jo Baron	Director of Medical Affairs
Claros Diagnostics, Inc.	David Steinmiller	Founder & COO
Clinton Health Access Initiative	Maurine Murtagh	Director of Diagnostic Services
Clinton Health Access Initiative	Trevor Peter	Scientist
Clinton Health Access Initiative	Amy Wong	Program Manager
Columbia University	Sam Sia	Assistant Professor of Biomedical Engineering
Columbia University, Earth Institute	Yanis Ben Amor	Associate Research Scientist
Daktari	William R. Rodriguez	Chief Executive Officer
Foundation for Innovative New Diagnostics	Mark Perkins	Chief Scientific Officer
Foundation for Innovative New Diagnostics	Lakshmi Sundaram	Advocacy Officer

International AIDS Vaccine Initiative	David Cook	Executive Vice President and Chief Operating Officer
International AIDS Vaccine Initiative	Wilson Lee	Director of Policy and Advocacy
InnoCentive	Dwayne Spradlin	President and Chief Executive Officer
Integrated Diagnostics	Albert Luderer	Chief Executive Officer and Former CEO of BioMerieux US
Knowledge Ecology International	James Love	Director
Knowledge Ecology International	Judit Rius Sanjuan	Attorney
LabCorp	Paul Billings	Former CMO
MIT, X Prize Lab	Erika Wagner	Executive Director
McGill University	Madhukar Pai	Assistant Professor & CIHR New Investigator
Médecins Sans Frontières	Katy Athersuch	Medical Innovation & Access Policy Adviser
Médecins Sans Frontières	Michelle Childs	Director of Policy and Advocacy
Office of Science and Technology Policy	Robynn Sturm	Assistant Deputy Chief Technology Officer
Prize4Life Foundation	Melanie Leitner	Chief Operating Officer and Chief Scientific Officer
ReaMetrix Inc	Bala Manian	Chief Executive Officer
Tethys Bioscience	Mickey Urdea	President of the Board
Tufts University	Will Masters	Professor of Food Policy and Economist
USAID	Wendy Taylor	Advisor on Innovative Finance and Public Private Partnerships
Vivacta	Neil Butler	Former CEO
X Prize Foundation	Eileen Bartholomew	Senior Director
X Prize Foundation	Francis Beland	Vice President Prize Development
PATH	Milton Tam	Former Technical Director