

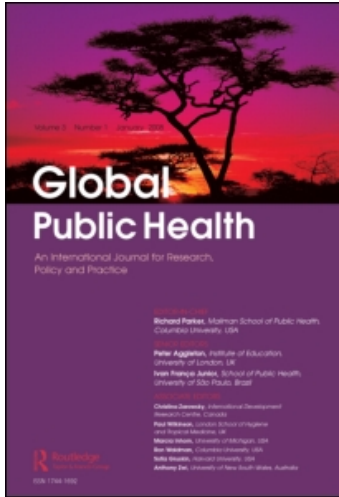
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University leadership for innovation in global health and HIV/AIDS diagnostics

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Medical products used in the developed world often fail to adequately serve resource-limited settings where electricity, transportation and health care workers are not readily available. We suggest that the problem is not only a lack of coordinated financial resources to purchase existing medical products, but also a lack of products that are specifically designed for resource-limited settings. While donor organisations with a focus on global health are increasingly willing to bear the additional financial risk for the research and development of such high-impact medical products, corporations are still reluctant to take their best scientists and engineers away from more commercially attractive projects. Universities, on the other hand, given their teaching and research missions, are well positioned to engage in such high-risk development projects. A group of biomedical, engineering, business and social science researchers at Northwestern University (NU) propose a creative model to address significant social and health needs. The team's initial product focus is a rapid test for diagnosing infants with HIV. The NU model aligns the incentives and expertise of industry, donors and academia to innovate medical products, such as the infant HIV diagnostic test, for resource-limited settings.

Keywords: research and development; market failure; HIV diagnostics for infants; public–private partnerships; intellectual property

Background

In 2007, an estimated 370,000 children under the age of 15 years became infected with HIV, increasing the total number of children living with HIV from 1.6 million in 2001 to 2.0 million in 2007 (Joint United Nations Programme on HIV/AIDS and World Health Organization [WHO] 2008). Over 90% of HIV-infected children live in sub-Saharan Africa, with very few new infections coming from developed countries (Joint United Nations Programme on HIV/AIDS and WHO 2008). In the USA, for example, HIV/AIDS was newly diagnosed in only 142 children throughout 2005 (CDC 2007). Nearly all newly infected children acquire the virus during pregnancy, birth or breastfeeding (Mulder *et al.* 1996). If untreated, 33% of these children will die during the first year of life (Newell *et al.* 2004). In 2006, an organisation called UNITAID was formed to reduce prices and increase access to this life-saving

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treatment (UNITAID n.d.). Since UNITAID's inception, the number of HIV-infected children on treatment has tripled to 170,000 in 2008 (UNITAID 2008). UNITAID funds an estimated 75% of the HIV-infected children on treatment and plans to increase the number of HIV-infected children on treatment to 400,000 by 2010 (UNITAID 2008). The UNITAID paediatric HIV programme allocates \$52.1 million annually towards paediatric HIV diagnosis and treatment, thereby creating market demand out of market need (UNITAID 2008). This demand has arguably increased the number of suppliers of paediatric HIV products and reduced their prices (UNITAID 2008).

Before an infant can be placed on life-saving drug regimens, the infants that are HIV positive must be identified. It is estimated that of the 30.9 million infants born in sub-Saharan Africa every year, approximately 9% are exposed to HIV (Aledort 2006). The HIV-exposed infants are often identified by either testing the mother or the infant with a rapid HIV antibody test (De Cock *et al.* 2006). Of those HIV-exposed infants, it is estimated that only 15–35% will actually become infected with HIV (Mansergh *et al.* 1996, Taha *et al.* 2000). One of the technologies used by the UNITAID programme to identify these HIV-infected infants is the DNA PCR test (UNITAID 2008). UNITAID, in partnership with the Clinton Foundation, has increased the number of sites with access to DNA PCR testing from less than 200 to 1400 in 2007 (Clinton Foundation Pediatric Program n.d.). Despite this initial success, there are a number of inherent drawbacks that remain with the existing DNA PCR testing technology. Not only is DNA PCR testing relatively expensive, but it also does not allow for same-visit results, and requires the transport of blood or dried blood spots to and from a centralised laboratory (Ginsburg *et al.* 2006). Studies have shown that testing conducted in centralised laboratories can take several months to return from the rural environments in which the blood sample was collected (Wilkinson and Habgood 1994, Stetler *et al.* 1997). This is likely due to poor access to roads required to get blood samples to and from the laboratory and the patient to and from the clinic. These structural limitations not only limit access for untested populations, but also delay treatment for infants who test positive (Aledort 2006).

According to an article in the journal *Nature*, 'there is an urgent need to develop and deploy a new easy-to-use HIV test, which could transform the management of paediatric HIV/AIDS in developing countries and avert millions of infant deaths' (Aledort 2006). If the product could make same-day results available, then there is evidence that the proportion of individuals who actually receive their test results would improve (Downing *et al.* 1998, Kassler *et al.* 1998, Malonza *et al.* 2003). More specifically, one study of adult rapid HIV tests showed that when turnaround time from blood collection to results delivery was reduced from 107 to 48 minutes, the percentage of patients leaving before receiving their results decreased from 55 to 20% (Kelen *et al.* 1999).

Research and development (R&D) dedicated to combat neglected tropical diseases receives less than 0.001% of the money spent worldwide on biomedical research and product development (Families USA 2007). One of the reasons for this disparity is the lack of incentive for the relevant parties to develop these products for these disease categories. A public company making R&D investments decisions will often prioritise those projects with the highest expected profits versus the highest expected health impact. While donor organisations with a focus on health care are

increasingly willing to bear the additional financial risk for the R&D of such high-impact technologies, they do not often have the technical experience needed to develop medical products themselves (OXFAM 2008).

A group of biomedical, engineering, business and social science researchers at Northwestern University (NU) propose a tripartite model to address significant social and health needs, such as the lack of HIV diagnostics for infants. The model aligns the incentives and expertise of industry, donors and academia, thereby narrowing the gap between supply and demand for health care diagnostics.

A need, but no incentive for innovation

Health care delivery environments in resource-constrained settings are noticeably different than those in traditional commercial markets. For example, the lack of health care workers available to draw blood, run complex laboratory equipment and interpret results of HIV tests is a problem for even the most developed of African nations. In South Africa, the ratio of health care workers is estimated at seven per 1000 compared with 56 health care workers per 1000 in the population in the USA (WHO 2007). In addition to the acute deficit of human skills, many African countries lack essential infrastructural components such as a reliable supply of electricity, which, for example, rules out existing devices that require sustained refrigeration. Furthermore, the ability of patients or health care systems to pay for medical diagnostics is significantly below the prices that for-profit corporations developing diagnostics need to charge in order to custom-design their health care products. Taken together, these factors suggest that manufacturers of medical devices for use in developing countries face an entirely different market compared to developed economies. As a consequence, simply donating existing equipment will not satisfy the existing need. Rather, sustained R&D efforts addressing the unique contours of these environments are needed.

For-profit companies are beginning to realise low-margin, high-volume financial opportunities exist in resource-limited settings. The important byproduct of these sustainable commercial ventures is that new products are introduced to individuals that would otherwise not have access to them. For example, Celtel International, a Netherlands-based company, earns a profit by providing mobile products and services in multiple African countries. Celtel 'serves as an encouraging model for other international companies who might otherwise be tempted to dismiss the whole sub-Saharan region apart from South Africa' (Bray 2005).

Although a growing number of companies recognise that financial opportunity exists 'at the bottom of the economic pyramid' many factors complicate this proposition for large diagnostic companies (Prahalad 2005). For example, the substantial cost and risk of R&D in the health care industry create a risk-averse environment. While R&D costs are not as high in the medical diagnostic arena as in the therapeutic space, the financial burden is still more significant than, for example, in the mobile phone market in which Celtel found success. Second, the differences between developed and developing world markets complicate the product development process. While the mobile phone customer billing models may vary across countries, the inherent R&D used to develop mobile towers and phones is largely the same. In contrast, diagnostic companies cannot necessarily hope to recoup the cost of product development for resource-limited settings in wealthy nations, because the

products are not sufficiently similar. For example, given the adequate access to refrigeration throughout the reagent supply chain in developed countries, a medical diagnostic company may forgo investment in a 'no cold chain' solution. Third, health care clients in under-resourced countries are not necessarily able to pay even at or below cost. Given the percentage of the population in these settings that make less than two dollars a day, it is not feasible for patients themselves to pay for their health care. In addition, governments are reluctant to pay for expensive diagnostic machines that may or may not work outside the capital city given the lack of human resources that can operate or service the equipment. In light of these challenges, researchers at NU developed the Global Health Initiative and the Center for Innovation in Global Health Technology to address these reasons for market failure by creating a new model for innovation in health care products.

The model

In 2004, NU, through the J.L. Kellogg School of Management and McCormick School of Engineering, spearheaded a new model of cooperation between public and private institutions. Such public-private partnerships are often forged to address market failures and provide goods to populations in need (OXFAM 2008). In the case of medical diagnostics, the NU investigators recognised the need to include academic institutions because they are uniquely positioned to catalyse partnerships between non-profit donors and commercial diagnostics companies (Gelijns and Their 2002), while contributing to the development of medical technology for the world's poor. This tripartite collaboration helps to bridge the gap between the existing markets for sophisticated lab-based diagnostics in wealthy nations and the need for point-of-care diagnostics to serve areas where the traditional lab-based diagnostic model fails.

In this model, the academic partners provide the broad range of talent and expertise necessary to develop the intellectual property (IP) and take the products to market. Schools of engineering provide the scientific and engineering talent necessary to modify existing IP of the corporate collaborators so that it better serves the populations in need. Schools of business conduct market research, gather product requirements and identify strategic direction. Schools of medicine provide clinical research and test the products in resource-limited settings. Schools of social science ensure that the cultural contexts in which products are developed are properly considered, thus ensuring ultimate adoption by the end users. The academic institutions are essentially creating a parallel R&D process for developed countries that mimics the one used at for-profit companies in developed countries. Our project applies similar rigor to scientific and ethical standards of research in data collection and analysis, choice of product focus and research methodologies. The NU approach is different from other academic models in its collaboration across different schools and disciplines. The student participants (under-graduates, MBA and Ph.D. students) benefit not only from the research experience, but also contribute to the teaching mission of the university.

Diagnostic companies donate technology or IP that is not necessarily appropriate for resource-constrained areas, but that serves as the starting point for the development of point-of-care diagnostics. NU currently works with two companies, Abbott Laboratories and Inverness Medical, to redesign existing IP into two

potential diagnostic devices that will detect HIV in infants. When the infant HIV product is further developed, the corporate collaborators obtain rights to NU product designs and the associated IP in exchange for a commitment to serve developing world markets. Agreements to serve developing world markets must be in place before a licence is granted to the corporate collaborators for commercial markets. Sales in commercial markets will include a reasonable royalty for any new IP created by NU during the course of the project. If the corporate collaborators choose not to manufacture the products in both commercial and developing world markets, then NU can operate in developing markets without having to pay the corporate collaborators a royalty fee.

The for-profit manufacturer would make specified quantities of product at or near cost in developing world markets. Costs include direct and indirect expenses associated with manufacturing, distributing and servicing the product but do not include R&D expenses. The rights to manufacture the product for distribution within developing world markets could be granted non-exclusively to ensure that there would be multiple suppliers if one failed to meet its commitments. None of the collaborators would be required to license the technology to competing manufacturers if it agreed to manufacture, either itself or through sub-contracting, in a manner that fulfilled the commitments to further the goals of the global access strategy.

NU is responsible for managing any new IP arising from the project. To help achieve the goals of this strategy, patent protection can be sought for those inventions that appear patentable and have commercial potential.

The R&D process benefits greatly from the funding provided by non-profit donors committed to solving global health problems. In the NU model, the Bill and Melinda Gates Foundation (BMGF), significantly contributes to the project by encouraging knowledge sharing and providing common shared services across all grantees. In addition to the BMGF, industry partners such as Abbott and Inverness Medical also provide experience in dealing with regulatory and government requirements in a variety of resource-limited settings.

Incentives and alignment

Public-private partnerships will only lead to sustainable success if all players have mutual and complementary incentives to participate in the model. The NU model links the relative strengths of each partner and offers a new approach for the challenges of interdisciplinary and applied research. Academic researchers and students directly benefit from access to a real work setting. The youth and exuberance of students willing to go to the field in search of experience can be deployed to produce additional research about the health care community. This exposure expands learning beyond classroom and laboratory settings, and enhances the career prospects of engineering, medical and business students through a distinctive educational experience. Participating researchers in all disciplines equally gain from the use of more practical cases, which helps to specify and guide their own research focus and enrich their teaching.

For-profit companies specialising in researching and developing diagnostic tools typically perform stringent cost-benefit and risk analyses for any new R&D venture. Industry partners are interested in reducing costs in order to expand the use of

point-of-care diagnostics tools. Funding from a donor source and the access to academic medical, engineering and business market research allow the participating industry partners to expand their R&D efforts with little additional risk. Projects with highly uncertain commercial prospects that would normally fail to satisfy the company's selection criteria are now undertaken by the university, wherein they do not constitute a 'risk' but rather an opportunity for innovative research and experiential learning. The results of the combined R&D initiative may even lead to viable markets, even though this is not its intent. Moreover, the research interaction with university researchers may trigger other, initially unrecognised product opportunities. Finally, individual employees draw job satisfaction from this commitment, as well as from collaborating with student researchers who benefit from their expertise.

Donor agencies are eager to support initiatives aligned with their organisational mission and to bring in additional players to solve global health problems. Given that donor funding is limited, it is important to leverage these resources and develop high-impact and sustainable strategies. Access to a health care company's technology at the outset, and to its manufacturing and distribution facilities at the completion of R&D, offers a promising direction for donors who lack competency in this area. Finally, many donor organisations are eager to bring business discipline and innovation to their own projects so as to limit costs and maximise impact. They gain from fostering partnerships between business and academic research to ensure pooling of knowledge and research efforts.

Challenges and opportunities

This tripartite model is not without its complications. The upfront cost and time spent to develop agreements among all academic, donor and industry participants can be overwhelming and lengthy. In the case of the NU model, it took over 2 years for all parties to agree to the terms of the technology transfer. The ownership of the IP is perhaps the most challenging component of this process. As academic institutions are typically more focused on the earlier stages of scientific discovery, their preferred model of connecting with industry is a technology transfer approach, i.e., licensing or selling their own IP to companies involved in later stages of development. In this model, however, academia needs to utilise already existing IP created and owned by commercial entities. This requires complicated consensus on the ownership of the new IP generated throughout the process. In the NU model, companies have agreed to forego revenues in resource-constrained markets. However, since the project also has the (unexpected) potential for success in developed markets, such as the USA, Japan and Europe, collaborators must agree at the outset on how to share the revenues generated from those markets.

In addition, students volunteering their time as part of their academic requirements must be properly trained and supervised by university faculty. The 'employee turnover' of a student-based work force is much higher in an academic setting than in industry, and collaboration involving an academic partner must retain a few key individuals to ensure continuity. Developing management processes for a 'work force of volunteers' can be challenging, especially if different student segments have different short and long-term needs and goals.

Developing research capacity and work force training in the recipient countries also requires innovative thinking. We are exploring new ways to engage in student

and research exchange programmes, where learning can occur for both NU students and students attending African universities. As a first step, a collaboration with the University of Cape Town (UCT) was created where faculty at both NU and UCT teach a class in Cape Town on product design. Ultimately, in-country product development, production and distribution could be an additional goal of this triangulation model.

The NU model attempts to rethink how the efficiency and innovation of the private sector can be harnessed to address social needs. On one hand, companies increasingly address the unique needs of emerging markets on their own. General Electric, for example, announced in 2006 that it plans to double its sales in countries such as China and India by the end of the decade. Yet, many companies continue to be reluctant to engage in the more nascent African economies because of increased risk and highly uncertain revenue opportunities. Academia and donors can help to overcome these hurdles by serving as a catalyst in the R&D process. If carefully managed, this triangulation model can provide a new approach for innovation to address global health needs.

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