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CHALLENGE OF IN-VITRO DIAGNOSTICS FOR RESOURCE POOR SETTINGS:
An Assessment

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CHALLENGE OF IN-VITRO DIAGNOSTICS FOR RESOURCE POOR SETTINGS: An Assessment

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[***Abstract***: *This article reviews the diagnostic needs and challenges of resource poor settings and the impact of present institutional and policy regime on the development of ecosystem for innovation making in case of in-vitro diagnostic technologies in India. Strong intellectual property rights, open economy regime of trade and investment, absence of stringent regulations of accreditation and quality control and continued domination of foreign firms define currently the eco-system of innovation making in in-vitro diagnostics for resource poor settings. In-vitro diagnostics for the management of priority diseases in resource poor settings remain a major challenge for the policymakers in India. 70 -75 % of diagnostics needs are met through imported and maladapted diagnostic innovations. Analysis of the emerging pattern of innovation making for resource poor settings shows that while the young start-ups are beginning to focus on some of the diagnostic needs and challenges facing resource poor settings, but the market for in-vitro diagnostics is dominated by maladapted imports being undertaken by the foreign and domestic firms. Continuing lack of coordination between the R&D institutions and the user ministry is reflected in the direction of search and institutionalization of R&D in in-vitro diagnostics for resource poor settings. Persistence of lack of collaboration between the national R&D institutions and the domestic firms for the benefit of innovation making for resource poor settings is a matter of concern. The challenge of alignment of the policy regime for industrial development and healthcare system needs to be urgently tackled by the government.*]

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1. Introduction

In India the challenges of innovation making for resource poor settings are context specific in the field of *in-vitro* diagnostics. The requirements of treatments for the prevailing diseases are quite distinct. There exists a major challenge in the form of resource constrained conditions of healthcare facilities to which innovations need to fit appropriately. Innovations that can easily perform and be easily maintained by well-equipped labs do not work well in the resource constrained healthcare facilities of rural and small town India. Innovations imported from the industrialized world do not perform properly due to the lack of basic healthcare facilities and absence of ambient temperature. Innovations being introduced thus need to have a close fit on the one hand with the challenges of diseases to be treated and on the other hand with the resource constrained conditions of healthcare system evolving to meet the requirements of accuracy for the wider adoption of *in-vitro* diagnostics.

Providing timely access to diagnostics and screening of diseases to a vast majority of the people has become a major challenge in rural and small town India[1]. Cost of inattention to the challenge of innovation making initiatives for resource poor settings can be heavy. We cannot expect the innovations developed in the context of United States and Europe to meet all our requirements of innovation making for resource constrained settings in the case of *in-vitro* diagnostics innovations. In order to deal with the problem of maladaptation of diagnostics for resource constrained settings India will have to source them from those players in the diagnostic industry who have the capabilities to develop such diagnostics and are ready to collaborate with the domestic users as well as the public sector research institutions. India needs a socially responsible innovation system framework to look after the specific challenges of innovation making in resource poor settings.

In this article we aim to study the impact of institutional and policy changes on the innovation trajectories under development and on the development of ecosystem for innovation making in the field of *in-vitro* diagnostics. The article explores the problem of how to tackle the gaps and needs of resource-constrained settings in the field of in-vitro diagnostics technologies as a challenge of science, technology, innovation and industrial policy in India. Emerging capability gaps, lack of perusal of self-reliance, absence of systematic technological indigenization and continuing dependence on imports are shown to be originating from the problem of alignment of the policies and institutions.

Keeping in view that the challenges need to be tackled by correcting the markets, governments and professions, we suggest that the failures of innovation making for resource constrained settings would have to be tackled by moving away from the

[1] Even today, in spite of some improvements in the availability of well-defined healthcare facilities for the urban population, a large portion of rural areas lack in the basic healthcare including facilities for diagnosis. Most patients visit health centers outside the village for diagnosis and treatment. Nearly half of the public health facilities don't have treatment facilities for major chronic ailments.

assumptions of neo-liberal pathway of global integration and through the re-alignment of the policies and institutions. Solution to the problem identified is shown to lie in the transformation of policy regimes under implementation in the spheres of science, industry, innovation and health.

Section 2 describes the unmet diagnostic needs and demand articulation for diagnostic technologies in resource poor settings of India. *Section 3* describes the structure and orientation of the *in-vitro* diagnostics industry in India. *Section 4* identifies in brief the gaps, needs and challenges of *in-vitro* diagnostics. *Section 5* undertakes the review of literature available on the problems and challenges faced in respect of learning and innovation making by the country. *Section 6* analyzes how the functions of innovation system occurring in the case of *in-vitro* diagnostics and ascribes their influence on the practice and policy of R&D, technology development and innovation making to the perusal of policy regime characterized by liberal and open policies of trade and investment and strong patents. It also gives an understanding of how the pathways of pre- and post-structural reform periods in India have received a lukewarm response from the established foreign and domestic firms. *Section 7, 8, 9* consist of discussion, conclusion and policy implication respectively.

2. Importance of In-vitro Diagnostics in Healthcare

Diagnostics serve a key role in healthcare value chain by directly influencing patient care, health outcomes and downstream resource requirement (The Lewin Group, 2005). Diagnostics have penetrated deeply into the healthcare. Almost 60-70 per cent of medical treatments are based on laboratory diagnostic tests (Armageddon, Falls Church, VA). According to a study published by a health research firm, diagnostics affect sixty per cent or more of downstream decision-making in disease-management, resulting in improved health outcomes and net cost saving for the healthcare industry (Lewin Group, 2005). The accurate diagnostics influence patient care in many ways: assessing disease risk sooner; targeting disease earlier-long before symptoms occur; targeting disease more specifically, with often less invasive treatment; estimating prognosis more accurately and managing chronic disease more effectively.

Over the period of last one decade *in-vitro* diagnostics has emerged to be an area of significant innovation, translating the practice of medicine into process, throughout the world. (Markets and Markets report, 2010). *In-vitro* diagnostics is one of the latest diagnostic technologies that are finding application in varied medical procedures globally with its growing popularity and success rate due to accurate detection of health risks and diseases at earlier stage, improved treatment and disease management (The Lewin Group, 2005). Most of in vitro diagnostic technologies that are developed today are based on either monoclonal antibody detection or nucleic acid amplification (BIO Ventures for Global Health, 2010).

In vitro diagnostic products are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body [FDA]. Technological advancement and the evolution of genetic and molecular biology have laid the foundations for the development of diagnostic test of importance to significant clinical conditions. In addition to it, advances in information technology led to the automation of many tests that were previously conducted manually[2].

The continuous process of innovation making with the use of above mentioned technologies have made in vitro diagnostics to take several forms i.e., from large bench top instruments that can only be used in sophisticated laboratories placed in urban areas to point of care tests (POC) that can be used in the most remote rural regions which lack basic healthcare facilities. Most of laboratory based tests in use are time consuming and expensive. Dependent on not only stringent transport conditions to maintain specimen viability but also as they require a constant supply of reagents and electricity, well-maintained equipment and adequately trained and supervised technologists, most of these tests have been found as not being very reliable for peripheral health centers or resource poor settings.

In this situation rapid point of care *in-vitro* diagnostic tests are required solutions because these test can be readily administered by a minimally trained healthcare worker or even self-administered without requiring a ambient temperature and also theoretically offers the ultimate "test and treat" model which reduces the likelihood of losing a patient to follow up in resource poor settings (BIO Ventures for Global Health; 2010). One of the most significant examples is the introduction of Rapid Diagnostic Test for HIV and Malaria in early 1990s which have major impact on the way diagnostic and treatment performed in resource poor settings as these immune chromatographic based assays provide information on patients' disease status with more sensitivity and taking less turnaround time comparable to laboratory based ELISAs. See *Table-1* for the estimation of potential of lives saved with new or improved diagnostics in resource constraint settings.

[2] Several breakthrough technologies which significantly contributed to the development and transformation of diagnostic technologies are: 1) Invention of monoclonal antibodies (MAb) by Koehler and Millstein in 1975, which made possible to detect minute amount of disease related protein biomarkers when combined with fluorescent labeling and chemistry in blood, cells, or tissue samples of patients' body. 2) Invention of the Polymerase Chain reaction (PCR) in the mid-1980s by Kary Mullis, that allowed the amplification of a few molecules of DNA or RNA by many orders of magnitude into diagnostically measurable quantities. 3) The success of the Human Genome Project in 2001, which paved the way for the determination of the complete genomes of many globally important disease causing micro-organisms, that provide a vast array of potential target sequences that could be used to measure the onset and progression of diseases.

Table-1: Estimated potential of lives saved with new or improved diagnostics in resource poor settings

Disease	*Population*	*Clinical Decision point*	*Sensitivity/ Specificity (%)*	*Potential Impact*	*Required features for new or improved diagnostics*
Acute lower respiratory infection	Children under 5 years	Identification of children aged < 5 years with bacterial ALRI	95/85	Saves about 405000 adjusted lives per year	Diagnostic or biomarker for distinguishing between viral and bacterial pneumonia
HIV/AIDS	Infants under 12 months	Identification of HIV in infants < 12 months	90/90	- Saves 108000 DALYs per year if 5% of the population has access to ARVs. - Saves 2.5 million DALYs if 100% population has access to treatment.	- Diagnostics for monitoring patients on antiretroviral therapy. - Biomarker for infant screening and diagnosis without interference of maternal anti HIV antibody
Malaria	Children under 5 years	Diagnosis in febrile children aged <5	95/95	Saves 1.8 million adjusted lives per year and prevents 396 million unnecessary treatments averted per year.	- Diagnostic panel for distinguish between malaria and other infection and enable appropriate treatment. - A Human host biomarker that confirms active malaria and distinguished from latent infections
TB	Symptomatic	Diagnosis of active infections, with or without concomitant HIV infection	85/97	Save about 400000 lives per year.	- Diagnostic that detects TB in HIV infected patients with greater sensitivity and require less turnaround time. - Biomarker to detect active TB from blood, saliva and urine other than sputum
Syphilis	Prenatal	Diagnosis of syphilis in prenatal	86/72	Saves 201000 DALYs and averts 215000 stillbirths	- Diagnostic for early detection with greater sensitivity and monitoring pregnant women on therapy to avoid over treatment monitoring pregnant - Pathogen specific biomarkers
Diarrheal diseases	Children under 5 years	Detection of G. lamblia, C. parvum and enter aggregative E. coli in children <5	90/90	- Reduce prevalence of diarrheal-related stunting by 12.5%. - Saves 2.8 million DALYs per year.	- Diagnostic with more accuracy and sensitivity. - Pathogen specific biomarkers

Source: Urdea *et al*. (2006) and BIO Ventures for Global Health (2010)

3. Structure of Indian Diagnostic Industry for Resource Poor Settings

Indian in vitro diagnostic market can be broadly divided into diagnostic services, diagnostic product and instrument market and is segmented into immunochemistry, biochemistry, hematology, microbiology, blood gas and electrolyte analysis, molecular diagnostics, urinalysis and coagulation diagnostics. The market has been historically led by revenues from immunochemistry market, with biochemistry and hematology being the second and the third largest segments respectively(KEN research report, 2013).Each of the aforementioned segments is governed by a gamut of different factors, with two important factors being the technology used and the nature of diseases.

According to (Cygnus Business Consulting and Research report, 2009) Indian diagnostic and pathology lab test services market valued at ₹5,590 crore in 2007 and is estimated to reach ₹13,900 crore by 2012. Instruments market is estimated at ₹185 crore while the reagents market is at ₹305 crore. The reagent market is further divided in to "closed systems" at ₹85 crore and the actual served open market at ₹220 crore. Size of the Indian *in-vitro* diagnostics market is estimated to be 531 m USD in 2011 (McEvoyand Farmer, 2011). It is considered relatively to be small in size by international standards by the industry.

While the market for *in-vitro* diagnostics based test services has been dominated by the local unorganized players for the past many years in India, but recently the industry has also witnessed the arrival of foreign players as well as increasing consolidation of business amongst the homegrown players. In the organized segment, the Indian IVD market is primarily led by foreign players. Within the organized industry the leading players in this segment include Transasia Bio-medical which was ranked as the top IVD Company in India by McEvoyand Farmer, US-based experts on IVD markets. The other major players in this group are Roche Diagnostics, J Mitra, Johnson and Johnson, and Beckman Coulter, Trivitron, Accurex,Tulip/Crest, Bayer-Siemens, Agappe, Randox, Span, Wipro Biomed, Merck, and Ranbaxy. Apart from these, there are 30 other smaller players operating in this market segment. Among the service providers in India there are about 40,000-50,000 pathology labs with less than 100 having accreditation. The major players in diagnostics and pathological test labs market are Metropolis, Religare SRL Diagnostics, Dr. Lal's Pathology, Piramal Diagnostics (formerly Wellspring), Thyrocare and Anand Labs. (Biospectrum, 2009)

The growth of these firms can be attributed to the increase in demand among both rural and urban populations for diagnostics due to rising prevalence of chronic diseases. The changing disease patterns, rising incidence of diseases, higher healthcare spending, and untapped markets create abundant opportunities for IVD manufacturers. Other arising factors like the demand for point of care testing, near patient testing, increased automation, hospital laboratory management and customer relationship management are also revolutionizing this segment and contributing towards providing accurate and

precise diagnosis at much faster rates(http://www.marketreportsonline.com).Within non-communicable diseases, diabetes and cardiovascular diseases are the biggest focus area of companies supplying diagnostics. New products introduced in the market for these diseases are not indigenous innovations.

There has been a prevalence of imported products from other countries, both as original equipment manufacturer and in finished form. Emphasis on indigenous research has been notably lacking amongst the local players (KEN research report, 2013). Owing to the deficiency of required skills, technical expertise and the infrastructure to support the elevated costs for conducting research and development for products, the share of domestic players has been considerably lowered. India has to look for imports to cater the demand due to which tests are found to be very costly that become unaffordable for majority of population.

4. Emerging Challenges, Gaps and Needs of Innovation System

Below we review the limited literature available on the capability gaps and challenges faced in respect of indigenous innovation system building and the evolving needs for innovation for resource constrained settings on the basis of the information collected from the desk research on the sector of diagnostics in India.

Import Dependency (Lack of Indigenization)

Seventy-five (75) per cent of medical diagnostics needs are met through imports. Most of the imported kits require the reagents for which the maintenance of ambient temperature is essential. The imported test kits are designed for well-equipped lab of industrialized world. Reagents used in these tests fail to give results in extremes temperatures of the resource constrained settings. Consequently the imported diagnostics are maladapted. The other relevant point emerging from her study concerns the absence of health technology assessment efforts. In addition to this, she notes that lack of capability in India for indigenous innovation in case of in–vitro diagnostics is still a major road block. Imports made in completely knocked down (CKD) or semi-knocked down (SKD) form tend to make the tests costly. Due to which these tests are unaffordable to poor population and often maladapted to low resource poor settings which lacks basic health care facilities (Jarosławski and Saberwal, 2013).

An important factor slowing down the pace of indigenization is limited funding for diagnostic research as compared to drugs and vaccines. In India, at present less than 2 per cent of annual spending on research and development (R&D) for diseases is allocated to diagnostics (WHO). Limited funding for healthcare in India also creates a great need and requirement for simple, high quality and affordable diagnostic products which require capacity development for indigenous innovation. If this situation is persisting, then the main problem is with the inability persisting with regard to the challenges faced in respect of the development of industrial R&D and lack of sufficient indigenous

capability for innovation making. India's test developers still lags well behind international leaders in case of molecular diagnostic this makes India to rely upon maladapted tests to meet its diagnostic requirement.

Regulatory Issues

In-vitro diagnostics to be effective, must be analytically and clinically validated (Analytic validity refers to a laboratory's ability to get the correct answer reliably over time, for example, to detect a genetic variation when it is present and not detect it when it is absent. Clinical validity refers to whether a particular genetic variation is associated with an individual's current or future health status. These validations requires accreditation of clinical laboratory performing diagnostic test to get certificate from regulatory body (NABL, CLIA and CAP) in India it is done by The National Accreditation Board for Testing and Calibration Laboratories (NABL) is an autonomous body under the Department of Science and Technology. (http://www.nabl-india.org)

The globalization of the Indian economy and the liberalization policies initiated by the government in reducing trade barriers and providing greater thrust to exports makes it imperative for accredited laboratories to be at an international level of competence. At present, less than 10 per cent of India's 20,000 clinical laboratories have been found to participate in external quality assurance programs. NABL has begun offering accreditation to clinical laboratories; however accreditation is non-mandatory and not widely sought after due to issues of cost, the burden of implementing a quality control program, and a general lack of awareness. (http://www.nabl-india.org)

In addressing the broader challenge of bringing quality assurance to India's healthcare system, a 2003 WHO regional office status report noted that, at present, there is no national policy for External Quality Assessment Schemes (EQAS). A 2005 Ministry of Health and Family Welfare and WHO India Country Office National Workshop on Accreditation and Standardization of Health Services found that in most states, there is little legislation regulating public and private health care facilities, laboratories, and diagnostic clinics, and hence quality and safety issues are not dealt with legislatively at this level. This has led to the market flooded with various substandard tests (WHO case study, 2006).

Seventy-five per cent of laboratories participating in the largest external quality assurance scheme exist in only five states, accounting for thirty per cent of the population. On this basis, it has been noted that the majority of the population has no access to laboratories participating in external quality assurance programs. Further, few laboratories participating in external quality assurance schemes belong to the public sector and largely private laboratories have sought NABL accreditation. It is likely that people with low incomes lack access to private laboratories, and therefore they are more likely to undergo substandard testing and to be subject to inadequate safety protection (WHO, 2006).

Lack of Training and Education

Effective translation of molecular diagnostics from bench to bed side (i.e. from laboratory to clinical settings) presents significant challenges as molecular assays requires extensive optimization before result can be interpreted correctly in the clinic. Therefore clinical laboratories require trained professionals specialized in this field but in India of the limited public spending, a very small portion is allocated to laboratories, and little funding is set aside for quality assurance. Adequately trained personnel are also in short supply. Specifically in the area of genetic services, a 2003 WHO regional report identified an urgent need for expansion of genetic testing and counselling services along with training of laboratory personnel (WHO, 2006). Over 90 per cent of India's medical colleges do not provide training and education in clinical genetics and genetic counselling, contributing to a lack of professionals specializing in these fields (according to a report appearing in the Indian Journal of Human Genetics).

Intellectual Property Issues

Adoption of Strong IPR as an incentive for knowledge generation and development has worked as a barrier for innovation in technology follower developing countries like India clears from studies like Sampath (2007) mentioned above. Further IPR issues results in delay of transfer of technology, for e.g., case of transfer of technology by PATH to Orchid India. PATH, a non- profit organization developed a rapid diagnostic test kit for a gonorrhea disease using monoclonal antibodies from US based company, and when PATH was planning to transfer this technology to Indian based Orchid group of diagnostic companies, the US based company was acquired by third party, resulting into delay of technology transfer for three years due to IPR issues.

Access and Alternatives to Strong IPRs

Over the past few decades, a number of push and pull incentives have been proposed by international public health organizations, NGOs and International donors like welcome trust, Bill and Melinda gates foundation, foundation for innovative new diagnostics and PATH etc., to incentivize research and development addressing the specific medical needs for resource poor settings of developing world. These efforts have yielded significant technological progress like development of immunochromatographic (dipsticks) technologies, which led the development of point of care lateral flow tests for malaria, HIV, syphilis. These tests are now widely used in resource limited settings because they are inexpensive, easy to use and transport and provide quick result. The WHO study conducted in 2008 has shown that with the use of these tests patients detected with HIV and malaria receiving anti-retroviral and anti-malarial compound has increased by 10 folds fromyear2002 to 2008. (BIO Ventures for Global Health, 2010)

5. Mapping the Functions, Interactions and Institutions of Innovation making for Resource Poor Settings

Work was started in the sector of diagnostics with the establishment of Center for Biosciences in1980sin India. The Centre for Biosciences was later renamed as Department of Biotechnology. During the period of 80s there were only two firms in the field namely, Ortho Diagnostic (a division of J&J, Mumbai) and Span Diagnostics, Surat. Both these firms are still involved in the area of manufacturing of IVDs. However, investigations indicate that India has not been able to keep up with the worldwide pace of development of technological innovation system. India lacks in industrial capabilities; production and new technology development related capabilities of the incumbent firms in diagnostic development are limited in breadth and depth. As far as the current situation stands in the sphere of in vitro diagnostics with regard to the development of value chain, the components essential to the development of indigenous technology development are even today mostly absent in India.

Investigations indicate that the value chain remains underdeveloped in the sphere of *in-vitro* diagnostics. Many of the components essential to the development of indigenous technology development are mostly absent in India. Traditionally the domestic private sector pharmaceutical firms did not consider diagnostics as an area of interest for investment due to low revenue returns (CII-KPMG report, 2010). Although recently few start-up firms have begun taking interest in both manufacturing and R&D for developing diagnostics for tropical disease for.eg specific disease related biomarkers, but their overall share in the market as compared to foreign firms is quite insignificant. At present only a handful of companies have manufacturing facilities in the country.

In the name of indigenization of the imported products, today most of them are importing the kits in completely or semi-knocked down conditions and repackaging the diagnostics product for sale in the country. At present production through the indigenous manufacture is confined to reagents and adjuvant for serological tests. Most of the diagnostics kits like molecular or nanotechnology based products are being imported from US and EU. High import duty and custom clearance procedures, competitions, logistics, lack of knowledge, licensing, slow pace of approvals from statutory authority, lack of national laboratory network for evaluation and approval of new products are cited in the trade literature as the factors slowing down the pace of indigenization. (Asian Diagnostics Market—Emerging opportunities—Diagnostics, 2014)

Further, at present more than half of the imported diagnostic kits have been found to be ineffective as they are not designed for Indian climatic conditions or variant Indian strains of microbes. There is lack of skilled and technical talent which is a big hurdle as the manufacturing process of diagnostics in very complex in nature which requires the expertise from science and technical field to work together. There is still gap between the industry and academia linkage. The Indian industry lacks in R&D competence and

infrastructure for the development and manufacture of *in-vitro* diagnostics (http://ehealth.eletsonline.com/2012/12/indian-diagnostics-a-leap-in-the-dark/).

However, recently the Indian diagnostics segment has definitely witnessed a small increase in activity for resource constrained settings through the build-up of young start-ups in this area. Examples are development of Low Cost Point of Care (POC) Device for Detection of Blood Glucose by BITS-Pilani (Hyderabad campus) that will cost less than INR 2 per blood sample. Another example is Forus Health's '3nethra' a low-cost, portable, intelligent, non-invasive, non-mydriatic eye pre-screening device that can detect 5 major ailments constituting 90 per cent of blindness- Diabetic retinopathy, cataract, glaucoma, cornea problems and refractive errors. Bangalore-based Bigtec Labs is at an advanced stage in the realization of a Micro Electro-Mechanical Systems (MEMS) based nucleic acid amplification platform (supported by the New Millennium India Technology Leadership Initiative from CSIR, Government of India) that can be extended to diagnose several diseases so as to meet low resource constraints of the Indian market (Finpro India, 2013).

Although the R&D activities in respect of the development of *in-vitro* diagnostic tests for resource poor settings are gradually underway now within the Indian system of innovation, but the successful commercialization and deployment of these tests within the national health system and their availability in the market remains a challenge in many ways. Issues include like setting the priorities to develop or innovate a test for disease which has high burden, developing an inexpensive test and making them accessible to large patient population. Most of the domestic industry is still lacking in the capabilities needed for developing tests for diagnosis of communicable diseases especially tuberculosis, malaria, dengue and hepatitis B and C. Well-developed infrastructure, high safety standards, sufficient know-how and time, are required for current tests to perform well. These are rarely available due to which test results may not always be reliable. Prenatal and neonatal testing would be important as infant mortality is still high in India. Nucleic acid based test for HIV in infants would be needed. At present it is not possible to diagnose HIV in infants younger than 18 months (BIO Ventures for Global Health, 2010).

Emerging Industrial Structure for Diagnostics for Resource Poor Settings

Assessing from the standpoint of the impact of these developments on the industrial structure the above mentioned examples are an outcome of an effort which is nascent. Although quite a welcome development, but the contribution of domestic firms to the production of finished products and components under establishment indicates the emergence of a major gap in the industrial structure. Analysis of 23 companies (6 domestic firms, 9 young start-ups and 8 foreign firms) active in *in-vitro* diagnostic development in India has been undertaken. Product profile of the companies illustrates that domestic companies are lacking in the development of finished diagnostic products for resource constrained settings. Foreign firms have large share in number of diagnostic

products in comparison to Indian firms. Foreign firms dominate the market of finished diagnostic products relevant for resource constrained settings. Young start-ups have entered finished product market in past few years. Compared to domestic companies young start-ups have taken far more interest in the development of markets for diagnostics relevant to resource constrained settings.

Assessment shows that the growing presence of young start-ups is an emergent distinguishing feature of the Indian innovation system. Compared to foreign firms more of young start-ups are showing interest in the segment of molecular diagnostics relevant to resource settings. The encouraging news from the market is about the growing involvement of young start-ups in the diseases such as TB, Malaria and HIV; known for their neglect by the industry and professions alike these diseases are on the radar of young start-ups now for investment.

See *Table-2, -3 & -4* for the current status of introduction of finished diagnostic products and components considered to be relevant for resource constraint settings. *Table-5* showing the disease wise number of products introduced in market for resource constraint settings.

Table-2: Number of in-vitro diagnostic products relevant to resource poor settings in the Indian market

Types of Firms	*Number of relevant products* for resource poor settings*	*Total number of products available in market (finished products /components of finished diagnostic products)*
Domestic	6	51
Young Start-ups	17	59
Foreign	48	303
Total	**71**	**413**

Notes: *Relevant products include finished products as well as components of finished diagnostic products available in the market.

Source: Compiled by the authors on the basis of information available on companies websites.

Table-3: Number of finished in-vitro diagnostic products relevant for resource poor settings in the Indian market

Types of Firms	*Total finished in-vitro diagnostic products available in market*	*Finished products relevant for resource poor settings*			*Total number of resource poor settings related finished products*
		Dx (diagnostics)	*CDx (companion diagnostics)*	*MDx (Molecular diagnostics)*	
Domestic	23	1	-	-	1
Young Start-ups	29	5	3	4	12
Foreign	134	14	6	9	29
Total	**186**	**20**	**9**	**13**	**42**

Source: Compiled by the authors on the basis of information available on companies websites

Table-4: Number of components of finished in-vitro diagnostic products relevant for resource poor settings in the Indian market

Types of Firms	*Total components of finished in-vitro diagnostic products available in market*	*Components of finished products relevant for resource poor settings*				*Total number of resource poor settings related components of finished products*
		Reagents	*Instruments*	*Diagnostic markers*	*Monoclonal/Polyclonal antibodies*	
Domestic	28	3	1	1	-	5
Young Start-ups	30	1	1	1	2	5
Foreign	169	6	1	3	9	19
Total	**227**	**10**	**3**	**5**	**11**	**29**

Source: Compiled by the authors on the basis of information available on companies websites.

Table-5: Disease-wise number of finished products and components of finished in-vitro diagnostics products relevant for resource poor settings in the Indian market

Types of Firms	*Total diagnostic products available in market*	*Diseases wise diagnostic products relevant for resource poor settings*									*Total number of resource poor settings related products*
		TB	*HIV*	*Malaria*	*Dengue/chikungunya*	*Diabetes*	*Hepatitis*	*Cancer*	*Bacterial/Viral Infections*	*Genetic diseases*	
Domestic	51	-	1	-	-	1	-	2	2	-	6
Young start-ups	59	2	2	1	-	1	1	5	4	1	17
Foreign	303	2	4	2	1	5	-	15	14	5	48
Total	**413**	**4**	**7**	**3**	**1**	**7**	**1**	**20**	**17**	**4**	**71**

Notes: Relevant products include finished products as well as components of finished diagnostic products available in the Indian market. Source: data collected from websites of companies

Source: Compiled by the authors on the basis of information available on companies websites

Emerging Structure of Innovation System

Biomedical innovations involves five main phases: i) identification of need, ii) research and development, iii) commercialization, iv) delivery, v) diffusion and each phases are interlinked to each other (OECD, 2010). All the five phases are equally challenging and need to tackle the specific problems facing the system to bring up appropriate technologies. In the case of innovation for resource constrained settings, interaction for the advancement of the processes of biomedical innovation is characterized by the flow of ideas between different actors not only while undertaking research but also while

pursuing financial and knowledge based intermediation. Feedback mechanisms are required to be constructed appropriately keeping in mind the context specific challenges faced in respect of the enhancement of innovative capacity and the development of innovations for resource constrained settings. In an emerging market economy, where the culture of innovation in industry is yet to take root, the role played by government and associated policymaking bodies is quite critical.

Extramural Research Projects for Diagnostic Development Focusing Resource Poor Settings

It is apparent that innovation making in *in-vitro* diagnostics for resource constrained settings will require the government to closely monitor user-producer interaction to organize the system of innovation in a systematic way. Analysis of EMR funding for diagnostic research projects indicates that during the period of 2000-11out of total 165 projects undertaken in the area of diagnostic development only 34 projects were focused on resource poor settings. See *Table-6* for the disease focus of diagnostics development projects through EMR projects. It indicates an uneven pattern of attention to the development of innovations in respect of resource constrained settings for different diseases that in the absence of steering and coordination from the side of research agencies. DBT, ICMR and DST are far more involved in funding compared to CSIR. Relatively speaking, cancers, viral / bacterial infections, TB, Malaria and HIV are better investigated in the case of resource constrained settings. There is the need of far more attention to the development of diagnostics for resource constrained settings in the case of diseases like Kala-azar, JE, Cholera and Typhoid and diabetes.

Table-6 : Disease-wise EMR funding for diagnostic research focusing resource poor settings (2000-11)

Funding organization	*Total diagnostic Projects funded*	*Diseases*													*Total number of diagnostic projects focusing resource poor settings*
		Viral/bacternal /infection	*kala-azar*	*Cancer*	*Chikungunia*	*HIV*	*hepatitis*	*TB*	*Malaria*	*filaria*	*leptosporosis*	*Asthama*	*Cholera/Typhoid*	*Diabetes*	
DST	35	2	0	2	0	1	0	0	1	0	0	1	0	0	7
DBT	51	4	0	3	1	1	0	2	1	0	0	0	0	1	13
CSIR	13	1	0	1	0	0	0	1	0	0	0	0	0	0	3
ICMR	54	1	1	2	0	3	0	2	1	0	0	0	0	1	11
AICTE	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
UGC	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DRDO	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
DAE	3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	**165**	**8**	**1**	**8**	**1**	**5**	**0**	**5**	**3**	**0**	**0**	**1**	**0**	**2**	**34**

Source: Data collected from NSTMIS Database of DST

Analysis of the composition in terms of allocations made to different types of research performers suggests that national laboratories, universities and institutes of national

importance receive a major part of the resources allocated for resource constrained settings under EMR funding. Compared to research institutions (RIs), universities (UNIs), institutes of national importance (INI) industry and medical colleges and Hospitals are far less active in applying for research projects, and their focus on diagnostics for resource constrained settings is even more disappointing. See *Table-7* for the emerging pattern of relatively small or negligible contribution of medical colleges and hospital research departments to the domain of R&D projects for innovation making in respect of resource constrained settings.

Table-7: Institutional LOCI of diagnostic research funding focusing resource poor settings (2000-2011)

Institutes	*Total diagnostic Projects funded*	*2000-03*	*2004-06*	*2007-09*	*2010-11*	*Total number of diagnostic projects focusing resource constraint settings*
RI	67	0	4	7	9	20
UNI	42	0	1	0	3	4
INIs	26	0	1	2	3	6
Medical Colleges/Hospitals	15	0	0	1	0	1
Industries	4	0	0	2	0	2
Others	11	0	0	1	0	1
Total	165	0	6	13	15	34

Source: Data collected from NSTMIS Database of DST

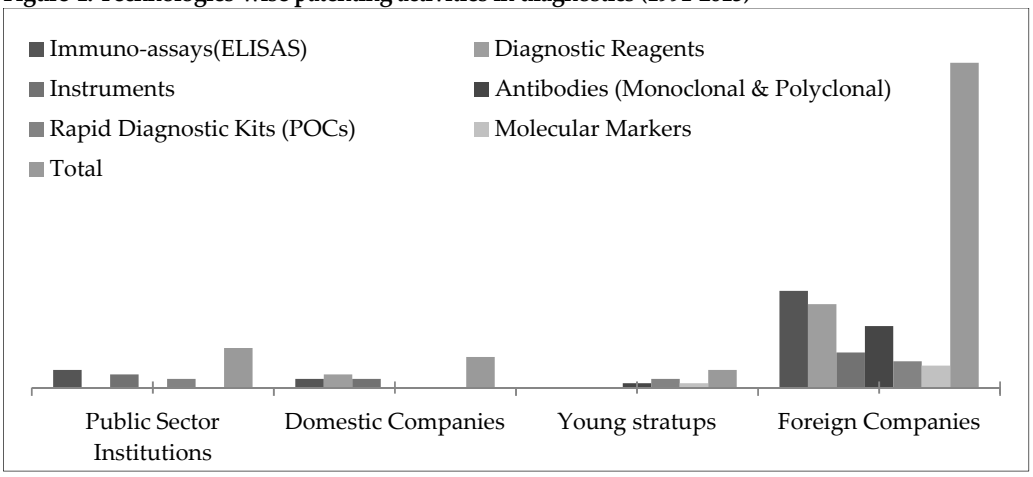
Patenting activities focusing Diagnostics for Resource Poor Settings:

Analysis of patenting in the area of diagnostic research shows that Indian research institutions and firm lack in-house technological capabilities for the development of new patentable diagnostics technologies found to be useful for resource poor settings. Analysis illustrates that there are very few patents for the diagnostics focusing high burdened diseases of resource poor settings (See *Figure-1*). Patents owned by Indian research institutes and firms are insignificant. Foreign firms hold maximum diagnostics patent in India. Most of the diagnostic needs are met through imports and the prices of diagnostics products are high which make the diagnosis unaffordable to vulnerable population of resource poor settings. As a result only some of these diagnostics have been introduced in National Disease Control Programs.

The dismal patent scenario indicates a slowing down of the pace of indigenization in diagnostics for resource constrained settings. Further, it also shows that Indian firms continue to lack in innovation capabilities in the areas of advanced diagnostic technologies like molecular markers and rapid diagnostic point of care test which are seen to have potential for the required solutions of diagnostics needs for resource constraints settings. Indian firms are more involved in developing diagnostics reagents and instruments. Most of the patents in the case of diagnostics for resource constrained

settings are owned by foreign firms. The possibility of Indian firms and scientists being blocked for the realization of success from the on-going efforts of research and development and innovation making is already a reality.

Figure-1: Technologies-wise patenting activities in diagnostics (1991-2013)



Source: Data collected from Indian Patent Office Database

Table-8: Disease-wise patenting activities in diagnostics (1991-2013)

Institutions	*Total diagnostic Patents*	*TB*	*HIV*	*Malaria*	*Dengue*	*Diabetes*	*Cancer*	*Bacterial/Viral Infections*	*Genetic diseases*	*Total diagnostic patents focusing resource constraint settings*
Public Sector Institutions	9	1	-	-	1	-	-	-	-	2
Domestic Companies	7	-	1	-	-	-	-	2	-	3
Young Start-ups	6	-	2	-	-	-	-	3	-	5
Foreign Companies	74	1	2	1	-	1	3	7	1	16
Total	92	2	5	1	1	1	3	12	1	26

Source: Data collected from Indian Patent Office Database

Although the young start-ups are seen to be playing in overall terms a far better role in the development of advanced technologies focused on resource constraint settings, but their patenting activity is very small. They have taken patents in the area of viral / bacterial infections. Foreign firms are present even in TB. Since these technologies are at the stage of experimental development and they are still to come in a commercialized product form in the market, it is difficult to predict in what manner foreign firms will use

the patents owned by them. Public sector patenting in the area of diagnostics for resource constrained settings presents again a disappointing picture. Analysis indicates that the advantage of patents rests with the foreign firms.

Diagnostics under Clinical Development

Diagnostics undergoing clinical development indicates that there are only three diagnostics related clinical trials which can be considered as relevant for resource poor settings. As diagnostic was not an attractive area for the firms because of high operational cost and low revenue return so most of the trials are undertaken by public sector institutes. Although the pharmaceutical companies are entering into new tradition i.e. the development companion diagnostic (CDx) development to overcome the current escalating costs of drug discovery, development and drug launch because companion diagnostics offer pharmacodiagnostic and theranostic descriptors which will helpful in developing drugs more safer and more efficacious and pharmaceutical companies must produce more genotype and/or phenotype- focused therapeutic agents, but Indian firms are lacking capabilities in this area.

Table-9: Disease-wise diagnostics under clinical development

Diseases	*Institute*	*Source of Monetary or Material Support*	*Primary Sponsor*
Malaria	Seth GS Medical College and KEM Hospital, Parel Mumbai	Department of Biosciences and Bioengineering, Indian Institute of Technology (IIT), Mumbai	Department of Biosciences and Bioengineering, Indian Institute of Technology (IIT), Mumbai
TB	Dept of neurology, CSMMU, Lucknow	NIL	DBT
Eye infection	Saravanan VR Coimbatore Tamil Nadu	Xcyton Diagnostics Pvt Ltd, Bangalore	Aravind Eye Hospital ; Coimbatore,

Source: Data collected from Clinical Trial Registry of India

Promotion of Research and Development and the Response to Development of Diagnostics for Resource Poor Settings

This section provides an analysis of the response to publicly funded R&D of the Indian government where public private partnership (PPPs) model is promoted. NMITLI of Council of Scientific and Industrial Research (CSIR), Drugs and Pharmaceuticals Research Programme (DPRP) and Technology Development Board (TDB) of Department of Science and Technology (DST), Biotechnology Industry Partnership Programme (BIPP) of Department of Biotechnology, Small Business Innovation Research Initiative (SBIRI) of Department of Biotechnology (DBT) constitutes the main examples of public private partnership based schemes.

Analysis shows that very few projects for diagnostic research are funded till date by BIPP and SBIRI of DBT. Furthermore, young start-ups are only using these promotional

schemes. They are focusing far more on the development of diagnostic technologies for point-of-care (POC) test, rapid diagnostic tests (RDTs) and molecular markers suitable for the use in resource constraint settings. Coming to the extent of focus on different types of disease areas, though emphasis is mainly on TB and Malaria, but these areas demand far more projects funding. Poor response from the side of domestic companies under these promotional schemes is a matter of concern. (See *Table-10, -11 & -12*)

Table-10: Diagnostics under development through BIPP support as on 2011

Companies	*Title of the Project Supported*	*Therapeutic area*
Bigtec Private Limited	Point-of-Care detection of infectious disease using handheld micro PCR	Infectious Diseases
Revelations Biotech Pvt. Ltd.	Development of low cost rapid quantitative PCR technology for molecular diagnosis	-
Chromous Biotech Pvt. Ltd.	Multiplex Fast-PCR based diagnosis and prognosis of tuberculosis	Tuberculosis

Source: Compiled by the authors on the basis of information available on website of Department of Biotechnology

Table-11: Diagnostics under development through SBIRI support as on 2011

Companies	*Title of the Project Supported*	*Therapeutic area/Technologies*
Arbro pharmaceuticals Ltd., New Delhi **in collaboration with** All India Institute of Medical Sciences, New Delhi and LRS Institute of TB and Respiratory diseases, New Delhi	Development and clinical validation of methods for diagnosis of tuberculosis and bacterial drug resistance by smear microscopy, culture and polymerase chain reaction using processed clinical samples and kit thereof	Tuberculosis
Bhat Bio-Tech India (P) Limited, Bangalore **in collaboration with** National Institute of Malaria Research, New Delhi	HRP-II/ p-LDH based diagnostic kits for the differential detection of malarial parasites	Malaria
Bisen Biotech and Biopharma Pvt. Ltd, Gwalior **in collaboration with** Jiwaji University, Gwalior	TB screen test for diagnosis of pulmonary and extra – pulmonary tuberculosis: evaluation of prototype kit at selected hospitals/ peripheral health centre/ research laboratories	Tuberculosis
Genomix Molecular Diagnostics (P) Limited, Hyderabad **in collaboration with** BITS, Pilani, NIMR, New Delhi, NIMR, Jabalpur, Osmania University, Hyderabad	Developing sensitive, inexpensive and hand-held diagnostic point of care (POC) instrumentation to detect Malaria and other pathogens	Malaria

Source: Compiled by the authors on the basis of information available on companies website of Department of Biotechnology

Table-12: Diagnostics under development through NIMITLI support as on 2011

Companies	*Title of the Project Supported*	*Therapeutic area/Technologies*
Big tech	Novel molecular diagnostics for eye diseases and low vision enhancement devices	Eye diseases
Big tech	Point of care rapid diagnostic kit	TB

Source: Compiled by the authors on the basis of information available on websites of CSIR.

International Donor and funding organizations supporting diagnostic research in India:

International donor and funding organizations are also active in supporting research oriented for poor related diseases affecting majority of population in developing countries. These initiatives have been taken to reduce 10/90 gap prevailing in research and development for poverty related diseases and led significant development over the past decade benefiting poor populations. *Table-13* shows the diagnostic project funded by these international funding and donor organization in India.

Table-13: Diagnostic project funded by these international funding and donor organization in India

International Donors	*Supporting to*	*Diagnostic Development*
Bill and Melinda Gates Foundation	ICGEB	TB
	Big-Tec Labs	TB, to make Cephied X-pert diagnostic test cost effective
Foundation for Innovative New Diagnostics (FIND)	DBT	Diagnostic technologies for detection of TB and mulit-drug-resistant tuberculosis.
PATH (International not for profit organization)	DBT	Lateral flow point of care test for TB, Malaria, HIV.

Source: Compiled by the authors on the basis of information available on websites

Significance of Young Start-Ups in Diagnostic Research in India:

Young start-ups have been seen to be playing a significant role in research and development in past few years in the area of *in-vitro* diagnostic development. Most of these start-ups have been developed by science professionals. Converted into technocrats they are playing a far more prominent role in the development of diagnostics for diseases related to resource poor settings of India. They are making diagnostic cost-effective. They are developing rapid point of care tests which do not require a sophisticated laboratory environment etc. They are working for the priority diseases. See *Table-14 & -15* for the details of activities in terms of the year of establishment of young start-ups active in India, product profile and disease area focused. *Table-16* details out significant diagnostic technologies useful for resource constraint settings in which young start-ups has been granted patents.

Table-14 : Young start-ups active involved in diagnostic development for resource poor settings in India

Young Start-ups	*Established year*	*Established by*
Mediclone Biotech Pvt. Ltd	1995	-
ABL Biotechnologies	1992	-
Xcyton Diagnostics Ltd	1993	Dr B.V. Ravi Kumar, a Physician-Scientist turned technocrat.
Bhat Biotech	1994	Dr Shama Bhat, an internationally acclaimed scientist. What began then as a determined attempt to bring affordable yet top quality diagnostic kits and biotechnological products into emerging markets
ReaMetrix	2003	Dr Manian a distinguished contributor to the Silicon Valley entrepreneurial community for the last three decades.
Achira labs	2003	Dr Suri Venkatachalam, Suri holds a Bachelor's degree in Chemical Engineering from Andhra University and a Ph.D. in condensed matter physics from Indian Institute of Science
BigTech Labs	2000	Chandrasekhar received his Bachelors and Masters in Chemical Engineering from BITS Pilani. He has worked in Senior Management positions with the Vittal Mallya Scientific Research Foundation.
Bisen Biotech	1997	Prof. Bisen earned Ph.D. in 1972 and D.Sc. in 1981. Professor of Microbiology in 1985 at Bhopal University. Prof. Bisen was Visiting Professor at Institute of Environmental and Biological Sciences, University of Lancaster, Lancaster, England and Visiting Research Professor at the Department of Biological Sciences, The University of Illinois at Chicago.
Revelations Biotech Pvt. Ltd	2004	Dr Chandra earned Ph.D. from International Centre for Genetic Engineering and Biotechnology in Molecular biology and structural biology, New Delhi.
Chromous Biotech Pvt. Ltd	2006	Dr Biswajit Roy, dis Ph.D. in molecular biology from the Bose institute, Kolkata, and has four years of post-doctoral research experience from Cleveland Clinic Foundation, US. He has 11 years of experience in firms engaged in molecular biology research

Source: Compiled by the authors on the basis of information available on companies websites.

Table-15: Product/services and diseases/ health condition focused by young start-ups involved in diagnostic development for resource poor settings in India

Young Start-ups	*Products / services*	*Diseases/ Health Condition Focused*
Mediclone Biotech Pvt. Ltd.	Monoclonal blood grouping antibodies, Immunoserological kits, Biochemistry kits, Rapid cards, Urinalysis strips.	Infectious Diseases & Snake toxins
ABL Biotechnologies	Reagents and immunoassays	Anti-bacterials, anti-virals

Young Start-ups	*Products / services*	*Diseases/ Health Condition Focused*
Xcyton Diagnostics Ltd	Molecular diagnostics and services (Syndrome Evaluation System (SES)for detection of infectious diseases	CNS infections, Blood stream infections (sepsis, pneumonia, dengue, antibiotic resistance, pyrexia, chikungunya). Immunosuppressed infections, ophthalmic infections, HPV infections
Bhat Biotech	Rapid Diagnostic Kits, Elisaand Contract research services	Pregnancy, HIV, Hepatitis, Malaria, Dengue, Chikungunya, Swine Flu (H1N1), Syphilis, TB, Cardiac Markers
ReaMetrix	Reagents, immunoassays	HIV/AIDS, Autoimmune diseases, stem cell analysis, Leukemia/Lymphoma, immunophenotyping.
Achira labs	Reagents, Instruments and Rapid diagnostic kits	Thyroid disorders, fertility, diabetes and infectious disease
BigTech Labs	Microfluidic devices, Elisa, PCR	TB and Infectious diseases
Bisen Biotech	Diagnostic reagents	Infectious Diseases
Revelations Biotech Pvt. Ltd	Molecular diagnostics	Infectious and non-infectious diseases, metabolic disorders and genetichoroscope
Chromous Biotech Pvt. Ltd	Molecular diagnostics, Immunology reagents, kits and contract research services	TB & other infectious diseases

Source: Compiled by the authors on the basis of information available on companies websites

Table-16: Important diagnostic technologies suitable for low resource poor settings developed by young start-ups in India

Companies	*Diagnostic technologies*	*Patenting Year*
Xcyton Diags	CheX: ELISA-based *in vitro* diagnostic (IVD) kit for HIV	1994
Bigtech	Micro-PCR device and reagents for low through put, rapid, point-of-care *in vitro* diagnosis of infectious diseases, suitable for harsh conditions	2006
ReaMetrix	Dry-Tri: Cold-chain independent and easy to use CD4/CD8 assay reagent for HIV management, suitable for harsh conditions	-
Achira labs	Immunoassay-based microfluidic chips and point-of-care device for low-throughput rapid *in vitro* diagnosis (biochemistry), suitable for low-resource settings	2009
	Immunoassay-based fabric chips for device-free, point-of-care *in vitro* diagnosis of infectious diseases	2010

Source: Compiled by the authors on the basis of information available on companies websites

Indigenous Product Development by Young-Start-ups under different categories relevant for Resource Poor Settings

Coming to the indigenous product development by these young start-ups, there are 17 indigenous diagnostic products developed by start-ups. Out of seventeen (17) nine products (9) have been developed with the help of with the support of EMR, govt. promotional funding schemes (NIMITLI, BIPP, SBIRI) and other International funding organizations. Further, it is observed that while out of nine (9) two (2) received EMR

support and three (3) products benefitted from government promotional schemes. Patents were granted only in the case of four products out of 17 indigenous products. TB and other viral and infectious diseases account for nine (9) out of fifteen (15) indigenous products. Only in the case of two (2) indigenous products there has been the absence of the role of government.

Big-tech labs, Bhat biotech, Revelations, Bisen and Chromous used the government schemes to develop indigenous products. Big-tech lab is playing a major role. It is significant that the promoter of Big-tech did his B. Tech and M. Tech from BITS, Pilani. It is a home grown firm, and it has benefitted from the promotional schemes introduced by the government in quite a significant way. See *Table-17.1 & -17.2*. As far as therapeutic area is concerned TB, HIV and infectious diseases has been given more priority See *Table-18*. Out of the total 15 indigenous products, 9 are available in market and 6 are under the stage of development. See *Table-19*.

Table-17.1: Indigenous product developments using extramural research funding by young start-ups

Companies	*EMR*
Mediclone Biotech Pvt	Development & manufacture of immunodiagnostic kit & post exposure prophylaxis of rabies using monoclonal antibody cocktail
ABL Biotechnologies	Development of Point of care diagnostic for cancer

Source: Compiled by the authors on the basis of information available on companies websites.

Table-17.2: Indigenous product developments by young start-ups using patents, government promotional schemes for PPPs and funding from international donor organizations

Companies	*Patent*	*Govt. Promotional schemes for PPPs*	*International donor organizations*
Big-tech labs	Micro-PCR device and reagents for low through put, rapid, point-of-care in vitro diagnosis of infectious diseases, suitable for harsh conditions.	- Novel molecular diagnostics for eye diseases and low vision enhancement devices - Point of care rapid diagnostic kit for TB - Point-of-Care detection of infectious disease using handheld micro PCR	For the development of Cepheid X-pert TB diagnostic test cost-effective.
ReaMetrix India	Dry-Tri: Cold-chain independent and easy to useCD4/CD8 assay reagent for HIV management, suitable for harsh conditions	-	-
Achira labs	- Immunoassay-based micro fluidic chips and point-of-care device for low-throughput rapid in vitro diagnosis (biochemistry), suitable for low-resource settings. - Immunoassay-based fabric chips for device-free, point-of-care in vitro diagnosis of infectious diseases.	-	

Companies	*Patent*	*Govt. Promotional schemes for PPPs*	*International donor organizations*
Xycton	CheX: ELISA-based in vitro diagnostic (IVD) kit for HIV	-	-
Bhat Biotech	-	HRP-II/ p-LDH based diagnostic kits for the differential detection of malarial parasites	-
Bisen Biotech	-	TB screen test for diagnosis of pulmonary and extra – pulmonary tuberculosis: evaluation of prototype kit at selected hospitals/ peripheral health centre/ research laboratories	-
Revelations Biotech Pvt. Ltd	-	Development of low cost rapid quantitative PCR technology for molecular diagnosis	-
Chromous Biotech Pvt. Ltd	-	Multiplex Fast-PCR based diagnosis and prognosis of tuberculosis.	-

Source: Compiled by the authors on the basis of information available on companies websites

Table-18: Disease wise indigenous diagnostic product development by Young Start-ups under different categories relevant for resource poor settings

Categories	*Malaria*	*TB*	*HIV*	*Rabies*	*Cancer*	*Eye diseases*	*Other Bacterial/Viral infections*	*Total*
Extramural Research				1	1			2
Patents			2				3	5
Govt. Promotional Schemes for PPPs	1	3				1	2	7
Any Other		1						1
Total	1	4	2	1	1	1	5	15

Source: Compiled by the authors on the basis of information available on companies websites

Table-19: Relation of products (finished/components of finished products) available in market with the indigenous products under different categories

Companies	*Total No. of Products in Indian market relevant for resource poor settings*	*Innovation making and Indigenous Products in market from young start-ups*				
		EMR	*Patents*	*Govt. Promotional Schemes*	*Other*	*Number of Indigenous Products*
Mediclone Biotech Pvt	1	1				1
ABL Biotechnologies	1	1				1
Big-tech labs	5		1	1		2
ReaMetrix India	1		1			1
Achira labs	2		2			2
Xycton	3			1		1

Companies	*Total No. of Products in Indian market relevant for resource poor settings*	*Innovation making and Indigenous Products in market from young start-ups*				
		EMR	*Patents*	*Govt. Promotional Schemes*	*Other*	*Number of Indigenous Products*
Bhat Biotech	1			1		1
Bisen Biotech	1					
Revelations Biotech Pvt. Ltd	1					
Chromous Biotech Pvt. Ltd	1					
Total	17	2	4	3	-	9

Source: Compiled by the authors on the basis of information available on companies websites

6. Government Policy and Initiatives for Diagnostic Development for Resource Poor Settings: Analysis of In–vitro Diagnostics Innovation System Functions

Table-20.1 shows the contribution of public sector institutes to the building of function of knowledge creation and development. In the recent times, this function has been considerably strengthened by the activities of institutions of DBT and Department of Health. Investment in basic and translational research projects is contributing to the emergence of young start-ups by focusing on the diagnostic need of resource constraint setting and by helping the young start-ups to develop point of care rapid diagnostic tests and tests based on advanced diagnostic technologies. Similarly, thanks to this support young start-ups are innovating in the area of reagents which can persist in harsh environment conditions or do not require ambient temperature for storage.

Table-20.2 describes the strengthening of function knowledge diffusion and transfer. This function is being strengthened and formed through the contribution of DBT, with the formation of activities such as: formation and growth of knowledge incubators like TSTHI and initiated a multi-institutional partnership program on Bio design called the National Bio design Alliance between Translational Health Science & Technology Institute (THSTI), Regional Centre for Biotechnology (RCB), International Centre for Genetic Engineering and Biotechnology (ICGEB), All India Institute of Medical Sciences (AIIMS), Indian Institute of Technology (IIT) Delhi, IIT Chennai and Christian Medical College (CMC) Vellore focusing on the development of diagnostic technologies useful for resource constraint settings.

For human resource development in the field of diagnostic DBT in collaboration with universities like Alagappa University and Bharthidasan University, Karaikudi, Tamil Nadu initiated Post M.Sc. Advanced Diploma course in Molecular Diagnostics and started Bio design fellowship for the students through national bio design alliance focusing on the development of point-of-care diagnostic technologies. A Taskforce has

been developed under Indo-US workshop conducted by DBT for training of manpower for the development of low-cost biomedical imaging technologies; low-cost, point-of-care diagnostic technologies for disease areas of greatest need. CDFD and AIIMS has transferred there diagnostic technologies to ArkaNanomeds Pvt Ltd and Arbro pharmaceutical respectively, contributing for knowledge diffusion.

Table-20.1: Knowledge creation & development through publicly funded S&T institutions

Departments	*Institutes*	*Basic Research*	*Experimental Development, Translational Research and Product development*
Department of Biotechnology	Translational Health Science and Technology Institute (THSTI)	- Novel sample processing for the simple and rapid diagnosis of TB, MDR-TB and XDR-TB. - Identification of Novel Protein Biomarkers for Early Diagnosis of Pregnant Women at Risk for Preterm Birth.	Development of multiplexed, "lab-on-chip" technologies to bring multiple biomarker tests on to a single, universal platform, instead of multiple diagnostic tests on multiple different instruments to be used in remote clinics and low-resource settings as well as secondary and primary hospitals.
Department of Health research (ICMR)	Centre for Research in Medical Entomology (CRME), Madurai	Detection of JE virus antigen in desiccated vector mosquitoes.	-
	National Institute of Malaria Research (NIMR)	-	Indigenous production of monoclonal antibodies PfHRPII and pLDH achieved for improved diagnostics for malaria.
	National Institute of Virology (NIV), Pune	A real time RT-PCR useful for early diagnosis was developed for detection of dengue viral RNA.	-
	Rajendra Memorial Research Institute of Medical Sciences (RMRIMS), Patna	-	Species-specific PCR developed for detecting Leishmaniadonovani, tested in the endemic area and widely utilized in referral labs as a confirmatory test.
	National Tuberculosis Research Institute (TRC)	-	New rapid molecular methods for detection of rifampicin, isoniazid and ethambutol resistance in TB developed.

Table-20.2: Knowledge diffusion/transfer

Departments	*Training Programs*	*Technology Transfer*
Department of Biotechnology	The Department of Biotechnology (DBT), Govt. of India has initiated a multi-institutional partnership program on Bio design called the National Bio design Alliance between Translational Health Science & Technology Institute (THSTI), Regional Centre for Biotechnology (RCB), International Centre for Genetic Engineering and Biotechnology (ICGEB), All India Institute of Medical	CDFD has licensed its Tuberculosis diagnostics" technology to M/s ArkaNanomeds Pvt Ltd

Departments	*Training Programs*	*Technology Transfer*
	Sciences (AIIMS), Indian Institute of Technology (IIT) Delhi, IIT Chennai and Christian Medical College (CMC) Vellore for the development of rapid point-of-care *in-vitro* diagnostic technologies.	
	DBT in collaboration with Alagappa University and Bharthidasan University, Karaikudi, Tamil Nadufor Post M.Sc Advanced Diploma course in Molecular Diagnostics.	DBT supported AIIMS to developed rapid diagnostic test for leishmaniasis and a test for extra pulmonary TB and this has been successfully licensed to Arbro Pharmaceuticals.
	DBT conducted a Indo-US workshop on "Low-Cost and Therapeutic Medical Technologies" at the Centre for DNA Fingerprinting and Diagnostics (CDFD) on behalf of Department and National Institute of Biomedical Imaging and Bioengineering (NIBIB), U.S.A. for the development of low-cost biomedical imaging technologies; low-cost, point-of-care diagnostic technologies for disease areas of greatest need	
	Biodesign fellowship initiated in diagnostic and biomarker development through national biodesign alliance focusing on the development of point-of-care.	

Table-20.3 shows the strengthening of function of knowledge creation and development through the development of innovative funding mechanisms and public private partnerships. DBT and CSIR have been contributing by initiating the promotional funding schemes like SBIRI and BIPP/BIRAP of DBT and NMITLI of CSIR. These schemes are allocating funds for promoting PPPs and private sector of young start-ups in the area of therapeutic, vaccine and diagnostic development for the diseases of national importance. At present in diagnostic development for resource constraint settings SBIRI is supporting 5 projects, BIPP/BIRAP supporting 3 projects and 2 projects are supported by NMITLI.

Table-20.4 shows the strengthening of the function of mobilizing the users for the adoption of diagnostics services for resource constrained settings. Market formation activities are being strengthened by the Ministry of health and family welfare and the Department of health research. The challenge of expansion of the use of diagnostic services in resource poor settings can be met through increasing mobile medical units in remote areas. Initiatives have been undertaken for the introduction of diagnostic technologies under several disease control programs under which diagnostic for Malaria, Japanese Encephalitis and CD4 test for HIV are being successfully introduced in National Disease Control Programs. In smaller measure initiatives have also been undertaken for empowering the workers for diagnosing and treating diseases in remote areas.

Analysis made of the performance of all the departments in terms of the important innovation system functions indicates that the Department of Biotechnology is playing a significant role in the shaping of the development of *in-vitro* diagnostic innovation

system. Diseases covered by the Department of Biotechnology for the development of diagnostics relevant for resource constraint settings involve TB, Cancer and other Viral and Bacterial diseases. Analysis also shows that Big-Tech is one of the few young start–ups to have benefitted from both NMITLI and BIPP. It appears that while JE is one of the priority diseases in India, the support for this disease has come from the department of health research which is a user department.

Table-20.3: Knowledge creation and development through public private partnerships

Departments	*Funding Schemes*	*Public Private Partnerships*
DBT	Biotechnology Industry Partnership Program (BIPP) in 2010 under the management of Biotechnology Industry Research. BIRAC has been set up with a vision to stimulate, foster and enhance the strategic research and innovation capabilities of the Indian biotech industry particularly SME's	- Supporting Big-Tech lab for the development of the Point-of-Care detection of infectious disease using handheld micro PCR. - Supporting Revelations Biotech for the development of low cost rapid quantitative PCR technology for molecular diagnosis. - Supporting Chromous Biotech Multiplex Fast-PCR based diagnosis and prognosis of tuberculosis.
	Small Business Innovation Research Initiative (SBIRI) in 2005. SBIRI is managed by the Biotechnology Industry Research Assistance Council (BIRAC). SBIRI is set up to promote Public Private Partnership.	- Arbro pharmaceuticals Ltd., New Delhi in collaboration with All India Institute of Medical Sciences and LRS Institute of TB and Respiratory diseases, developing diagnostic for TB. - Bhat Bio-Tech India (P) Limited, Bangalore in collaboration with National Institute of Malaria Research, developing diagnostic for malaria. - Bisen Biotech and Biopharma Pvt. Ltd, Gwalior in collaboration with Jiwaji University, developing diagnostic for TB. - Genomix Molecular Diagnostics (P) Limited, Hyderabad in collaboration with BITS, Pilani, NIMR, New Delhi, NIMR, Jabalpur, Osmania University, developing diagnostic for malaria.
CSIR	CSIR launched the programme of New Millennium Indian Technology Leadership Initiative (NMITLI) in 2001. NMITLI is set up to promote public-private-partnership.	- Supporting Big-Tech labs for the development of novel molecular diagnostics for eye diseases and low vision enhancement devices. - Supporting Big-Tech labs for the development of Point of care rapid diagnostic kit for TB.

Table-20.4: Mobilizing users for the adoption of diagnostics services for resource poor settings and market formation

Departments	*Action Taken*	*Illustrative Examples*
Ministry of health and family welfare	Ministry of health and Family Welfare is undertaking initiatives to provide diagnostic services through various national level programmes to control Communicable and Non-communicable diseases	- Mobile Medical Units increased from 363 in 2010 to 442 in 2011 in order to provide diagnostic and outpatient care closer to hamlets and villages in remote areas under national rural health mission program. - Initiatives has been taken for empowering grass-root workers in diagnosing and treating malaria cases in remote and accessible areas by scaling-up the availability of bivalent Rapid Diagnostic Kits (RDK) and Artemisinin-based Combination Therapy (ACT) under NBVDCP.
Department of Health Research	DHR has introduced diagnostics under several National Disease Control programs	- A kit for Japanese Encephalitis developed and supplied for national programme. - Bivalent rapid diagnostic malaria kits tested, approved and successfully introduced into the National programme. - CD4 count test for HIV are introduced by NACO to provide this test free of cost in govt. hospitals.

Source: Compiled on the basis of information available on Departmental Websites

7. Discussion

From the above analysis, while it is quite clear that the role of government R&D support and promotion is critical, but the public sector agencies are functioning without any plan in the area of development of *in-vitro* diagnostics. As the performance of these functions is important for providing the necessary conditions for developing required institutions and regulations the government can take steps for the creation of a clear vision and plans as well as for the supply and allocation of resources for the adoption of molecular diagnostics resource poor settings in a far greater way. Analysis of the innovation system functions under implementation indicates that contribution for the functions like "institutionalization and legitimization" and "guidance & direction of the search" can be improved if there was a better coordination among the publicly funded R&D agencies. Steering and coordination of innovation making and diagnostic research for resource constrained settings are still lacking.

The innovation system development functions will have to be mainly formed by the government; the role and policies of the government are critical to obtaining success in the area of innovation making for resource constrained settings. Although in the 12th FYP of CSIR and DBT a beginning has been made with the implementation of a few select niche products, and the efforts are to bring the publicly funded research and innovation into the public-private partnerships for their commercial development, but

apparently the systems of innovation under institutionalization are not yet fully fit to deliver the required relevant innovations for resource-constrained settings.

Failures are occurring in respect of the steering and coordination of the activities of public sector research agencies and of the activities of Ministry of Health and Family Welfare. The government should set up a common mechanism for steering and coordination to coordinate and stimulate the users of *in-vitro* diagnostics for resource constrained settings to take part in the process of development of indigenous products. Even while the challenges of innovation making are being attended in terms of the early stage work by the public sector research system failures at the end of product development are continuing because the market formation is still largely in the hands of foreign firms.

Affordability of diagnostic test is another issue of concern; *in-vitro* diagnostic market is largely import dependent. Import duty waiver is applied only to basic techniques like ELISA and CLIA test that are increasingly replaced by more advanced techniques like the polymerase chain reaction (PCR) based diagnostic s for better sensitivity and accuracy. Import of PCR based diagnostics attracts 37 per cent of tax, making these diagnostics expensive thus escalating the cost of diagnostic and burden of patients (Bio spectrum India). A case of recently noted unaffordable PCR based diagnostic test is Xpert® MTB/RIF (developed by U.S.-based Cepheid Inc.), an automated, cartridge-based nucleic acid amplification test (NAAT) that can detect TB, as well as drug-resistance, within 90 minutes and is found suitable for usage in resource constraint settings. This Xpert MTB/RIF are yet to be scaled up in India because its cost is a big barrier for the public sector, although a field demonstration project on Expert has been launched by the Revised National TB Control Programme (RNTCP) in India. The RNTCP is currently underfunded and will need substantially higher resources to scale up new technologies (Madhukar Pai 2011).

8. Conclusion

Analysis shows that the regime of open trade and investment and strong IPR is not favouring by itself the large domestic firms to participate in the creation of biomedical innovations in the case of diagnostic development. The regime of open trade, investment and strong IPRs continues to favour the practice of complete freedom for the companies to undertake innovation making for resource constrained settings in a manner that they are not affordable and the market formation is very taking place very slowly for the innovations being brought out by the young start-ups. Although the young start-ups are the backbone of innovation making for resource poor settings in India, but we need to facilitate them through a new set of push and pull mechanisms.

There is evidence that the present regime is impeding the development of technological capabilities whether for performing basic research or translating basic research into product development. Strategic use of patenting by foreign firms under strong IPR has

made significant technologies in diagnostic field like proteomics and genomics based are monopolized which is blocking further innovations in same field for technology follower country like India which may be due to high transaction cost, royalty stacking or licensing fee. The challenge of formation of markets and elimination of patent restrictions on the use of patent needs to be tackled upfront; influences of the post-external liberalization regime characterized by liberal and open policies of trade and investment and strong patents are required to be monitored on a regular basis to take suitable policy actions to produce favourable results in respect of competence building and innovation making for the implementation of public health priorities.

Analysis also indicates that while young start-ups can be seen to work prominently for innovation in diagnostic research especially considering diagnostic needs of resource poor settings but still they are facing a lot of challenges like shortage of funding, lack of standard regulation which needs to be considered. Evidence indicates that various push and pull initiatives are gaining ground quite slowly. Appropriate models of public-private partnerships for affordable health that would allow the country to delink the price of medical technology from the costs of R&D are the need of the hour.

9. Policy Implications

India is still lacking in the use of appropriate policy instruments in order to build the national system of innovation for resource constrained settings. Development of appropriate technologies in diagnostic sector requires the government to take the following initiatives:

- A generic model for health technology Assessment for diagnostic should be established to determine whether a new diagnostic technology address a country's public health needs and to make technologies cost effective and affordable to the majority of populations.
- A strong and transparent regulatory framework is needed with harmonized regional and national regulatory standard to check the quality of test.
- Public private partnership should be encouraged to foster R&D through government schemes and funds especially to incentivize young start-ups which seem to plays a significant role in innovation making.
- The issue to development of appropriate licensing mechanism and public funding of clinical trials in the case of diagnostics for resource constrained settings needs to be addressed in order to speed up the formation of public and private markets.
- The government needs to analyse patent information and take steps to eliminate restrictions being put by the system of intellectual property rights to speed up the development of a robust innovation system for the benefit of innovation making for resource constrained settings in India.

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About the PHFI

The Public Health Foundation of India (PHFI) is a public private initiative that has collaboratively evolved through consultations with multiple constituencies including Indian and international academia, state and central governments, multi & bi-lateral agencies and civil society groups. PHFI is a response to redress the limited institutional capacity in India for strengthening training, research and policy development in the area of Public Health.

Structured as an independent foundation, PHFI adopts a broad, integrative approach to public health, tailoring its endeavours to Indian conditions and bearing relevance to countries facing similar challenges and concerns. The PHFI focuses on broad dimensions of public health that encompass promotive, preventive and therapeutic services, many of which are frequently lost sight of in policy planning as well as in popular understanding.

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