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Development of 'TrueNat' Innovation System in India for Detection of Tuberculosis and COVID-19: A System Based Perspective

Nidhi Singh and Kirti Tyagi*

Abstract: The ongoing COVID-19 crisis has alarmed the government, scientific community and healthcare segment to develop domestic technological capabilities to deal with the severe consequences of the contagious disease in India. In this study, an attempt is made to present the characteristics of an ecosystem for the successful development of indigenous diagnostic technology, called 'TrueNat', which have dealt the context-specific challenges associated with Tuberculosis (TB) diagnostics and has been validated by the Indian Council of Medical Research for addressing the specific challenges related to COVID-19 testing. Using the functional characteristics of the Innovation System approach, we examined different facets of the system-building activities of various actors involved in the formation of "TrueNat Innovation System" for the diagnosis of Tuberculosis and COVID-19. The development of innovation system for TrueNat reveals that once the system building activities are oriented towards non-market based social calculation, a self-reliant responsible innovation system is formed for dealing with the specific health care needs of the country. The study argues that the experience of "TrueNat technological innovation system" has set a successful pathway for building future indigenous technological development for the medical diagnostic sector in India.

Keywords: TrueNat, Indigenous Technological Innovation, System Building Activities, Tuberculosis, COVID-19.

Introduction

At present the Indian technological capability ecosystem for advanced medical diagnostic innovation system is at a very nascent stage with several issues and challenges at the science base, translational base and industrial base level. Furthermore, the existing policy structure for system building for medical diagnostic activities is guided largely

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by the commercial and profit-making motive in the market (Singh and Abrol 2017). However, the recent development of an indigenous medical diagnostic technology, known as *'TrueNat',* reveals a unique and successful pathway for realising self-reliance in the Indian medical diagnostic technology based on social calculations.

TrueNat is a Polymerase Chain Reaction (PCR), a battery-operated portable diagnostic platform developed by Goa-based Indian domestic firm named 'Molbio Diagnostics.[1] Since inception, TrueNat has proven its potential in addressing the context-specific diagnostics challenges of Tuberculosis (TB) control and management in India (WHO *Rapid Communication Report* 2020). After proving its significance for TB diagnostics, "TrueNat" (Truenat Beta CoV test) has claimed its significance for COVID-19 testing[2]. Recently the Indian Council of Medical Research (ICMR)[3] validated TrueNat for screening as well as a confirmatory test for COVID-19 disease (ICMR *Press Release* 21 May 2020)[4]. This is a significant innovative effort by an indigenous company in the context where there are several country-specific diagnostic challenges associated with TB and COVID-19 detection in India.

Since the last decade, the Research and Development (R&D) effort for effective TB diagnostic test has evolved and grown in absolute size. Even though these are significant achievements, the innovating actors have failed to perform at an optimal level as desired by the specific diagnostic needs of the country. For example, according to the World Health Organization (WHO) estimates, the TB treatment does not reach 41 per cent of India's estimated patients. The WHO Global TB (2019) has reported that an estimated 10.0 million people fell ill with TB in 2018, out of these cases, 27 per cent were reported from India, making it a country with the highest number of TB cases. The challenges of the Indian healthcare system for TB management and control are very context-specific. *Firstly,* the system is dealing with the challenges of highly-priced imported test and its limitations in using under resource-limited settings (Steingart *et al* 2014). *Secondly,* the increasing incidence of multidrug resistance (Nikam *et al* 2014).

In the same way, the current episode of COVID-19 viral disease has alarmed the scientific community and policymakers to find solutions to deal with the emergency which has already killed thousands of people and infected millions globally (WHO *Corona Virus Dashboard* 2020). At the time of writing this paper, there are 883185 active COVID-19 cases with 107416 deaths in India (MOHFW 2020) making the total number of cases to 6.98 million. The case recovery rate increased to 42 per cent in May, 2020 from an initial 7.1 per cent in April when the first lockdown was announced (Ray, 2020). Currently, the case recovery rate from disease stands at 85.81% (MOHFW, 2020).At Present scenario there is no approved drug or vaccine available against COVID-19 virus. The current challenge is to have a sufficient amount of diagnostic kits that can screen and confirm those infected to avoid the community transmission of the disease. At present, India is depended on the imported tests that are highly priced and are found to be of low quality (Thacker 2020; *Financial Express* 2020).

The diagnostics challenges associated with both the diseases discussed above has, in turn, created an opportunity for the Indian scientific community and domestic firms to develop capabilities for effective low cost indigenous diagnostic tests. The present study attempts to present the case of 'TrueNat' as one of the successful development experiences of an indigenous diagnostic technology which is potentially useful for detecting both TB and COVID-19. Furthermore, the study delineates the successful collaborative efforts between the State, the scientific community and the domestic firm by focussing the non-market based social calculation were able to develop an ecosystem for the development of an indigenous technology suitable for context-specific needs and requirements. For an effective practical application, there is a need to understand how the nature of system building activities performed by the actors and institutions involved in the formation of TrueNat innovation system that has dealt with multiple challenges in a context-specific way. As such, the study uses a holistic approach to understand the challenges of the system

from the development of TrueNat diagnostic innovation system which can be usefully adapted for other indigenous medical technological development. We recommend that the system-building activities involved in the formation of technological capabilities for "TrueNat" need to be set up as one of the successful conduits that have favoured indigenous innovation.

The rest of the paper is organised as follows. Section 2 outlines the analytical framework of the study. Section 3 discusses the status and challenges of TB diagnostics in India and explains the characteristics of system building activities for the development of an ecosystem for TrueNat innovation system for TB diagnosis. Section 4 discusses the status and challenges of COVID-19 diagnostics and provides the case of the development of "TrueNat" for addressing these India-specific diagnostic challenges. Section 5 provides concluding remarks and discusses the channels through which new and improved indigenous technologies would address these challenges.

Analytical Framework

In this study, the development process of TrueNat is identified as an 'innovation system'[5] and, therefore, the analytical framework consists of appraising the performance of key actors, institutions and their system building activities over time. We follow the innovation system perspective as an analytical approach and uses the *Technological Innovation System (TIS)* [6] framework to identify the innovation actors and institutions and their functions involved in the development of TrueNat innovation system. The study follows secondary research based on published research articles and direct personal interviews of the innovation actors involved in the development of 'TrueNat' diagnostic technology.

We know that the traditional innovation system analysis focuses mainly on the structural component and characteristics of an innovation system. In contrast, the focus of TIS is on the dynamics of the *key processes or functions*[7] that directly influence the development, diffusion and use of *new and emerging technology* on the performance of the

innovation system. The dynamic perspective of TIS suggests *seven key processes (functions)* involving different actors activities towards developing an innovation system for emerging technologies (Bergek *et. al.* 2008; Hekkert *et al* 2007). These are the development and creation of knowledge, the diffusion of knowledge through networks and externalities, entrepreneurial activities, guidance and direction of search, market formation, resource mobilisation and institutionalisation and legitimisation of technology. The major characteristics of these functions are explained in detail in Table 1.

The performance of system building activities of innovation actors under each of the innovation system function will reveal the direction of performance i.e., whether they are oriented towards market-based calculations or towards non-market based social calculations to meet the context-specific needs. The system-building activities directed towards the non-market based social calculation will lead to the emergence of the responsible innovation system, which is analysed in Section 4 and sub-section 5.1 in this study.

Table 1:Technological Innovation System Functions and Characteristics

Innovation System Functions	Characteristics required for System Building
Knowledge Creation and development (learning)	The major requirements of an emerging innovation system are R&D, knowledge creation and different modes of learning. R&D, search and experimentation, learning-by-doing/using and imitation are regarded as the main determinant. They may combine old and new technologies in innovative ways and reuse old knowledge by imitation.
Knowledge diffusion through networks and positive externalities	The central issue of this function is the formation of networks required for knowledge, policy, market and competitor interaction. This induces 'learning-by-interaction and knowledge spillovers. Exchanging information is the essential characteristic of networks, such as changing norms and values. The diffusion may lead to a change in R&D agendas.

Table 1 continued...

Table 1 continued...

Entrepreneurial activities	Entrepreneur activities are the core process for the formation and growth of emerging innovation system. Entrepreneurs turn the potential of new technology into concrete action and take full advantage of opportunities.
Guidance and direction of the search	This function involves the activities of several actors that lead to the formation of priorities in technology which affect the directions of actors and consumers. Activities can positively affect the visibility and clarity of specific needs. Expectations are also included.
Market formation	For emerging technology, the market may not exist or underdeveloped, leading to the severe problem of entry. As firms fail to compete, it is important to create support space and institutional changes such as protected markets by the formation of temporary niche markets, the formation of standards, and tax regimes of minimal consumption quotas.
Resource mobilisation	Both finance capital and human resources are necessary for the formation of other functions in emerging technology system. The main part of the function is to mobilise human resources through education and training and provide financial support for technological activities.
Institutionalisation and Legitimation	The emerging technology requires coping with existing institutional pattern and the creation of new institutional infrastructure. Formation of advocacy coalitions and interest groups for the technology will lead to mobilise the necessary resources; to form the new demands; to be considered appropriate and desirable by relevant actors. The advocacy coalitions can function as a catalyst to place a new technology and grow in terms of size and influence to brisk up the spirit of creative destruction.

Source: Adapted from (Bergek *et al.* 2008; Hekkert *et al* 2007).

Status and Challenges of TB Diagnostics in India

Healthcare system for TB control and management in India is dealing with the increasing incidence related to the treatment and control programme of multidrug-resistant (MDR) TB.[8] As per the WHO Global TB report (2019), there were about half a million new cases of rifampicin-resistant TB (of which 78 per cent had multidrug-resistant TB) in 2018. As per the Indian National TB Tuberculosis Elimination Programme (NTEP)[9], the routine diagnosis to detect TB cases is sputum smear microscopy, which suffers from poor sensitivity and inability to diagnose multi-drug resistant forms of TB. By the time patients identifies sputum smear-positive and initiates therapy, they may have already infected at least five to fifteen others in their community (WHO *TB Facts* 2020). Compared to the public sector healthcare settings, the vast, unregulated private healthcare sector, catering over half of overall TB patients, often diagnose TB with inappropriate diagnostic protocols making the sputum smears largely underused (Deo *et al* 2019). The early diagnosis and treatment of patients with MDR TB is the major area where NTEP needs to expand their work efforts. Although there are some efforts in terms of diagnosis on Rifampicin resistant, there is lack of evidence for commercial diagnostic methods for other forms of MDR-TB resistance, such as resistance to Isoniazid (Sulis *et al.* 2020).

In recent period, the WHO has endorsed effective diagnostics for TB such as rapid molecular diagnostics like *Xpert MTB/RIF (GeneXpert)*[10] *and line probe assays*[11]. These tests are highly accurate with the sensitivity of 88 per cent with a specificity of 98 per cent when compared to Gold Standard culture and smear tests and can detect MDR-TB. However, their accessibility to patients in a resource-limited setting is limited because of the lack of infrastructure and high expenses involved in polymerase chain reaction (PCR) testing (see Steingart *et al* 2014).

The challenges of TB diagnostic discussed so far suggest an urgent need for new or improved tests for TB control. Many researchers and policymakers found innovating new diagnostic tests for TB are one of the greatest challenges. According to Swaminathan (2014), former Director-

General of ICMR, TB control in India requires locally generated tools, solutions and strategies in the areas of diagnostics and treatment. There is a need to invest more in research and development and bring together the public and private sectors for effective translation of academic leads into useable products.

In such a scenario, the ideal treatment is possible only through developing a robust and accurate diagnostic technology which is suitable, accessible and easily useable in local resource constraint settings. In the following section, a case study of indigenously developed diagnostic technology 'TrueNat' is analysed within the framework of system building activities for the formation of the innovation system functions suitable for addressing the persisting challenges in the system.

Development of "TrueNat" for TB Diagnostics: Analysis of System Building Activities for the formation of Innovation System functions

The system-building activities for the development of *TrueNat* started to shape up with the formation of two innovation system functions, namely, *"Guidance and Direction of Search"* and *"Entrepreneurial Activity"* as evident from the effort of Chandrasekhar B Nair, an Indian based engineer converted entrepreneur, who focuses on innovations in systems, science, and engineering for the benefit of the society. He is the director and CEO of 'Bigtec Labs', a product innovation company focused on making gold standard diagnostics that are affordable and accessible at the Point of Care (POC) in resource-limited healthcare settings. He preceded the idea of social innovation under his 'Frugal Innovation Mission' for the development of Molecular Diagnostics (MDs)[12] for infectious diseases like TB with the formation of 'Molbio Diagnostics', a joint venture company between Bigtec Labs and Tulip.

The development of TrueNat is a part of Chandrasekhar's idea of the development of MDs for infectious disease prevalent in resource-limited settings, has been supported with the formation of *"Resource Mobilisation function"* as evident from the financial assistance of Grand Challenges Canada. This financial association was supportive during all

the stages of product developments which culminated in the development of fully automate sample processing and engineer it to run on a battery-operated portable device. Since the major barrier associated with the implementation of technology at the POC is the sample processing, the development carried under the financial assistance eliminated human error, minimised staff training needs and ensured that MDs could be carried out in the most minimally equipped health centre. Apart from foreign source funding, the development has been significantly supported by the financial assistance (*Resource Mobilisation function*) of Indian Government through schemes such as New Millennium Indian Technology Leadership Initiative (NMITLI), Biotech Industry Partnership Programme (BIPP), Small Business Innovation Research Initiative (SBIRI) and Technology Development and Demonstration Programme (TDDP). The BIPP and SBIRI helped in the providing grants for the validation of test, NIMITLI supported with the grant of soft loan.

The three innovation system function aspects mentioned earlier led to the creation of the base for the formation *"Knowledge Creation and Development function"*. The major challenge associated with the development of TrueNat was to build a knowledge system that fills the following diagnostic gaps, namely, (i) uncertainty in the causative agent leads to misuse of anti-microbial and consequently a build-up of drug resistance, (ii) need of faster and better diagnostics which would lead to an automatic reduction in patient suffering and the spread of disease, and (iii) constraints of high cost and paucity of trained technicians and labs.

The multi-disciplinary teams of engineers, chemists and biologists of Molbio Diagnostics along with sustained partnerships with prestigious institutions like All India Institute of Medical Sciences (AIIMS), New Delhi; Christian Medical College (CMC), Vellore; Indian Institute of Science (IISc), Bangalore; Indian Institute of Technology (IIT); National Institute of Virology (NIV), Pune; etc., have succeeded in the development for new *Knowledge Creation and Development Function* for catering a specific need. This has given the TrueNat a special characteristic specially designed for resource-poor setting, as

the technology is a MEMS-based (Micro Electro Mechanical System based) real-time micro PCR[13] device[14]. In contrast, the traditional PCR equipments which needs extensive laboratory infrastructure and skilled operators, is largely expensive and inaccessible to the marginalised sections of society who are affected predominantly by infectious diseases. TrueNat is a portable and battery-operated cost-effective device designed to be used by minimally skilled technicians. It also offers rapid detection time of 45-60 minutes.

To evaluate the clinical performance of TrueNat, a validation study has been conducted with the Hinduja Hospital Mumbai and the result is published in *PLOS One,* a highly reputed international journal, in 2013 (Nikam *et al.* 2014). This study finds that TrueNat has sensitivity greater than 99 per cent in smear-positive (S+) and culture-positive (C+) cases of TB. It can detect all the TB strains verified by an evaluation study using a panel from WHO/TDR that contains over 220 geographic diverse strain of TB (see Nikam *et al.* 2014) According to this study, the specificity of Truenat vs Smear is 43.98 per cent (36.29 -51.88 per cent). The specificity of GeneXpert is also comparable, 40.96 per cent (33.40-48.85 per cent).In case of comparison with culture, the specificity of Truenat is 52.85 per cent (43.64 -61.91 per cent). The specificity of GeneXpert is also comparable, 50.41 per cent (41.25-59.54 per cent). However, the specificity of Truenat in both cases is on the lower side, but still higher than that of GeneXpert. TrueNat has the following advantage over imported highly-priced Gene-Xpert test:

- Diagnosing TB using Truenat can be comparatively cheaper than GeneXpert. The technology is chip-based and not cartridge-based like GeneXpert that can be more environment-friendly.
- Compared with one ml of sample needed when GeneXpert is used, only about 0.5 ml is required for a test with TrueNat MTB.
- The main advantage of TrueNat over GeneXpert is that only when samples are tested positive for TB, the tests for rifampicin resistance[15] will be carried out. This reduces the use of reagents which help in making the test cheaper.

- TrueNat would be useful for paediatric and extra-pulmonary TB, where the TB bacilli count in a sample is generally low.
- While GeneXpert is a closed cartridge system, in TrueNat MTB the DNA is first extracted and the testing is carried out using a portion of that DNA. If results are not analysed based on one test then one can always retest the sample using the remaining DNA. This can be used for any other molecular confirmatory test or for testing rifampicin resistance if the test result is positive for TB. GeneXpert requires additional sample if the test has to be repeated. Drop-outs (patients not returning to provide the second sample) can be avoided since TrueNat does not need two samples.
- TrueNat would be used at the primary health centre level thus stepping towards decentralising the TB testing in India, which cannot be done using GeneXpert as it needs an uninterrupted power supply and air conditioning.

According to Lee *et al* (2019), TrueNat is cost-effective when deployed at POC. The model-based analysis done by authors showed that when TrueNat is used as a POC device replacing smear microscopy, it increases the number of correctly detected cases and linkage to care by 590 per 10,000 individuals with presumptive TB. Deploying TrueNat POC instead of GeneXpert increased 5-year expenditures by $270 million, due mostly to treatment costs. WHO generally analyses new technologies for TB diagnosis under the "Grading of Recommendations Assessment, Development, and Evaluation" (GRADE) process (Cobelens *et al.* 2012). If analysed in terms of the WHO's target product profile (TPP) of the "smear replacement test" TrueNat device agrees with many minimal TPP standards. This includes battery-powered operation, <2 hours to provide test characteristics, i.e. sensitivity for TB detection comparable to Xpert (WHO *Rapid Communication Report* 2020). However, minimal standards for the price (i.e., <$6 per reagent and <$1,400 per instrument) can be met by providing proper funding to the manufacturer as well as by reducing the cost of production of reagents and of the device without compromising the quality of the product . As mentioned earlier, TrueNat

will help de-centralise the TB diagnosis, which is currently relevant to policy formulation in a high TB burden country like India.

The knowledge creation and development function for meeting specific needs to develop further through the effective functioning *"Knowledge diffusion"* and *"Institutionalisation and Legitimation"*. At present, the system-building activities for the formation of both of these innovation functions are progressing gradually. The major issue is the validations of the test once it is ready. Currently, TrueNat has completed performance validation and operational feasibility testing by ICMR (Tripathi *et al.* 2019). The study is provided with technical assistance and resources by the Foundation for Innovative New Diagnostics (FIND) helping for test commercialisation. ICMR plans to take the test to public health centres, which currently uses smear samples to test for TB, with a sensitivity level of only 50 per cent and about half of what the newer method has achieved. TrueNat uses sputum samples and is being tested in the field in 100 designated microscopy centres in 50 districts in 10 Indian States. The one-month study took place in August 2017 with 10878 samples. The diagnostic tool has already been installed across 80 per cent of designated microscopy centres for testing. The validation study carried by ICMR at four sites tested nearly 5,000 samples from 2,500 patients. The samples were also tested for resistance to the drug rifampicin. Besides validating the performance, the focus is on operational feasibility in field settings. The motive of this operational study is to see the functioning of the machine in hot and humid conditions and whether the machine can work in the absence of power and lab technicians along with the feasibility to operate the machine using minimum training (Tripathi *et al.* 2019).

All the above innovation systems are functioning collectively to contribute to the creation of "*Market Formation"* system building activities. Since the demand is significant, the estimated market size for TB testing ranges from 20 million tests per year to over 40 million tests per year (UNITAID 2016). However, considering the reported number of TB suspect patients presenting to NTEP, approximately 25 million tests are done per year. Therefore, the system-building functional actor

is adopting market strategies to promote TrueNat even to the smallest labs and Primary Health Centres (PHCs) all over the country which could otherwise not even dream of doing a PCR test (Nikam *et al.* 2014). Recently, the Andhra Pradesh government adopted TrueNat for TB diagnosis at various health levels like Community Health Centre (CHCs), Primary Health Centres (PHCs) and Designated Microscopy Centers (DMCs).

Status and Challenges of COVID-19 Testing in India

India's innovation system building activities for disease management is facing the scarcity of validated tests for COVID-19. This is mainly because of the lack of capabilities in medical supplies and the inability to supply adequate testing. The current diagnosis needs are primarily satisfied through imported products which are largely inadequate in terms of supply and reliability. Nucleic acid amplification test (NAAT) based Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) is the prescribed testing and diagnostic tool for dealing with COVID-19. However, it has several technological challenges.

The successful working of the NAAT test requires an adequate supply of reagents and consumables on time (Padma 2020). To run an RT-PCR test, firstly RNA has to be extracted from the nasal/throat swab sample. This requires the timely availability of viral transport medium and RNA extraction kits. Another challenge is the false-negative results reported by RT-PCR tests (Cohen and Kessel 2020). Even if these challenges were resolved, the biggest roadblock is the seamless supply of reagents and other consumables for essential running of the test, which includes supply chain demand, storage as well as logistics.

The recent incidence of failure of imported rapid tests has alarmed the Task Force Committee of ICMR on its reliability. India received 5,50,000 kits from two different Chinese manufacturers, which were distributed across various states. However, within weeks, the ICMR had to put a hold on the use of these kits because of the complaints from the several Indian States regarding the reliability and quality of the results.

Promptly ICMR issued an advisory to conduct field testing and found the sensitivity of the kits to vary across units (Kaul 2020).

Development of "TrueNat" for COVID Testing: Analysis of System Building Activities for the Formation of Innovation System Functions

The innovation system building activities formulated for TB diagnostics has enabled TrueNat to emerge as a promising technology to be used for COVID-19 testing on the existing Truelab machine with a portable cassette not bigger than a mobile phone in size. System building activities performed for the development of two innovation system functions, i.e., *Entrepreneurial Activities* and *Knowledge Creation and Development* are the major ones: the vision of Chaderashekhrar Nair, a senior technical officer of Molbio to develop diagnostics suitable for resource-poor settings, has shaped the knowledge creation for the formation of a strong scientific base for TrueNat development. TrueNat for COVID-19 testing is designed in such a way that it has the following advantage over other PCR based tests:

- TrueNat machine comprises of the inbuilt RNA extraction system, RT-PCR chips, collection swabs and viral lysis medium (VLM) that overcome the challenges of having separate RNA extraction kits and viral transport medium kits.
- The single assay has a turnaround time of 35-50 minutes for 1-4 samples with a total of 12-48 samples being tested per day, depending upon the type of machine.
- The biosafety and biosecurity requirements are minimal given the sample being collected in VLM, which inactivates the virus.
- The test can be used at the level of district hospital/primary health centres.
- Its priced at Rs.1,200 including kits and reagents, which is half the rate of other PCR based test. The reagents are currently manufactured in India. Truenat is a closed system, therefore, reagents provided by the same manufacturer have to be used.

The system-building activities for the development of TrueNat received continuous financial support (formation of *Resource Mobilisation* innovation system function) since 2019 by the India Health Fund (IHF), through the Centre for Health Research and Innovation (CHRI). IHF is an organisation seeded by Tata Trusts to identify and support breakthrough innovations for the elimination of infectious diseases in India (*Biospectrum* 2020).

ICMR at present is the leading agency for COVID-19 testing and, moving with a vision to promote *Make in India* products, recognised the potential of TrueNat Beta CoV test. ICMR has contributed to fostering and strengthening the system building activities for innovation system functions *Knowledge Diffusion* and *Guidance and Direction of search.* ICMR has successfully validated the TrueNat system with E-gene screening assay on April 10 and approved it as a screening test. (*ANI* 2020).

The Molbio has got the license from Drug Controller General of India (DCGI) for testing for its COVID-19 kits (Rajagopal 2020). DCGI license has served as the first step for the company to launch these newly developed kits in the domestic market which shaped the system building activities for the innovation system function (*Market Formation)*. Currently, TrueNat™ beta CoV test on Truelab™ has been stated in the Mokokchung district hospital, Nagaland where 664 samples were tested (*The Hans India* 2020). Along with Nagaland, Andhra Pradesh has also been using Truenat system for COVID-19 testing (240 machines). TrueNat kits for nCoV are also being used in Nellore district (300 kits). Since April 2020 more than 1.3 lakh screening tests using TrueNat have been conducted by states.

However, the major limitation associated with TrueNat test was the lack of TrueNat confirmatory assay. All the TrueNat positive samples had to be confirmed by RT-PCR-based tests like GeneXpert either located in the same or different laboratory (*Firstpost* 2020). To overcome this limitation, the Molbio's strong scientific base has created a system building that has further shaped the innovation system function by

Creating New Scientific Knowledge through the development of an RdRp gene-based confirmatory assay of TrueNat. This confirmatory test has been successfully validated by ICMR and has been found to have high sensitivity and specificity. Both the validations have been stringently conducted by the Department of Health Research (DHR)/ICMR Virus Research and Diagnostic Laboratory (VRDL) at Bangalore Medical College and Research Institute, Bengaluru.

Thereafter on 20th May 2020, the ICMR has issued revised guidelines for TrueNat testing for COVID-19, stating the "TrueNat system is now a comprehensive assay for screening and confirmation of COVID-19 cases»(ICMR*Press Release* **19 and 22** May 2020). According to the guidelines, TrueNat will be used in two steps:-step one which is a E gene screening assay (Truenat Beta CoV) for all COVID-19 suspect samples which is to be followed by step two for the RdRp based confirmatory test (Truenat SARS CoV-2) in all E gene positives. The guideline also states that all samples that test positive by this assay must be considered as true positive. Hence, no further RT-PCR based confirmation is required for samples that are positive after step 2 of the assay. All positive and negative results must be reported to the ICMR portal in a real-time manner (*Deccanherald* 2020). To summarise, great harmony has been observed in COVID-19 detection, when it comes to introducing TrueNat in the existing testing framework on the healthcare system.

To summarise, both case studies have demonstrated that when innovating actors perform based on non-market oriented societal goals and challenges, there is ample scope to develop technologies that suit the requirements of a wider section of the society. It is remarkable to witness that even under severe resource constraint, a young start-up firm became successful in developing a sophisticated yet cost-effective medical diagnostic technology to effectively diagnosis of TB and COVID-19 on a wider scale. This also points out that such society's need consideration can result in collaboration of science base, industry base and translational base innovating actors to achieve a common goal and product development**.**

Concluding Remarks

The case study of the development of "TrueNat" system for the diagnostics of TB and COVID-19 has shown that the problem-solving approach directed towards system-building activities have made it possible for the development of indigenous technology in a context-specific way. The system-building activities that are guided by the non-market based social calculations have favoured the technology for this development of social innovation. The interaction between different actors is the significant characteristic of the ecosystem developed for the formation of system building activities under each innovation system functions. The conducts and performances of innovation actors for building up of innovation system functions were found to be specifically oriented towards the local needs. Since the study has noted the critical role of government in shaping various innovative functions, it is evident that the continuous support from the government financing schemes and ICMR is what has provided strength to the system building activities.

The special feature of the ecosystem for innovation developed for "TrueNat" technology is the orientation of entrepreneurial activity for social innovation and initiative undertaken for frugal innovation by the innovator firm. The continuous interactions with various prestigious institutes of science base have helped in overcoming the challenges and strengthened the knowledge creation for indigenous innovation. Since the technology is biomedical, the system-building activities for translational research, i.e. its clinical evaluation and validation, have been significantly supported by the ICMR to confirm its clinical effectiveness. The case study confirms that when the system building activities are guided by the issue of solving non-market based social calculations, it assists in building an ecosystem for the development of an indigenous technology required for addressing country-specific needs and challenges.

Similarly, the study presented the challenges of diagnosis associated with the current emergency of COVID-19 testing and has also shown the potential of TrueNat technology. The study opines that the system-building activities for ecosystem development of TrueNat innovation

system for COVID-19 are at a nascent phase. The system-building activities are being formulated through innovation system functions like knowledge creation and diffusion, entrepreneurship development which is already developed for TB diagnostics. ICMR has been a catalyst in validating and supporting system-building activities for the translational use of the technology. At present, the ecosystem of innovation of system building activities to support three main functions; guidance and direction of search, institutionalisation and legitimisation and market formation are still evolving. These functions need to be facilitated further to obtain a fully-fledged innovation system to deal with the COVID-19 pandemic crisis that has led to unprecedented health and economic crisis in India.

To conclude, we argue that ecosystem development for TrueNat System is a success story of an indigenous technological development towards dealing with India's specific diagnostic challenges. It is evident that when the system building activities with a problem-solving approach are directed towards socially responsible manner through steering and co-ordination between all the stakeholders, the goal of self-reliance would be easily realised and sustained.

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Disclaimer: The study is based on the authors' personal views on the subject. However, the study doesn't purport the views or official policies of DHR-ICMR. The paper also does not reflect the views of RIS.

Endnotes

[1] Molbio diagnostics a Joint Venture between two domestic firms: Bigtec Labs, Hyderabad and Tulip Diagnostic, Goa. The former focuses on R&D infrastructure to develop the indigenous innovative diagnostic tools specifically for local needs and the latter has an extensive manufacturing and marketing expertise for domestic and international markets.

[2] However, the causative agents of both COVID-19 and TB are different in terms of one being a virus and another being bacteria, but both cause the infection of the respiratory system and are contagious in nature. Being microbes, both *SARS-Cov-2* (virus causing COVID-19) and *Mycobacterium Tuberculosis* (bacteria causing TB) can be accurately diagnosed using a molecular diagnostic test, such as, TrueNat that involves the diagnostic principle based on Reverse Transcriptase Polymerase Chain Reaction (RT-PCR).

[3] The Indian Council of Medical Research (ICMR), New Delhi is the apex body in India for the formulation, coordination and promotion of biomedical research in the country through intramural and extramural research. It is also one of the oldest medical research bodies in the world. ICMR's research agenda is in line with national health priorities. These efforts are made by the institute so that the total burden of disease can be reduced and also to promote the health and well-being of the population. Presently ICMR is the leading agency for performance, evaluation, validation and coordination of COVID-19 testing and research in India.

[4] As mentioned in the press release of 21st May, 2020 ICMR has validated 11 indigenous RT-PCR based assays for diagnosis of COVID-19. All of these assays are based on PCR based amplification of target genes i.e., RdRp, N, E etc. for confirmation of presence of virus in a patient's sample. These indigenous assays although similar in principle with the TrueNat assay but differ in the respect that TrueNat is a complete diagnostic platform (including both RT-PCR assay kits and the RT-PCR machine) that does not require RNA extraction and analysis to be done separately. Detailed comparison of these indigenous assays is however, beyond the scope of this article.

[5] The innovation system is a "system constituted by elements and relationships which interact in the production, diffusion and the use of new and economically useful knowledge" (Lundvall 1992).

[6] TIS is defined as a "network of agents interacting in a specific economic/industrial area under a particular institutional infrastructure or set of infrastructures and involved in the generation, diffusion, and utilization of emerging technology" (Carlsson and Stankiewicz 1991; Bergek *et al* 2008). The focus is on the working of technological functions of a particular economic system.

[7] The main function in System of innovation is to pursue innovation process that involves creation, diffusion and use of knowledge. The determinants factor that influences the functions of innovation systems is known as the system of innovation activities (Edquist 2005).

[8] MDR-TB occurs when TB strains become resistant to isoniazid and rifampicin, which is the most critical first-line TB drug.

[9] In December 2019, Revised National Tuberculosis Control Programme (RNTCP) has been renamed as the National Tuberculosis Elimination Program (NTEP) by the government of India

[10] GeneXpert MTB/RIF assay is a cartridge-based nucleic acid amplification test (CB-NAAT) which simultaneously detects DNA of Mycobacterium tuberculosis complex (MTBC) as well as resistance to rifampin (RIF) (i.e. mutation of the rpoB gene) in less than 2 hours (Tankeshwar 2016).

[11] Line Probe Assay (LPA) is a rapid technique based on polymerase chain reaction (PCR) that is used to detect Mycobacterium tuberculosis (MTB) complex as well as drug sensitivity to two major drugs used for TB treatment in India, i.e. rifampicin (RPM) and isoniazid (INH). It is used as a diagnostic tool for drug-resistant TB under NTEP. However, only sputum samples that are smear-positive for acid-fast bacilli (AFB) can be tested by LPA. (Desikan *et al.* 2017).

[12] Molecular Diagnostics (MDs) is a broad term describing a class of diagnostic tests that assess a person's health at a molecular level, detecting and measuring specific genetic sequences in deoxyribonucleic acid (DNA) or ribonucleic acid (RNA) or the proteins they express (Constance 2010).

[13] PCR is the gold standard in infectious diseases diagnosis because of its high level of sensitivity and specificity to the disease case.

[14] The device comes in a Chip based Real Time PCR kit which comes with individually sealed pouches, each containing: 1. Truenat MTB micro PCR chip, 2.Microtube with freeze dried PCR reagent, 3. DNase and RNase free peptide tip and 4. Desiccant Pouch. The reagents are provided in freeze dried form (reagent for performing real time PCR). Firm claims that their value addition contributes to more than 80 per cent to the imported reagents. Therefore considering this, as per, the recent circular of Department for Promotion of Industry and Internal Trade dated 04.06.2020 to promote Make in India policy, if the firm contributing more than 50 per cent to the amount of value addition then it comes under class- I local supplier.

[15] This is one of the loop holes in the technology of TB diagnosis that, at present, for both Truenat and GeneXpert, only Rifampicin resistance test kits are commercially available. This highlights a strong need for development of testing kits for other types of resistance, for example, Isoniazid resistance.

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