MOLECULAR DIAGNOSTIC TESTS IN BANGLADESH: CHALLENGES AND OPPORTUNITIES

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ABSTRACT

Molecular diagnosis is rapidly becoming an inseparable part of disease diagnosis. This cutting edge technology can be used to diagnose both malignant and infectious diseases as well as to help in determining drug dosage, tissue types for organ transplant and risk of inherent disorders. An added advantage is that it provides an indication of therapeutic choice and disease prognosis. A survey was conducted among diagnostic laboratories and research institutes of Bangladesh to observe the existing range of molecular diagnostic tests in Bangladesh. Challenges faced in establishing as well as sustaining these tests were noted and opinions recorded from stakeholders regarding further opportunities to improve this area. Challenges in development of molecular diagnostics in the country are variable. There is limited knowledge on molecular genetics among physicians. The meagre human resource available in the country is inadequately utilized. Strong advocacy and marketing strategies of neighboring countries favour medical services abroad. Customs regulations are unfavorable in terms of high tax rates and complicated procurement system. Strong policies are lacking to ensure after-support from the suppliers. Service available is centered in the capital. Most of all, there is no reference laboratory in the country. Bangladesh has immense potential for development of molecular diagnostics in the country. Review of policies regarding import and support of cutting edge technology in diagnostic sector with involvement of available experts in this field is essential to make this sector viable. Establishment of specialized institute on molecular diagnostics can provide an opportunity to yield a score of professionals. Strong commitment from physicians, molecular biologists, financial companies, and government policy makers together is required to bring molecular diagnostics to the doorstep of every citizen of our country.

KEYWORDS: MOLECULAR DIAGNOSTICS, BANGLADESH, CHALLENGES, DISEASE, PROGNOSIS

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INTRODUCTION

An essential component of improving global health is the use of appropriate diagnostic tools. Due to the amazing strength of molecular diagnostic tests in developing individualized therapeutic strategies, molecular diagnostic tests are becoming increasingly popular all over the world and are gradually replacing the conventional diagnostic algorithms. Hospitals and diagnostic laboratories are currently using molecular techniques that guarantee the highest levels of reliability and the greatest speed. Molecular diagnostics is making it possible to detect as well as to monitor infectious diseases, STDs, genetic diseases and cancer more accurately. It is also addressing the need for tests that monitor the prognosis and therapeutic efficacy of pharmaceuticals. Molecular diagnostics is therefore becoming an integral part of disease management and therapy, drug regimen selection, toxicity avoidance, therapeutic monitoring and detection of predisposition to disease.

Despite their high performance levels, these tests usually require greater levels of infrastructure and technological capabilities that are generally beyond the resources of developing countries. Again some tests are too costly to be used and are therefore accessible to fewer people. Though it is a fast-growing business in developed countries, molecular diagnostics is therefore somewhat new in Bangladesh. This paper outlines an approach to realize the benefits of molecular diagnostic tests as a health diagnostic tool in the face of the existing challenges.

WORLD WIDE APPEAL OF MOLECULAR DIAGNOSTIC TESTS

Molecular diagnostics has captured particular attention in recent years because of the deep insights these types of tests bring to diagnosis and treatment. All over the world molecular diagnosis is flourishing swiftly. Food and Drug Administration (FDA) in USA has approved human genetic tests for various malignancies (leukemia, Prostate cancer, Bladder cancer, and breast cancer), inherent disorders (Cystic fibrosis, coagulation factors and chromosome abnormalities), tissue typing for heart transplant and microbial genetic tests for certain viral, bacterial (various species of *Enterococcus*, *Chlamydia*, *Streptococcus*, MTB, etc.) and Protozoan (*Leishmania* species, *Trichomonous vaginalis*, etc.) infections[(1)].

The global molecular diagnostic market is witnessing a period of profound growth. The overall global market for diagnostics was valued at $45.6 billion in 2012 and is expected

to grow at about 7% annually over the next five years to reach a market size of $64.6 billion in 2017[2]. The Frost and Sullivan report has also shown the molecular diagnostics segment to represent 11% of total global IVD sales (Fig 1). Other reports state that the global molecular diagnostics and is expected to grow at a CAGR of 11.1 % from 2013 [3] and double its market size in 2017 from the market of 2012 [4] to reach an estimated value of USD 8.7 billion in 2019 [5].

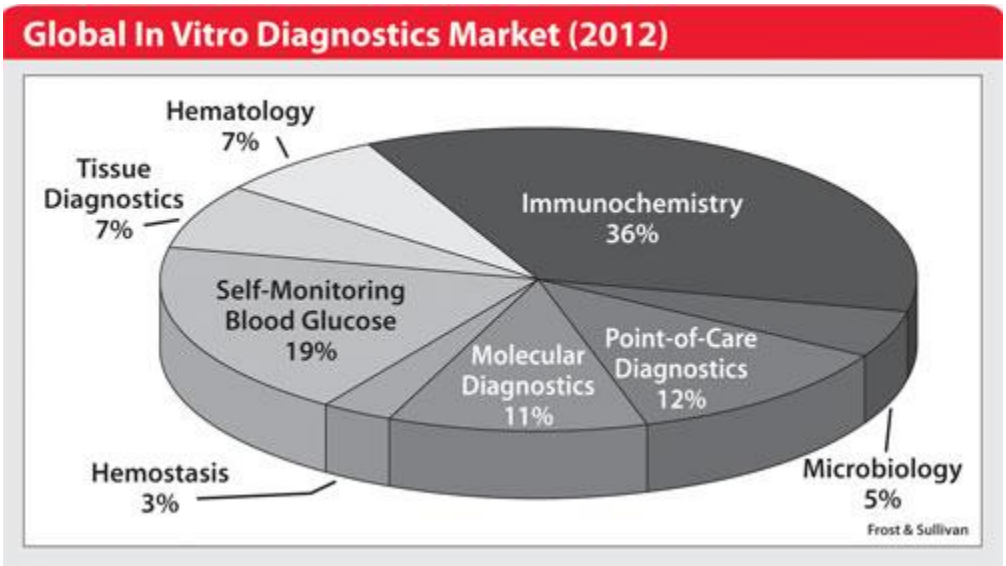


Figure 1. Molecular diagnostics market in the world as compared to other in vitro diagnostic tests as observed in the year 2012[1].

APPLICATIONS OF MOLECULAR METHODS IN MEDICAL LABORATORIES

Molecular diagnostics is one of the most dynamic and transformative areas of diagnostics, leading to advances in research and treatment that are revolutionizing health care across a wide range of diseases and health conditions [6]. This branch of medicine is mainly the study of nucleic acid, in order to detect specific sequences in DNA or RNA that may or may not be associated with disease, including single nucleotide polymorphism (SNP), deletions, rearrangements, insertions and other types of aberrations. Its application cannot be limited within the arena of disease diagnosis as molecular diagnosis can be used to determine disease prognosis, drug doses, tissue types for organ transplant and risk of inherent disorders.

Clinical applications of molecular diagnosis can be found in at least six general areas: infectious diseases; oncology; pharmacogenomics; genetic disease screening; tissue typing; and coagulation. Conventional diagnosis of infectious disease involves long period of microbial culture. Molecular diagnostic methods can reduce the duration of

disease diagnosis process, with the indication of therapeutic choices and disease prognosis as added advantage. PCR-based tests can detect the infectious organisms like mycobacterium tuberculosis (MTB), Hepatitis B virus (HBV), Hepatitis C virus (HCV), Human Immunodeficiency virus (HIV), Human Paplilloma virus (HPV), various respiratory viruses, etc. from sputum/ bronchoalveolar lavage (BAL), blood, cerebrospinal fluid (CSF) and other bodily fluids and determine its drug resistance in the same day.

Traditional diagnosis and staging of malignancies, both hematological and non-hematological, as well as the evaluation of response to therapy, is based on tissue morphology. Small number of reliable and specific cancer biomarkers was of little benefit. As DNA alterations were established as the main cause of neoplastic development, molecular studies is becoming a much preferred tool for cancer diagnosis and monitoring of minimal residual disease. Besides cancer causing genes (oncogenes), various DNA modifications such as methylation, transcription to mRNA, transcription to micro RNA (miRNA), translation of proteins, post-translational modification of proteins and synthesis of metabolites are also considered potential targets of cancer studies.

Pharmacogenomics study can give an effective therapeutic strategy when adverse drug reaction (ADR) is concerned. Knowledge of a patient's genetic ability to metabolize and utilize drug is very crucial in determining effective drug dosage, especially chemotherapeutic drugs for patients suffering malignancies. Genetic analysis is important to identify inherited disorders like Huntington's disease, Sickle cell anemia, Thalassemia, Cystic fibrosis, Phenylketonuria, Duchenne muscular dystrophy, Hemophilia, etc. at an early stage. Patients requiring an organ transplant must have a perfectly matching organ from the donor to avoid graft rejection. The most reliable technique to find such matching graft is HLA typing.

Molecular tools have also proven useful in discovering and characterizing emerging viruses and bacteria such as Sin Nombre virus (hantaviral pulmonary syndrome), hepatitis C virus, Bartonella henselae (cat scratch disease, bacillary angiomatosis), and Anaplasma phagocytophilum (human granulocytotropic anaplasmosis). The feasibility of applying molecular diagnostics to dangerous, fastidious, and uncultivated agents for which conventional tests do not yield timely diagnoses has achieved proof of concept for many agents. The ongoing challenge to the field of molecular diagnostics is to apply contemporary knowledge to facilitate agent diagnosis as well as to further discoveries of novel pathogens [(7)].

METHODS OF MOLECULAR DIAGNOSIS

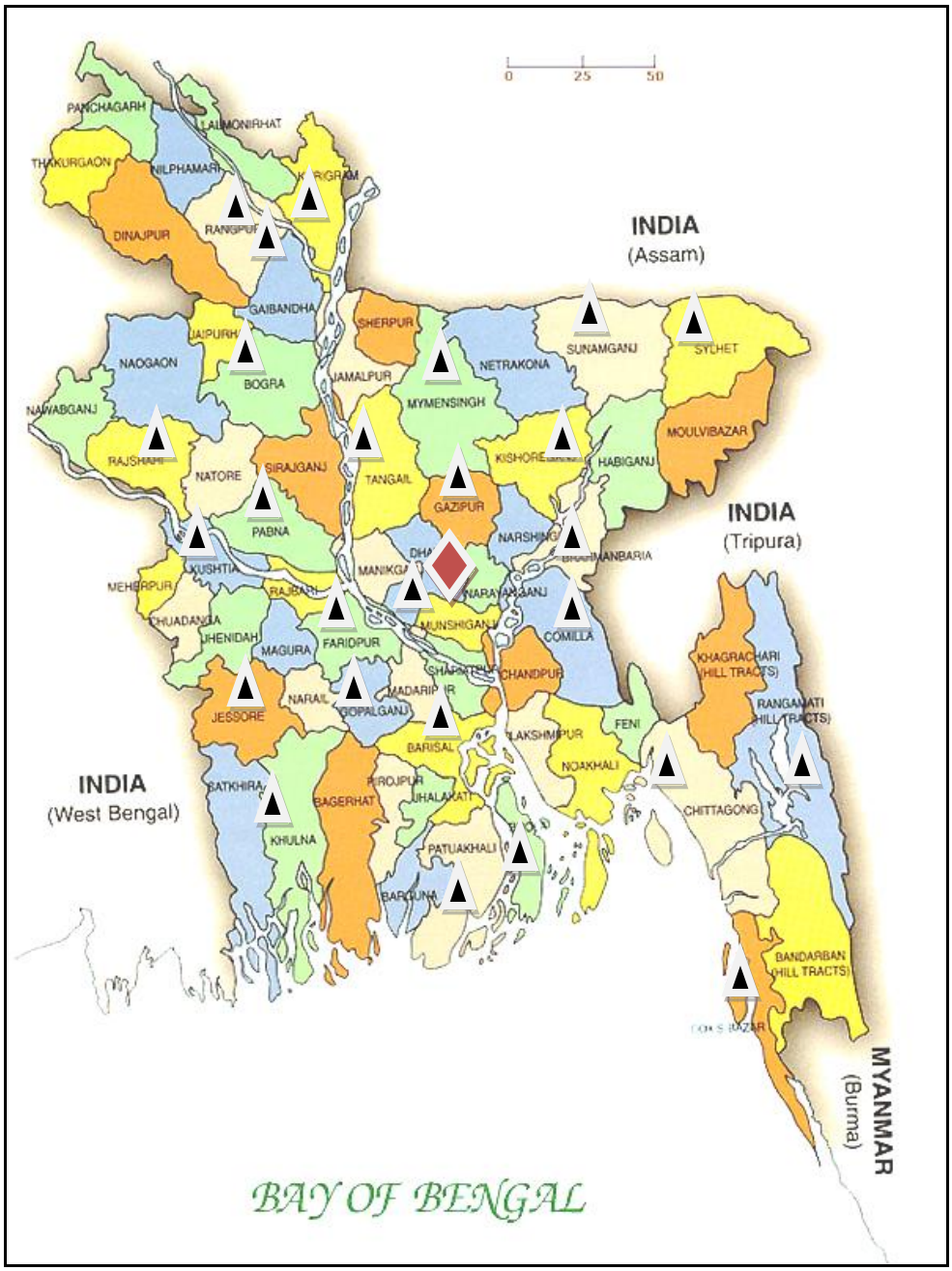
Molecular diagnostic tests involve PCR based and non-PCR based methods. Conventional PCR amplifies target DNA, which is observed by gel electrophoresis. Other PCR based methods are rtPCR (reverse transcriptase PCR), Real-time PCR, PCR-RFLP (restriction fragment-length polymorphisms), PCR-ARMS (amplification refractory mutation system), MLPA (multiplex ligation-dependent probe amplification), linkage analysis by SNP (single nucleotide polymorphism) or STR (short tandem repeats) mapping, PCR-ELISA, etc. Some non-PCR based methods use hybridization techniques i.e. FISH, Branched DNA assay, Comparative Genomic Hybridization (CGH) etc. DNA sequencing, gene chip (microarray) are direct methods to detect DNA alterations. All these methods are remarkably sensitive and require very small amount of samples. Mutation of Insulin gene can be identified from the DNA of any kind of somatic cells, collection of pancreatic cells is not at all necessary. In case of infectious disease, classical culture methods require more than 48 hours to detect pathogen and its drug resistance, with the distinct possibility of contamination. Molecular diagnostic methods can give highly specific result in the same day. Some pathogens cannot be cultured at all, but their DNA can be analyzed. Tissue samples from a biopsy that are fixed in formalin cannot be cultured because the organism is dead, but their DNA remains intact, so can be isolated and diagnosed. Microscopic study of malignancies requires expert hematologists and histopathologists with years of vast experience while staining of slides should be performed with equally expert personals. Even then the study may not be deemed undisputable. PCR based methods may give a definite answer to any doubtful insights.

THE BANGLADESH SCENARIO OF MOLECULAR DIAGNOSTICS; BIRTH TO PRESENT

The journey of molecular medicine per se started in Bangladesh at the end of the twentieth century and was focused mainly towards various diarrhoeal diseases, a public health concern in this region [8]. Molecular research was predominantly restricted to sophisticated laboratories like icddr'B until the dawn of the twenty-first century when the country experienced a series outbreak of Dengue viral infection. The first diagnostic laboratory to engage in molecular research was BIRDEM where the genotype of dengue virus was exposed [9]. These studies were yet however, not used as diagnostic or prognostic tools; they rather served the academic interest. The first diagnostic molecular test available commercially in the country was in the form of viral marker assays for hepatitis [10] . The only instance of a government supported molecular diagnostic service is in the area of tuberculosis, one of the most prevalent diseases as well as a major health concern of the country. The idea of utilizing molecular methods for the diagnosis of

tuberculosis, was harbored at BIRDEM in the early years of the last decade [11]. Finally in 2012, these early research activities were endorsed by Government of Bangladesh and a real time PCR-based fully automated nucleic acid amplification test (NAAT), namely GenExpert technology was launched under the National TB Program supported TB CARE II Project of United States Agency for International Development (USAID) [12] . This is the only molecular diagnostic service available at present outside the capital (figure 2). According to the annual report published by Directorate General of Health Services (DGHS) in 2013, this service that was initiated at the National TB Referral Laboratory (NTRL) at Mohakhali, presently encompasses two regional TB referral labs (RTRL), 21 chest disease clinics, other government hospitals and stretches to even tertiary level private organizations and autonomous institutes like BIRDEM and BSMMU respectively [13]. Researchers of Bangladesh are continuing to search for potential opportunities to develop a more tailored approach suitable for our community [14] Molecular diagnostics in oncology has an even younger history [15] and is yet available mainly for haematological malignancies, namely detection and quantification of bcr-abl gene, the fusion gene present in chronic myeloid leukemia and PML-RARα gene, another fusion gene pathognomonic for acute promyelocytic leukemia, a potentially curable class of leukemia. The last decade has brought forth an inspiring bloom in the molecular diagnostics trade in the country, and various medical laboratories and diagnostic centres have picked up the option of molecular tests to enrich their services. A dedicated private laboratory has also been established in the capital, offering solely molecular diagnostic services.

Certain institutes, hospitals and diagnostic laboratories presently offer molecular diagnostic services in Bangladesh (figure 2).



Government supported test for TB

All other molecular tests

Figure 2. Distribution of molecular diagnostic services in Bangladesh. All molecular diagnostic services are centered in the capital except the government supported GenExpert test for tuberculosis.

Various malignancies, infectious diseases, haemoglobinopathies, tissue typing tests are performed in these centers (Table 1). A drawback is that the service providers are all centered in the capital city, so molecular diagnostics is less available to the people of the furthest regions of the country.

Table 1. List of molecular diagnostic services in Bangladesh.

Name of the Lab/ Institution	Location	Type of Organization	Services Provided		
			Virology	Oncology	Others
BIRDEM	Dhaka	Private	HBV, HCV, HPV	BCR-ABL, PML-RARA	TB
BSMMU	Dhaka	Autonomous	HBV, HCV, HPV	BCR-ABL	TB
Icddr,B	Dhaka	International	HBV, HCV, HPV	BCR-ABL, PML-RARA	E Coli, STD
Popular Diagnostics Ltd	Dhaka	Private	HBV, HCV, HPV		
Medinova Diagnostics Ltd	Dhaka	Private	HBV, HCV, HPV		
Lab-Aid Diagnostics Ltd	Dhaka	Private	HBV, HCV, HPV		
CARe Hospital (Pvt) Ltd	Dhaka	Private	HBV, HCV, HPV		
AFIP	Dhaka	Government	HBV, HCV, HPV		
Ibn Sina Laboratory	Dhaka	Private	HBV, HCV, HPV		
NTP (31 centres)	All over the country	Government			MDR-TB
Square Hospitals (Pvt) Ltd	Dhaka	Corporate	HBV, HCV, HPV		
Dhaka Shishu Hospital	Dhaka	Autonomous			
DNA Solutions Ltd	Dhaka	Private lab (dedicated to molecular diagnostic tests)	HBV, HCV, HPV	BCR-ABL, PML-RARA	

SCENARIO OF CHALLENGES IN DEVELOPED COUNTRIES VERSUS DEVELOPING COUNTRIES

UNIVERSAL CHALLENGES

Molecular diagnostic services all over the world are constantly challenged by various factors. There are some universal factors that affect any country as well as some specific challenges faced by low resource settings like in developing countries. Excitement about the future of this field must therefore be tempered by recognition of the challenges. In the developed world, the challenges include regulatory hurdles, coverage and reimbursement issues, and practical and ethical (privacy) issues associated with generating and storing large volumes of highly detailed and personal health information.

CHALLENGES OF THE DEVELOPED COUNTRIES

The fast pace of technological development in molecular diagnostics, and the rapidly growing body of research regarding biomarkers challenges regulatory bodies to stay constantly updated. Clear understanding of regulatory expectations for multiplex tests, companion diagnostics and next generation sequencing as well as the increasing investments necessary to generate the clinical evidence required for approval or clearance will be integral. There are questions regarding the patenting of gene sequences currently working their way through the courts.

The ability and capacity to capture store and analyze the tremendous and rapidly increasing amount of diagnostics data, particularly with gene sequencing tests, is an ongoing challenge. IT systems must have enough power to process and analyze these huge volumes of information. In addition, another key challenge is the need for data standards that would speed interpretation of these complex genomic data sets and make the results relevant for specific patients. This task is further complicated by the fact that the patient's medical record is often in many unconnected places, whether in multiple out-patient offices, multiple hospitals, or multiple pharmacy systems.

In countries that have a structured health service scheme with adequate health insurance system, the challenge is to convince the insurance companies or other stakeholders about the strong value proposition of diagnostics overall, since payers are increasingly asking for health economic evidence supporting the use of specific tests, which often requires further evidence generation above and beyond regulatory requirements. Finally, ethical questions are also being raised about the disclosure and use of genetic information. Genetic markers are being identified that can signal the propensity of a patient to develop a disease over their lifetime and the question has been raised of how, if at all, such

information should be disclosed, particularly in cases where prevention or treatments are not yet available. Policy makers continue to grapple with these challenges.

SPECIFIC CHALLENGES FOR BANGLADESH

In countries that are at the other end of the line like Bangladesh, the burden of cost falls on the individual. Lack of strong guidelines regarding utility of the tests, poses a threat of abuse of these investigational facilities where they are not clinically indicated. At the end of the story, it is the treatment of the patient that is always at stake.

The process of establishing and sustaining a high tech area like molecular diagnostics involves multiple stakeholders as shown in figure 3.

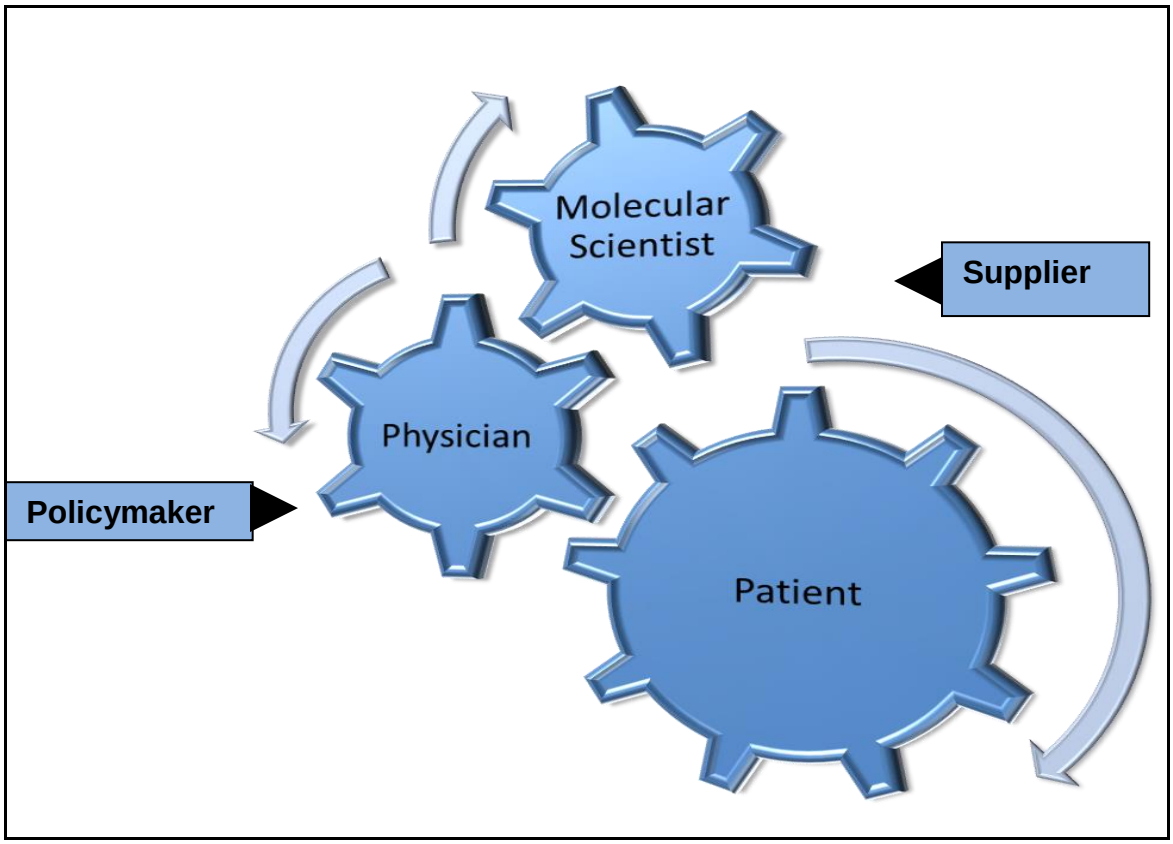


Figure 3. Stakeholders involved in molecular diagnostic services

THE PATIENT

The healthcare challenges faced by the developing countries are vastly different from those in the developed nations. Owing to the high poverty levels, there is a great dependency on the state for healthcare.

With very limited budgets available for healthcare, the developing countries have not been able to put up any significant infrastructure to address sophisticated issues like molecular technology. In a country where there is no national health insurance policy and the per capita income is one of the lowest in the world, the major financial brunt of such tests is borne by the patient. There is limited information in the community about newer technologies that are employed currently in disease management. Although molecular tests are expected to have a shorter turnaround time, due to the low frequency of requests, samples are usually pooled and performed to make them cost effective for the lab. This poses a general delay in availability of reports which lead to delay in initiation of treatment and increased anxiety and apprehension for the patient. It also calls for a longer in-hospital stay, which again accentuates the burden of treatment related expenditure.

THE PHYSICIAN

The undergraduate and postgraduate medical education curriculum of the country does not impart sufficient and updated information regarding molecular diagnostic tests. The only option that remains for them is to get self-educated in this branch. As a result, most of our physicians do not have ample opportunity to utilize this technology optimally. There is lack of information regarding when to order a test, which test or tests to order, how often it must be repeated, as well as how to interpret a test. The support they receive from local labs is irregular and inadequate. They also face difficulty in comparing and interpreting results from different labs. The strong advocacy and ease of sending samples to foreign labs tips the balance towards an efflux of the samples to laboratories abroad. The major bulk of the services are being provided by neighboring countries like India, Singapore etc. Certain agencies employed by these foreign countries are collecting the samples from Bangladesh and sending the samples abroad to the testing centres. They are again collecting the reports and delivering to the patients orphysicians concerned. There are a number of issues in this process that raise concern. Firstly, in respect of air transport, World Health Organization (WHO) have categorized all diagnostic samples as Category B [(16)] under the substances identified as dangerous goods or hazardous material (HAZMAT) by International Air Transport Association (IATA) [(17)] and they stringent conditions like appropriate labeling and packaging before any air freight is ready to carry them. Most sample collecting vendors avoid such complications and send the samples by road tot eh neighboring countries. This raises the concern whether proper temperature is

maintained throughout the duration of transportation of the sample from the patient to the lab. Moreover, there is a delay in availability of the report. On top of that, if there is a reason that the sample has to be recollected e.g. due to inadequacy or deterioration, the situation is even more complicated. Lastly, the physicians barely get a chance to contact the lab personnel regarding any test report. Neither is there a chance to develop local human resource through training from the same labs. There is however, a general ignorance among the physicians about limitations of tests done abroad.

THE LABORATORY MOLECULAR SCIENTIST

Expertise in this field is sparse in the country. The limited expertise is also inappropriately distributed or utilized due to various bureaucratic reasons. The laboratories that struggled against the storm to establish molecular tests face a constant difficulty in procuring reagents in time, of the required quality and at a sustainable cost. There is no reference institute for quality maintenance and standardization of methods, kits and equipment, which makes quality control difficult. In such a nascent atmosphere of molecular technology, peer review is considered essential to develop a sound service. This system or rather culture is not present in the country. On top of that, they face a constant threat of competition with foreign labs. The situation is made tougher by the lack of motivation of institutional or government policymakers regarding rationale of introducing molecular tests.

THE SUPPLIER

The suppliers face some specific problems in importing the reagents for these tests. The manufacturer usually provides the ex-works price. The importer has to pay freight, insurance, duty, taxes and local handing cost. Duty and taxes are calculated on product cost as well as freight charge. Combined with the low bulk of these special reagents, the overall cost in procuring them is almost doubled. The high tax rate on importing reagent and machineries keep the overall cost of test procedure fairly out of reach of poor patients. On top of that, some companies like Qiagen prescribe a minimum quantity of a one-time order, which is often lower than the requirement of the consumer labs. Direct electronic transfer is very difficult process from Bangladesh and requires additional cost.
The customs regulations of the country have not yet been tailored to the need of these special tests. Reagents involved in molecular tests often require to be maintained at ultra-low temperatures. The reagents are cleared according to the same regulations as all other medical laboratory reagents which do not have such specific requirements. As these reagents are cold chain items, they need to be cleared very rapidly from airport. The airports in Bangladesh do not have enough space in cold room neither do they have ultra-refrigeration facilities. The situation is further complicated by bureaucratic

complications. All these create possibilities of deterioration of the performance of reagents.

Expiry date is another problem. Some reagents have very small shelf life. Low volume labs cannot consume reasonable quantity within the expiry period. Both the supplier and customer face difficulty in overcoming this problem. These issues serve as obstacles in establishing newer technologies or low volume tests.

There is also lack of information about these specific issues among other sectors that have a stake in the process, mainly the administrative bodies and other relevant sections of the laboratory or hospital like store, finance department etc. The authorities and sometimes even the lab personnel sometimes select a vendor only in respect of the price they offer without adequate information about the quality. This allows various companies to offer molecular products of a dubious quality at an attractive price. The competition with cheaper but low quality products makes it difficult for suppliers of internationally renowned high quality products to survive in the field.

PROSPECTS FOR MOLECULAR DIAGNOSTICS IN BANGLADESH

The prospect for molecular diagnostic tests in a highly-populated country like Bangladesh is immense. The emergence of ultra high-end tests is in general accompanied by consumer concerns of high cost. The initial introduction of such tests therefore must often be targeted to the economic sector that can afford such tests. The recent years have perceived a striking increase in purchasing power among the middle- to upper-tier economic groups. Along with the increasing wealth of Bangladeshis is the emergence of a more Westernized attitude. Thus, although esoteric testing and disease-screening programs are largely at an embryonic stage compared to the West, the shift in economics and attitude provides for a more encouraging outlook in terms of the success of such efforts in the future. The benefit to the overall medical community in Bangladesh will be perceived once market penetration has been achieved. The combined factors of financial return from investment coupled with advancing technology are then likely to lead to cost reduction, allowing greater economic segments of the Bangladeshi society to afford these tests. Efficient communication among the various sectors may help alleviate the problems faced today and help to groom this nascent technology in the country.

MOLECULAR TECHNOLOGY AND RESEARCH

Research has to play a significant role in developing molecular diagnostic tests in Bangladesh. Ample support is required from both the government as well as other funding agencies to create and sustain a group dedicated to the progress of this branch of life science. There may be a phase-wise approach in this regards (figure 4).

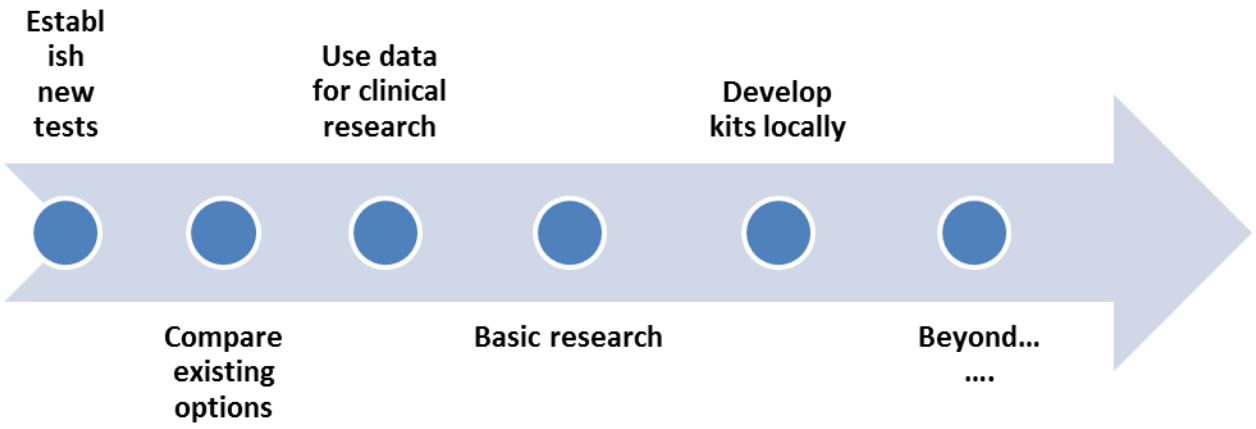


Figure 4. Phases in research activities for the development of molecular diagnostic tests in Bangladesh.

In the first phase, services that are not available in the country have to be established. This will lead to a decrease in the lag period between sample collection and report delivery. It will also increase access of the physicians to the labs and help build our human resource and create employment opportunities. Various established methods or commercial kits may be compared to find the ones most suitable for the community both in terms of cost and disease heterogeneity. The data obtained from the molecular tests will give opportunities for clinical research in relevant areas of international standard. Basic research that is ongoing may also be boosted up with the aim to develop kits locally. This will play a significant role in overcoming most of the challenges in reagent procurement leading to a decrease in cost of the tests. All these will help boost up the national economy and the scientific community of the country.

SUMMARY AND CONCLUSION

In this densely populated country, where doctor to population ratio is 1:4,719, it is of paramount importance that quality infrastructure and manpower is developed to ensure proper diagnosis. Currently various training courses are ongoing in institutes such as BIRDEM, icddr,b. Various molecular researches in public, private and medical universities are also helping in building an expert pool, yet the rate is very slow. Inclusion of molecular medicine in the medical graduate and post-graduate curriculum

should be considered for the future doctors and clinicians. Molecular diagnostics is faster and much more reliable than conventional methods, so tax cut on certain level may even make it cheaper for the populace. Some equipment suppliers provide quality support, but a BSTI equivalent establishment in this regard is necessary to maintain and improve the quality. If financial companies, pharmaceuticals and government policy makers strongly held their focus on this field, Bangladesh has the potential to flourish in future.

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