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Diagnostic Landscape in India – A Review

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Abstract: **Healthcare in India is continuously undergoing transformation. The possibilities for sustainable solutions in healthcare delivery and expanding global industry leadership of biotech and pharma are being driven by technologies. Innovation is a common numerator for catalyzing growth, value creation and sustainable competition. In this report, we review the key trends in healthcare segment with particular emphasis on the diagnostic landscape in India.**

A robust growth has been witnessed by the diagnostic space which was driven by expansion in overall healthcare delivery, increased use of diagnostics and better healthcare access. The diagnostic segment being more receptive to adoption of advanced technologies is expected to continue its growth by 15-20%. This segment is seeing adoption of new products of innovation including genomics, less invasive testing approaches such as liquid biopsies, and more sensitive and multiplexed Point-of-Care tests across primary care, critical care and home use products. The notable trends in diagnostic delivery include consumer convenience, home collection of samples, digitization of reports and continuing pursuit of PPPs as a means to bridge the infrastructure gap. The innovation landscape in India is very encouraging; however, challenges to widespread adoption need to be addressed for realization of the country's innovation pipeline value.

Keywords: **undergoing transformation, widespread adoption, diagnostic landscape in India.**

1. CHANGING TIMES

Private healthcare accounts for almost 74 per cent of the country's total healthcare expenditure, and it shares 74 per cent of hospital care services and 40 per cent of hospital beds. The private sector is emerging as a vibrant force in India's healthcare and is attracting international investments. Healthcare is set to become largest sector in terms revenue and employment generation. The healthcare industry is expected to touch USD160 billion by 2017 and USD280 by 2020. Per capita healthcare expenditure is estimated to rise to more than USD68.6 billion beyond 2015. Non-communicable diseases are caused by high cholesterol, high blood pressure, obesity, poor diet and alcohol consumption. The telemedicine market is expected to raise USD 18.7 million by 2017.

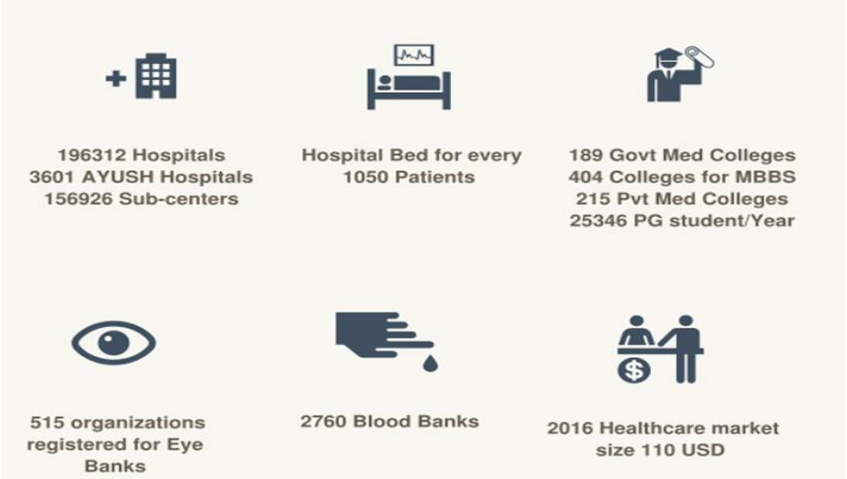

Figure 1: Summary of health care in India as of 2015

Multiple factors are contributing to this raise, mainly a) rise in the income b) easier access to high-quality healthcare facilities c) greater awareness of personal health and hygiene d) greater penetration of health insurance e) affordable generic drug market. In India, life style diseases have replaced traditional problems. This could mean extension of services to tier II/III cities with low cost consultation. New trend with private players in the healthcare industry is set- up hospital chain. This has been effective in reducing the cost by a) High procurement of medical supplies b) High-volume by high capacity utilization and staff productivity c) Good human capital management d) Leveraging the benefit of Information Technology to reduce cost and improve healthcare delivery. Few of the hospitals are entering into Private-Public-Partnership as corporate social responsibility to extend their services in rural India. Indian health sector is also getting recognition for health tourism. Skilled manpower has strengthened India's position in global market. Other factors which are contributing to its growth are world class facilities and treatment costs. Medical tourism market in India is expected to reach USD 8 billion in 2020. Government of India is also promoting yoga, meditation, Ayurveda, allopathic and other traditional methods. A summary of the health care scenario in India is represented as an infograph in Fig 1. With a number of drivers in place, the healthcare industry, diagnostic and laboratory services are experiencing significant growth in India. Although, Indian diagnostic market is unorganized, it is presently valued at approximately USD 2.2 billion and is expected to double to USD 5.5 billion by 2020. Major players in diagnostics and pathological test labs market are Religare SRL diagnostics, Metropolis, Dr Lal's Pathology, Thyrocare and Onquest. India is fast emerging as the diagnostic capital of the world. The number of tests conducted in the last decade has doubled from 189 million to more than 425 million. Specialists have now started competing for high-end diagnostics to cater the industry need and demands.

Main challenge for growth is lack of regulation, use of cheaper products, and kickbacks for prescribing doctors. Although India hasn't become a full-fledged manufacturing hub for medical devices, things are changing. Diagnostic device manufacturers are now finding India as better market place. Now global markets have accepted the quality products produced from Indian manufacturer companies. Medical devices supplies market presently is approximately USD 1.19 billion. Consumer home-use medical device is USD 5 billion approximately. High value imported products include cancer diagnostics, PCR technologies, NGS among others. Imports constitute over 50 per cent of market, and have high gross margin. However, market is increasingly competitive due to low entry barriers, and relaxed laws. Now, Indian companies are looking forward to having alliances with foreign companies either to import and distribute their products in India or become licensed manufacturers of foreign brands. Local companies are also investing on R&D and developing IVD kits for local market. Government needs to create more academic centers to meet the technological and regulatory demands. This emerging industry needs assistance for testing facility for devices, pre-clinical and clinical studies, and government agencies should compliment. Private equity (PE) and venture capital (VC) investors are looking to step up investment in Techno Health segment. There is strong opportunity to tap the market for healthcare services in semi urban and rural areas.

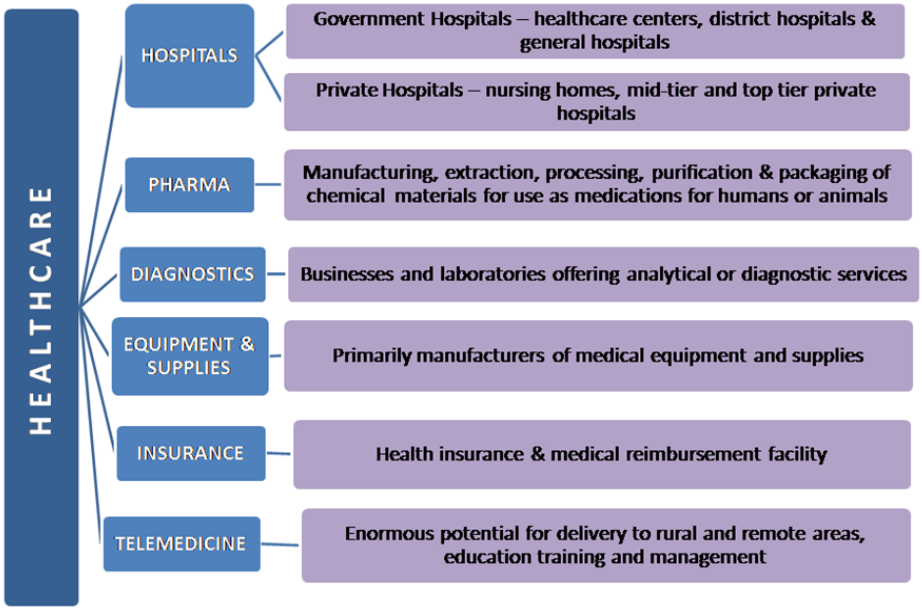

Figure 2: Health care functions through five segments

Healthcare functions through five important segments (**Fig 2**), and the industry has had a marked public and private equity interest this year. The sector also has several other positive highlights to look back on, including a billion-dollar inbound acquisition in the pharmaceuticals segment involving a Chinese investor, a big multispecialty hospital deal, the emergence of start-ups and easing of rules to attract foreign investment in pharmaceuticals companies. Syngene International, the research arm of Biocon, has set the tone with a blockbuster IPO. This was followed by IPOs of diagnostics chain Dr Lal Path Labs and drug maker Alkem Laboratories. Multispeciality hospital chains like Narayana Hrudayalaya, Healthcare Global Enterprises (HCG), have also made inroads into market. These are early indicators for that healthcare enterprises are branching out from dominated pharmaceutical companies. Now, healthcare delivery is a more straightforward line of business in comparison to complicated pharmaceutical segment. It is reflecting that investors are interested in both multi-speciality and single speciality hospital networks. Hong Kong based PE firm ADV Partners have invested in eye-care chain Dr Agarwal's Eye Hospital Ltd. Mother-and child care, Oncology, and in-vitro fertilisation (IVF) segment has also attracted PE investment. Multi-speciality hospitals enhanced their presence with Dubai-based PE firm Abraaj Group buying a majority stake in Hydrabad-based CARE Hospitals from PE firm Advent International. Regional multi-speciality hospitals including Cygnus Medicare and Asian Institute of Medical Sciences are also looking to raise the funds.

However, in terms of value pharmaceutical segment will remain high. China's Fosun Pharmaceuticals (Group) Co. Ltd acquired a majority stake in Hyderabad-based Gland Pharma Ltd from PE firm KKR and the company's founders. The second biggest overseas acquisition by an Indian pharmaceutical company was when Temasek-backed Intas Pharmaceuticals acquired Teva Pharmaceuticals' assets and operations of Activis Generics in the UK & Ireland. Similarly deals between Dr Reddy's, Cipla and Aurobindo Pharma bought products of Teva in the US. This year Sun Pharmaceuticals acquired 14 prescription brands from Swiss firm Novartis AG in Japan for USD 293 million to establish a strong footprint in the world's second largest pharmaceutical market. Cipla has cleared all regulatory hurdles to formally float its consumer healthcare business, which is backed by PE firm Eight Road Ventures. Piramal Enterprises Ltd has also brought brands from drug maker Pfizer. Dr Reddy's Laboratories Ltd has acquired a half dozen OTC brands from Ducere Pharma, to increase its presence in healthcare business. In coming days, one can expect Indian Healthcare to be a cost-effective model at the global level.

Corporate India has raised bars for healthcare delivery system. It is no surprise that clinical diagnostic market is also undergoing rapid change towards consolidation and standardization. However, proper scaling of pathology services is the key to quality health care. Laboratory services contribute to 70% of healthcare diagnosis. Apart from the rise of universal healthcare, other factors like aging population, rising prevalence of chronic conditions like obesity and diabetes, introduction of new technology (Genomic medicine, NGS, and Point-of- Care testing) are driving change in pathology market. Existing players are still in search of key to scale-up in a price sensitive Indian community.

2. BUILDING A BRIDGE

Healthcare is unique industry, where one can't always think of business and profit. If done so, physician and support system may lose human dignity and spirit to fight back. Community teaching should be a part to understand the healthcare policies and initiatives. Universities, Medical schools and Hospitals that doesn't understand the value of pathology is never going to succeed at delivering value based and accountable care. Young minds choosing medicine as career should have a strong commitment to give back to the community. Respect and appreciation from the community they serve should make them an appealing career option. There is need to rethinking on how we do the business of science and medicine.In spite of the dire geographical infrastructure, and paucity of labs, staff, equipment and facilities, the dedication and compassion of the healthcare delivery system can be presented with pride. With increasing healthcare costs, preventive health needs to be promoted in a captivating, thought-provoking, emotional, and inspiring way.

Government department should take pride inspiring research and innovation. Government policies should get out of the way and enable reduction of the administrative burden and allow healthcare providers to be creative and engage with scientific discoveries. When healthcare providers need support, government should rethink its policies on fresh acquired knowledge and public health in mind. They need to be caring, ethical and humane, while integrating research outcomes in public health. Policy makers need to understand the problems faced by stakeholders in healthcare industry and motived to solve them. They need to work with legal, and experts to bring in consensus for new treatment options available to end stage patients. This could be frustrating, when outcomes attained with no consensus derived. It is important that variety of projects is percolated at the same time. If one reaches the dead end, there are other always ways that can be productive. The concerned Government departments should make effort to credit the healthcare organization with special privileges

and grants to compensate working cost of diagnostic services. They should work to nullify outside factor like cost and resources to influence or curtail new ideas and technologies of independent investigators. Department of Science and Technology needs to include and fund diagnostic services, based on scientific output in terms of healthcare data being generated and effective policies being implemented. Centralized unified approach to problems and their solutions with regards to public health & research needs to be collected and shared with investigators. The goal of government is to save lives quicker in humanitarian disasters and public health emergencies.

Private-Public-Partnerships (PPP) needs to be continued to be promoted by visionary bureaucracy and from civil society. Local governments need to experiment on a wide spectrum of models to include rural-urban mix, for-profit and not-for-profit partners, primary versus speciality care services, clinical services to insurance schemes, laundry to telemedicine, etc. For any model to be successful, government needs to hold consultants and facility-level managers accountable. In country like India, players from private sectors needs to initiate the projects and government should look at feasibility. Replicating successful projects in other regions is a daunting task. PPP model cannot be uniform across all the regions, because such initiative need local political and community support. Designing partnership agreements requires sufficient capacity-building measures, and local leadership is ideal for achieving this aim. Pricing tariffs for services should be based not only competitive tendering process, but also on a standard calculation of competitive rates. Government needs to realize that PPP model is not a substitute for provision of public healthcare services. It needs to partner to rent or lease existing basic healthcare infrastructure and human resource capacity to private sector.

Insurance companies should realize reflex testing and new technologies are a necessary guide towards precise diagnosis and cost-effective treatment benefits. They need to invest and partner with new diagnostic companies to reduce cost and therapies. Pathology department function needs to be analysed along with professional (pathology) organization and financial controllers. Local skill based services can be extended to regions where the performance is below the expected guideline. Local governments need to build patient information, disease specific groups, and clinical effectiveness diagnostic services. Then they can reap benefits of allocating and effectively utilizing resources.

3. SKILL & QUALITY TRAINING PROGRAMS

Complete automation of laboratory is far stretched dream, where human capital is cheaper and affordable. However, there is gap between qualified workforce and skilled workforce in diagnostic industry. Mushroomed educational institutes have delivered a qualified workforce. Now it is important to generate employment and teach them key skills 'on the job'. Stake holders in diagnostic industry, and government need to find ways to collaboratively work with academic work force in universities. Best way forward is to comprehensively develop crash courses for professionals in form of Continuing Medical Education, online courses, workshops and ad hoc training related to specific projects. Other requirements to support the skilling needs are highlighted below -

i. ***Increase in training budgets*:** Stakeholders needs to realize that training managers should have resources, to make sure they develop an acute appreciation of and desire for efficiency.

ii. ***Adopt newer technologies**:* push boundaries of creativity and include newer technology, new teaching styles, bold training material to maximize chances of gaining and holding trainee's attention.

iii. ***Trainer's awareness**:* It is important for the trainer to keep abreast of the latest developments in diagnostic field. A passion for learning will make this less a chore and more of spirited endeavour.

iv. ***Need based approach:*** Flattering of productivity is just a symptom. One needs to do root cause analysis to identify an inability to focus, a distraction environment, and customer need or technology challenges.

v. ***Trained trainer:*** It is important for the organizations to identify training manager, who has a deep and thorough understanding of the business requirement and vision of organization. Training manager should maximize company resources and build and efficient and productive workforce, by designing and evaluating training programs that are integrated and measured to achieve organizations strategic goals.

vi. ***Communication**:* Training managers should understand the problems, convey ideas and communicate through words. However, words are nothing if it's not tempered with empathy, rooted on the understanding of how people learn, and backed by good interpersonal skills. One need to hone the skills of breaking complex ideas down to components that make for easier understanding, and ability to draw the best out of trainees and help them to learn the same.

4. TRANSLATION MEDICINE

Underutilization actually costs the healthcare system more money than overutilization. Focus of academic department should be to develop diverse educational programs and to support clinical services. Sometimes universities needs to understand that productivity required achieving tenure as research scholar may be less than tenure to qualify as certified practitioners. Universities need to cover and support regional diagnostic facilities, as 'Hub- Spoke' model. There is need for competition between major universities. Supporting effective test utilization and patient management are crucial to educational programs. Source of rivalry between universities, private & government diagnostic service providers should be purely based on patient and clinician input. Funds need to be diverted to formally train the graduates in research methodologies (integrating basic and translation research), beginning at the under graduation.

Importance of translation medicine is growing in healthcare industry. Main emphasis is on early patient testing, evaluation and management. It is defined as interdisciplinary branch of the biomedical field, supported by bench side (bridging technologies and discoveries in laboratory), bedside (Clinical research and practice) and community. It is a rapidly growing discipline in biomedical research and aims to expedite the discovery of new diagnostic tools and treatment by using a multi-disciplinary, highly collaborative; "bench-to-bedside" approach. It attempts to directly connect basic research to patient care. In the last few years advances in basic sciences have high lightened complex patterns of pathogenesis, involving the regulation of multiple genes and their protein products. Outcomes of practice of evidence based medicine have identified bias in clinical research and serious errors in judgement. It is thus becoming evident that for several trivial issues, there is often waste of expensive treatments, while for many serious conditions there is no effective intervention and lack of research targeted at them.

Nano-particles can be much more reactive than larger volumes of the same substance. The biological application of these nano-particles must confirm to requirements of public health, safety and environmental protection. Advances in diagnostic nanotechnologies, will enable sensitivity, speed and flexibility of biological tests measuring the presence or activity of an analyte. These nanotechnologies are applicable to both DNA and proteins, suited for body fluid using relatively small sample volumes. Scientists are working on nanotechnologies that enable early detection of infection, disease and cancer. In the era of personalized medicine, this has both positive impact on both clinical decision making and treatment costs. Nanoparticles for targeted drug delivery in cancer enable combination of diagnostic and therapeutic and act as adjuncts to hyperthermia and photodynamic therapy. Nano biotechnology will facilitate the development of personalized medicine, i.e. prescription of specific therapeutics best suited for an individual. The use of nanotechnologies for diagnostic applications shows great promise to meet the rigorous demands of the clinical laboratory for sensitivity and cost effectiveness. However, there are some concerns about the safety of nanoparticles introduced into human body and released into environment. Presently, there are no FDA directives to regulate to regulate Nano biotechnology; there is some legal and practical concern, related to the existing regulations in the field of Nano diagnosis. Some have raised certain ethical concerns related with the testing of blood. If a Nan chip is used to analyse our entire DNA sequence from a drop of blood, would it be morally correct for hospitals to know an individual's entire genetic makeup? Should not individuals have some say in whether or not hospitals have access to these records? If the answer is NO, what if it is used by government agencies for greater good of public health?

Traditionally, basic research has been separated from the clinical practice of medicine by series of regulations and policies, that is when new drugs were developed independently of the clinic, and were rooted back for safety testing and clinical trial. It is important that biomedical researchers work collaboratively with practitioners. This would enable them exchange their ideas, information, and knowledge across organizational, governance, socio-political, and cultural boundaries. They can share resources like scientific literature, experimental data, summaries of knowledge of gene products, diseases, and compounds, and informal scientific discourse and commentary by creating information ecosystem. Many pharmaceutical companies are building these bridges to facilitate interaction between basic research and clinical medicine, particularly clinical trials. Translation research in laboratory medicine could create new opportunities for earlier and more accurate diagnoses and resultant cures, especially with the application of clinical trial. This should be regarded as 2-way street: from bench to bedside and bedside to bench. However, most of the new testing technologies are unfamiliar to most laboratory professionals; hence lack appreciation of the inter-laboratory performance, standardization, and quality control that are required to move from method discovery to clinical practice. Greatest challenge is crossing the boundaries from research to clinical application requires experimental evidence that the use of diagnostic test in question improves clinical and/or economical outcomes. The role of translation medicine in clinical practice encompasses:

i. Clinical investigations in humans which define the pathogenesis and provide the scientific foundation for development of new or improved therapies for human disease.

ii. Non-human or non-clinical studies conducted with the intent to advance therapies to the clinic or to develop principles for application of therapeutics in human disease

iii. Basic science studies which define the biological effects of therapeutics in humans.

iv. Clinical trials initiated based on # 1-3 with any endpoint of therapy including toxicity and/ or efficacy.

v. To ensure clinical adaptation of best practices that lead to greater understanding of the link between clinical experience and patient outcomes

vi. Help in product development for clinical use in various stages of investigational clinical trial.

5. ENTREPRENEURIAL MEDICAL SCHOOL

Practice of medicine has emphasized the art rather than science. Early disciplines to be established were Medicine and Surgery. Discovery of causes of infection (Theory of contagion) as well as observation of tissue changes in disease state that followed the discovery of microscope, and set the stage for recognition of pathology as speciality. In the last decade or so, there is apparently growing gulf between the art of the practice of clinical medicine and surgery and the rapidly advancing basic sciences. Over the years few misconceptions have been generated regarding the practice of pathology. Most importantly, 1) Autopsies formed the bedrock of practice of pathology. Hence, pathologists were considered as 'inquisitors' with basic aim to unearth and publicize mistakes of clinical colleagues. 2) Academicians have over emphasized the laboratory aspect of pathology practice, neglecting completely their clinical role. 3) Rapid advancement in biotechnology has churned out data from the research laboratories, which is confusing the clinician. This has once again brought pathologists back to their role as 'patient-advocates' 4) Role of pathologist in planning different investigations, interpreting the results, especially where essential internal quality control measures have been undermined by the working within laboratory premises.

Practice of medicine, now is not solely based on patient's history and physical examination. Laboratory and imaging procedures together form an integral part of clinical medicine practice. Change is always difficult. Most pathologists are secure looking at microscope. Next generation of pathologist needs to understand, pathology as a branch was formed on the basis for quest for more knowledge, and better understanding of the mechanisms underlying various disease processes. It is time we looked beyond microscopic vision. Face of pathology is changing as fast as its disciples can keep up. Pathologists face many challenges, especially in the new era of molecular testing and precision medicine. It is indeed difficult for pathologists to change their basic skills to adopt new technologies and new ways of performing tests. Pathologist must leave the laboratory and interact with entire patient care team to ensure the best possible treatment for the patient and even when seated at the microscope, might be digitally viewing samples from across the world. Communication will be important sort after skill in pathologists. Most rewarding aspect of pathology is the ability to interact with multidisciplinary team on so many different topics. On-going evolution of the discipline, and the way it brings people together is invaluable to one experience.

It is important that pathology services need to be centre of attention, attracting young talent, who in turn bring new perspective into translation research. So far pathology has been cost-effective modality to arrive close to clinical interpretations. With new technologies and increased cost of treatment, patients should be willing to shell out price of quality incurred for diagnostic test. Most of the pathologist educated in traditional methods, find molecular biology a bit of a black hole. Being closer to patients than basic science researchers, pathologists have greater advantage of reaching out and make changes to the way molecular testing is done. They are due for recognition they deserve. Young pathologists have started accepting the challenges associated with making diagnosis using all the new testing and technology available to them. In future, pathologists job will involve gathering variety of information- morphology, immunology, molecular data, imaging – and provide it to clinician so that they can make appropriate treatment decisions. They need to spend lot of time in interdisciplinary clinical boards, complete scientific projects and attend mortality meetings. In summary, the average pathology graduate need to have strong scientific background, training across almost all areas of medicine and entrepreneurial mind set.

Creating a diagnostic business is nothing but one way to deliver customer defined value. Diagnostic industry includes research and academics (Science, biology, medicine), as part of healthcare delivery system. Pathology as a discipline has

unique advantage of catering curiosity of biomedical researchers, gaining confidence of clinical colleagues and understands the suffering of patient. This should fascinate 'Patho-preneurs' by the possibility of combining research and clinical diagnostics. But, greater challenge is to balance scientific productivity with the business of pathology. Collaboration is the key; no one can be a better catalyst in healthcare reforms than pathologists.

Most of the present good pathologists are so involved with academic practice, they don't know how to adapt to fee for service medicine. Diagnostic work needs to be complimented with research wings within clinical laboratories. They need to split their 'Job-Time' to acquire new knowledge, and act as transformed manager of testing facility to provide services of powerful diagnostic methods. Pathologist uniquely poised to change promise of new technology into practice realities. Resource rich organizations need to share their philosophy, and spend time with young pathologists, mentor their aspirations and generate curiosity to contribute to back to society. We need to work towards making pathology as one of the most scientifically productive and cost effective departments in healthcare system. Pathology departments needs to realize that we live in an entrepreneurial society, hence should create entrepreneurial pathologists (Patho-preneurs). The survival of the 21st century pathologist will require the ability to adopt and change practice according customer value. In a value based care, there is need for cultural change to enable the next generation pathologist to be the expert in diagnostic medicine. Next generation of pathologists needs to be taught, how to run the service line, and not just individual laboratory. They need to be exposed to multidisciplinary team of surgeons, oncologist, pathologist, molecular biologists, chemists, computational biologists and biostatisticians. Pathologist bring with them a relentless effort and focus, informed view, open mind and genuine sense of purpose. Training pathologists to partner with clinical colleagues, to effectively and succinctly communicate patient data (genomics and informatics), simple tests will minimize the risk of future complications, poor health and higher costs. Effective test utilization by pathologists to manage blood products, patient's safety and quality assurance is critical in healthcare delivery system. This is a good sign for healthcare business and diagnostic industry.

Being an entrepreneur one can learn the monetary value and that could make one a better doctor with ethics and in the end patients are beneficiaries. The goal should be to graduate students with entrepreneurial mind set who can cater customer defined value in whatever form they decide to do it, including starting and running a business model. Entrepreneurship can hone three essential characteristics of a pathologist.

i. ***Focus*** – Medical students often enter school with genuine passion. Entrepreneurship can give them vision to perceive their dream and experiment with their ideas.

ii. ***Perseverance*** – Number of Top students opting for medicine is constantly declining. They know physicians face constant grind of night shifts and never ending exams and pressure of litigation. Through entrepreneurship, they can be on a mission and get rewarded for an effort in projects.

iii. ***Purpose*** – Direct interaction with patients in clinical research work can provide them daily dose of purpose, and set a realistic goals.

However, there are recognized dichotomies that exists between entrepreneurs and graduates in pathology. Entrepreneurs are generally risk-seeking whereas pathologists are risk averse, rebellious Vs obedient, impatient vs. patient, imaginative vs. "imaginectomy" and scale-driven vs individual driven. The first four splits appear to widen further as one practices, both because of decreased opportunity with golden handcuffs by clinical colleagues and decreased tolerance for diagnostic errors in the clinic or operating room. With corporate hospitals there is no room for "Lean Doctor". Despite these general differences, pathologists can fix the broken parts of the healthcare system. This could be process innovation, experience innovation or analytical tools to lower cost and improve outcomes. Innovation should be described and measured by technology transfer metrics (patents, licencing revenues), experiments with new technology, learning and knowledge transfer opportunities. Going to medical school can impart many vital pieces of knowledge from critical thinking skills and pathology of disease to healthy –living practices and most importantly saving the lives. In summary, medical schools should bring in innovative processes of effectively conceptualizing, implementing and studying ways to improve the healthcare delivery in clinical practice.

i. Eliminate policies that discourage faculty-industry collaboration

ii. Give faculty promotion and tenure recognition for mentoring students/residents in innovative projects and entrepreneurial accomplishment

iii. Hold every student accountable for innovative research and entrepreneurial mind-set

iv. Transform research grants into seed funding, asset investment , and training

v. Hire outsiders to develop, promote and work collaboratively for technology transfer and outsource the function

6. POINT-OF-CARE TESTING

Information technology has changed the service industry. Physician and patient alike are so much dependent on laboratories; they want results in real quick time. Goal of laboratory is to provide immediate, convenient, and easy-to-use diagnostic testing that shortens the therapeutic time. POCT and real-time assessment of patient data represent a new frontier in the application of medical technology and a new opportunity for pathologists. It fulfils the objective to provide rapid diagnostic information that permit immediate management decisions. In coming years, new devices should enable seamless, real-time capture of patient data collection, analysis, and evaluation to determine new approaches to improve patient safety, satisfaction and not to mention clinical outcomes. Increasing demand and need, now POCT is being used at major university medical centers, hospitals, clinics, physician offices, pharmaceutical clinical trial sites. Beyond home glucose testing, other POCT in the home will be a major growth segment to support management of chronic disease. It is expected that the next phase of POCT will be lab-on-a-chip (combining several analytical methods on single micro-fluidic and nano-technologies).

As per CLIA-88 criteria, POCT can be designated as waived or non-waived testing. In general POCT- Coordinators and Laboratory directors have preference to waived testing. The reason is attributed to decrease in regulatory and oversight requirements, particularly for labs performing waived testing under a certificate of waiver or a certificate for physician provided microscopy and not accredited by regional agencies. As per FDA, POCT fall under the category of in vitro diagnostic products. Devices intended to be used at home are referred as 'Over-The- Counter', and these are categorized as waived tests by the FDA. However, use of these devices in hospital environment raises concerns of validation. Such concerns can be only addressed by all stake holders (healthcare professionals, manufacturers, regulators, and standards organization) through 'Fit-for-Purpose' and meaningful discussions. Stakeholders need to work towards a) a desire to improve the patient care b) Eliminate problems caused because the laboratory cannot improve TAT c) Overcome problems experiences with laboratory process that prove difficult or impossible to improve. d) To ensure that the quality of POCT is of the same high standard as those tests performed in the laboratory. This undoubtedly will result in new guidelines, standards for evaluation and performance of POCT devices. If executed properly, there are benefits of point-of-care testing, like a) Positive patient identification b) Reduced test and therapeutic turnaround time c) Elimination of issues related to phlebotomy, centrifugation, volume of blood collected, and transportation. Current quality laboratory systems need to be more patient centric approach. Concepts of centralized laboratory/ referral laboratories were developed to suite requirement of diagnostic industry in late 60's or early 70's. Changes in instruments, technology, and methods have enhanced the capabilities of diagnostic industry.

POCT technologies include meters and strips, urine chemistry strips, occult blood slides, lateral flow immunoassay devices, photometric methods, DNA/RNA-based molecular methods; and several non-laboratory methods. Development of Nano-chips and DNA/RNA – based molecular diagnostic tests will expand the POCT test menu and POCT utilizations. These varieties of analytical methods are used to measure a specific analyte such as a routine chemistry, biomarker (protein or peptide), DNA/RNA, or a pathogen. Laboratories strategies need to shift to identify disease-specific test panels, and it is necessary to the facts on evolving research. Greatest accomplishment would be when combined effort would be, when laboratories work outwards through the use of transportable, portable, and handheld instruments and test kits. Pathologists need to work along with clinicians to identify patients at risk or, once diagnosed, patient compliance with therapy or effectiveness of therapy. The primary goal in healthcare is to reduce medical errors, and this requires routine calibration and excellent agreement to definitive method in use.

7. MEDICAL GENOMICS

The field of medical genomics involves translating high throughput genetic methods to the clinic, in order to improve diagnostic efficiency and treatment decision making. Medical genomics enables to simultaneously query the diagnostically relevant set of genes in a given person for clinical decisions.

However, the main foreseeable challenge will be interpreting the clinical significance of the variants observed in a given patient, as well as their significance for family members and for other patients. The pipeline for interpreting the genetic variants is schematically shown in **Fig 3**.

More than a decade has elapsed since the human genome was mapped. This period of progression has witnessed the dramatic reduction in the cost of sequencing a human genome from US$2.7 billion for the initial human genome project to <US$1000 in 2015 (Hayden 2014). And now as we write this manuscript the DNA sequencing giant Illumina in January 2017 has unveiled a new machine that the company says is "expected one day" to order up the whole genome for less than $100. Illumina's new machine comes in two models — NovaSeq 5000 and the NovaSeq 6000. The wealth of information and cost reduction has already delivered a range of genetic research and testing options. Further lowering the cost and increased speed could not only give the testing companies a larger margin in profits but the ability to process faster and possibly bring in a higher load of customers.

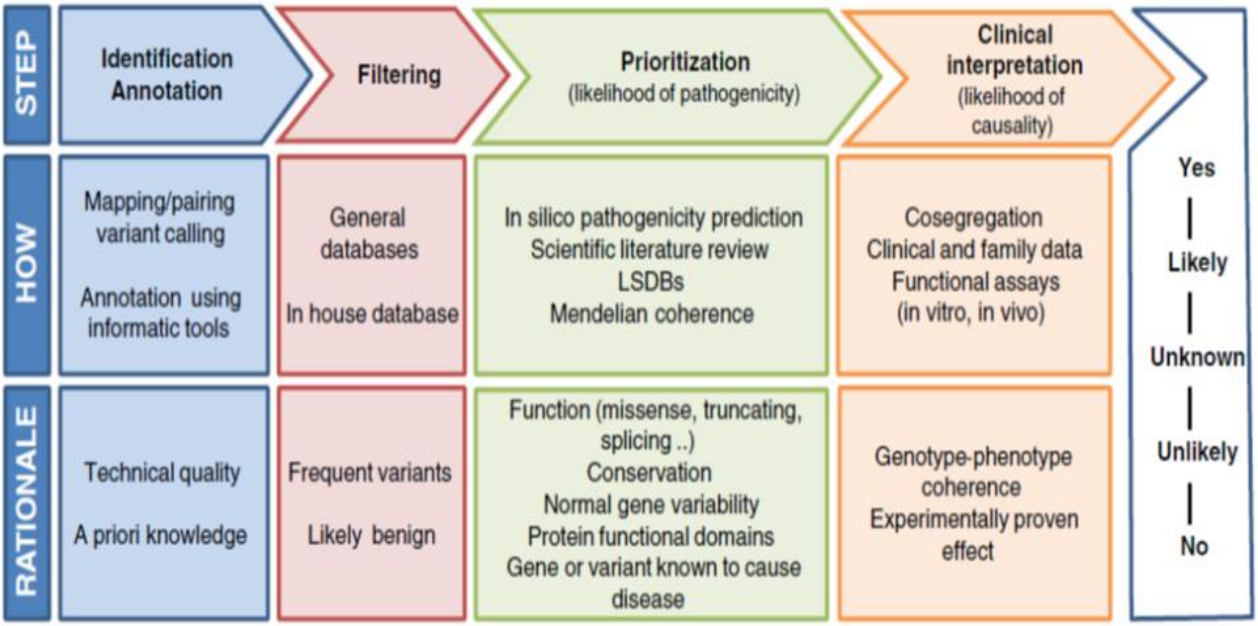

Figure 3: Schematic representation of the pipeline for the work flow for clinical interpretation of the genetic variants (B. Quintáns et al., 2014)

With a paradigm shift toward more personalization in the practice of medicine, personalized healthcare would yield promising results. Personalized health care is an emerging field and has wide-ranging implications for all the stakeholders. In the west genetic tests both monogenic and multiplex genetic profiles are being commercially offered to consumers, often without the medical professional's consultation, through the internet and are referred to as direct-to-consumer genetic tests (DTC GT) (Rafiq et al, 2015; Vlahovich et al., 2016). However in India Individuals are usually referred for genetic testing by their physicians, although there is about a 10% self-referral by patients. Moreover it is debatable as to what extent testing is affordable and accessible to the population.

Servant et al., 2014 describe the P4 medicine, which is based on a model of healthcare that is –

i) **predictive** (considering the genetic background of the individual and his/her environment),

ii) **preventive** (adapting lifestyle, taking prophylactic drugs),

iii) **personalized** (tailoring the treatment to the individual's unique features, such as the patient's genetic back- ground, the tumor's genetic and epigenetic landscape, his/her life environment) and

iv) **participatory** (many options about healthcare, which require in-depth exchanges between the individual and his/her physician).

Genomics has been extensively used to study the cancers. After more than a century since it was proposed that cancer may arise from chromosomal abnormalities (Boveri, 1914), it is now understood that cancer is a disease caused by the accumulation of mutations occurring in critical genes (oncogenes and tumor-suppressor genes) and resulting in the alteration of key molecular pathways. The intrinsic complexity of cancer and its heterogeneity (each tumor being genetically unique) render this pathology as a prime target for P4 medicine approaches. The last decade has witnessed the development of high-throughput technologies such as microarrays and next-generation sequencing which paved the way

to personalized and precision medicine especially in the field of oncology. The progression made in precision oncology is depicted in Fig 4.

Although there is great promise in the benefits to be obtained by analyzing cancer genomes, numerous challenges hinder different stages of the process, from the problem of sample preparation and the validation of the experimental techniques, to the interpretation of the results.

The development of Next Generation Sequencing (NGS) has not only helped identify genetic variants but also, it represents an important aid in the study of epigenetics (DNAseq and ChipSeq of histone methylation marks), transcriptional regulation and splicing (RNAseq). The combined power of such genomic data provides a more complete definition of 'cancer genomes' (Vazquez et al., 2012).

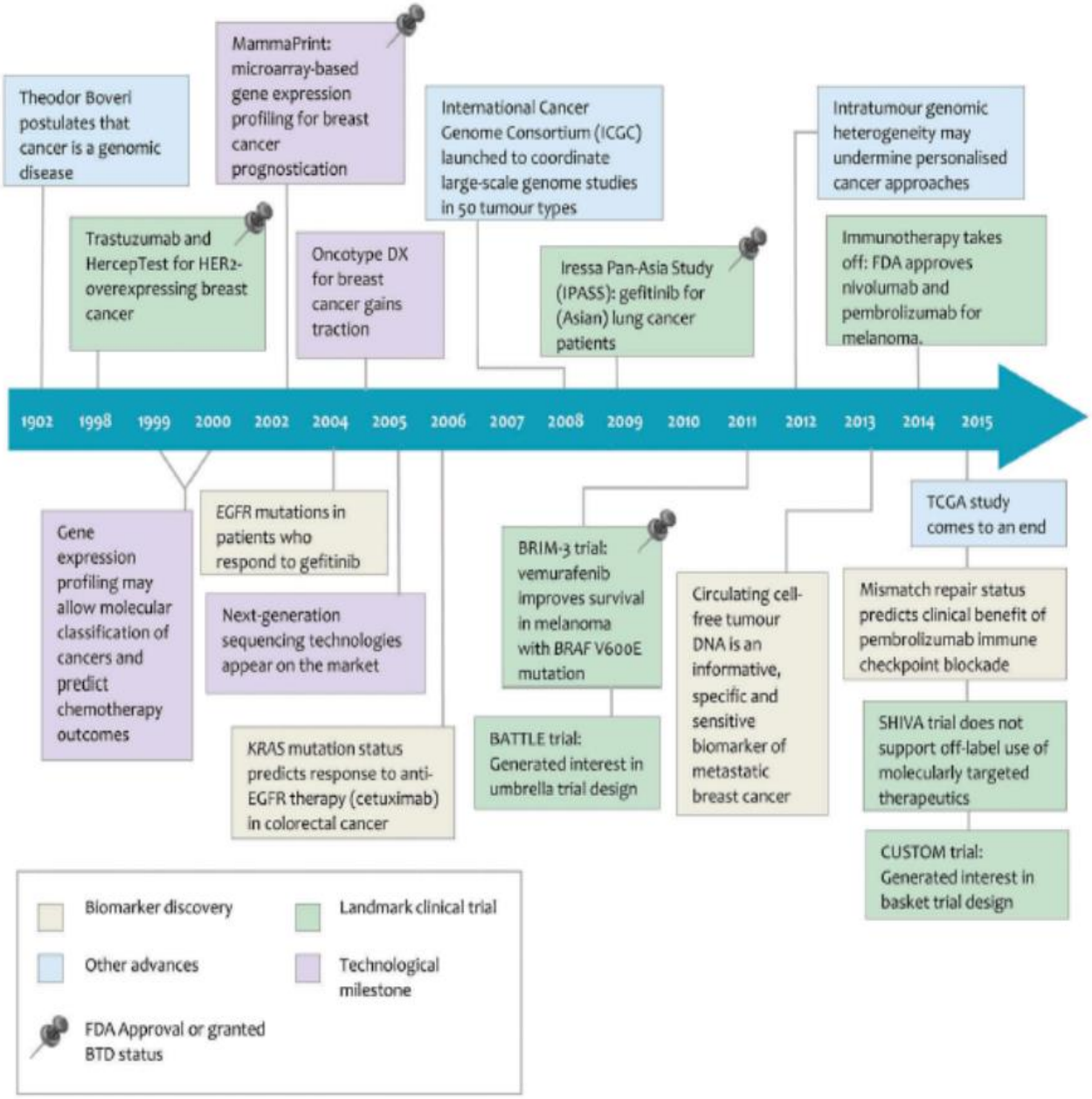

Figure 4: Progress in precision oncology. Although personalized cancer therapy is still in its infancy, a number of pivotal lessons gained over the past two decades have helped to usher in new paradigms for the genomic age (Syn et al., 2016).

The newer technologies to sequence the genome have been able to generate an overwhelming amount of data and the field of oncology has entered the so-called big data era as the particle physics did several years ago. Servant et al., 2014 describe the 4 V's perspective of the big data (Volume, Variety, Velocity and Value) where a large volume of patients'

data is being created across various databases which is increasing at huge velocity, while to extract value from this big data a lies the challenge. Building of an efficient health-informatics comprising of both informatics and bioinformatics architecture is the challenging bridge that needs to be built and crossed to enable querying and the easy retrieval of any data that might be useful for therapeutic decision in real-time thus allowing clinicians to propose the tailored therapy to the patient in the shortest delay.

Nevertheless, the large number of studies has helped to comprehensively characterize the molecular landscapes of large numbers of tumour samples and some themes have emerged from these large-scale molecular profiling studies (Syn et al., 2016) mostly highlighting the complexity of cancer pathology, a few of them are listed below -

i) ***Convergence of cancer types:*** Several distinct cancer types converge into common subtypes. For example, a multi-platform analysis of 12 cancer types found that lung squamous cell, head and neck, and a subset of bladder cancers coalesced into one subtype defined by TP53 alterations, TP63 amplifications and enhanced expression of genes involved in the proliferation and immune pathways (Hoadley et al, 2014). Nevertheless this also highlights the potential for pathway-driven roadmaps to cancer classification and treatment.

ii) ***Cancer fro same organ represent heterogeneous groups:*** This theme is based on the fact theat that cancers originating from the same organ site may represent a heterogeneous, divergent group of tumours with different underlying genomic alterations. It appears to be paradoxical with the earlier theme. For example, gastric adenocarcinoma is thought to comprise four molecular subtypes: (1) chromosomal instability (CIN), characterized by high levels of aneuploidy, focal genomic amplifications & deletions, and TP53 mutations; (2) microsatellite instability (MSI), with elevated mutation rates (~50 mutations per megabase); (3) genomically stable (GS), which are associated with diffuse type histology, RHOA hotspot mutations or structural variants affecting the RHO-family GTPase-activating proteins; and (4) Epstein-Barr virus (EBV), which is associated with recurrent PIK3CA mutations, the highest levels of global DNA methylation, and PD-L1, PD-L2 and JAK2 amplification (Bass et al., 2014).

iii) ***Mutational signatures associated with exposures:*** Mutational signatures in cancer genomes can provide major leads into biological processes which initiate and are operative during tumorigenesis, such as specific carcinogenic exposures opening new possibilities for preventative, diagnostic and therapeutic approaches. For example, through an analysis of almost 5 million mutations from 7,042 cancers, 20 distinct mutational signatures were identified, including those associated with the APOBEC family of cytidine deaminases, age at diagnosis, ultraviolet (UV) exposure, smoking and DNA maintenance (Alexandrov., et al., 2013).

iv) ***Mutations in non-coding regions:*** **The** profound ways in which non-coding regulatory variants may contribute to cancer development is now being recognized. Although many pathogenic mutations have been identified in protein-coding regions, which spans 1–2% of the human genome, ~80% of DNA sequence is assigned some sort of biochemical functionality by the ENCODE (Encyclopaedia of DNA elements) project (Bernstein et al, 2012). With stronger bioinformatics tools to aid in its identification as well as increased motivation to search for cancer-causing mutations outside of protein-coding regions, a number of likely disease- causing, non-coding recurrent mutations have been described.

v) ***Intra- and Inter-tumoural heterogeneity:*** A great deal of intra- and inter-tumoural heterogeneity exists, which may pose an obstacle for precision medicine as clonal diversity and genetic heterogeneity is associated with therapeutic resistance and poorer outcomes (Nik-Zainal et al., 2012 and Almendro et al., 2014). Gerlinger et al., 2014 found that 63% to 69% of the overall mutation spectrum was not detected in every tumour sample, including mutations in the mTOR kinase, multiple tumour suppressor genes, SETD2, PTEN and KDM5C. This intra-tumoural heterogeneity may lead to underestimation of the somatic genomic landscape as portrayed from single biopsy samples

7.1 Liquid biopsy:

To fully enable P4 medicine it is desirable to follow the molecular makeup of a patient's tumor longitudinally through an easily accessible, minimally invasive method. Additionally tissue scarcity is a real challenge inhibiting the molecular classification of tumours to guide precision treatment.

Moreover, to enable appropriate therapeutic reassignment repeat biopsies are necessary to monitor the tumour evolution over time, while their invasiveness with potential morbidity make it impractical to apply routinely. Hence, Liquid Biopsy approach presents itself as an appealing solution where the genetic makeup of the tumor can be assessed through a

biofluid sample (serum, urine, saliva and malignant effusions or ascites), whereby samples are derived from less-invasive procedures and used as surrogates for traditional biopsies.

Tissue biopsies pose some challenges as described above and to overcome these challenges less invasive techniques capable of capturing tumor heterogeneity and the molecular changes cancer cells undergo either during disease progression or when they are exposed to therapy are needed (Murtaza et al., 2013; Diaz et al., 2012 and Mattos-Arruda et al., 2013).

Circulating tumor DNA can in principle provide the same genetic information as a tissue biopsy necessary to interrogate key companion diagnostics. Accessing the bloodstream has clear advantages (Diaz and Bardelli, 2014)-

i) It is a source of fresh DNA, unhampered by preservatives.

ii) Sampling the blood from a needle stick is minimally invasive and avoids the dangers of biopsies.

iii) Blood can be drawn at any time during the course of therapy and allow for dynamic monitoring of molecular changes in the tumor rather than relying on a static time point.

iv) Investigating plasma from patients can account for molecular heterogeneity, because ctDNA fragments are collected from all tumors in a patient's body through circulation

Circulating tumor DNA fragments contain genetic defects identical to those of the tumors themselves; these DNA alterations span the types of genomic alterations identified in the tumor and include

i) Point mutations (EGFR and KRAS),

ii) Rearrangements (EML4-ALK),

iii) Amplifications (HER2 and MET),

iv) Aneuploidy

The current evidence suggests that ctDNA likely represents a molecular proxy of the overall disease, however more studies are needed to understand the conditions under which the multiple metastatic lesions located in different organs shed ctDNA homogeneously. The sensitivity of these liquid biopsies for patients with stage IV disease seems to be approaching 100% (Diehl et al., 2005; Diehl et al., 2008; Higgins et al., 2012).

Table 1: Comparison of the analysis capability of CTCs, cfDNA and exomes (Brock et al., 2015)

Analysis Capability	Examples	CTCs	cfDNA	Exomes
Mutations	Point mutations, InDels, amplifications, deletions, translocations	YES	YES	YES
Epigenetic modifications	Methylation patterns	YES	YES	YES
RNA transcription profiles	Levels/activity of mRNA, Micro RNA, Long non coding RNA, RNA splice variants	YES	NO	YES
Phenotypic studies of cells from the tumour	Cell morphology, protein localization, *in-vivo* studies	YES	NO	NO
Inflammatory response, stromal and other systemic changes	Inflammatory RNA and protein markers	NO	NO	YES
Analysis of RNA as well as DNA and Protein profiles from cells	Separate or in combination	YES	NO	YES
Can utilize biobanked samples	Frozen plasma, urine and other bio-fluids	NO	YES	YES

CTCs=Circultaing tumor cells; ccfDNA= cell free DNA; InDels= Insertions/deletions

7.2 Neonatal Medicine:

Another most successful application of genetic testing has undoubtedly been in the field of newborn screening, aimed at identifying treatable conditions.

Over 4000 Mendelian disorders are known to have a genetic etiology at present, and a significant fraction of these present in the perinatal period with one or more of these clinical presentations.

Clear estimate of the burden of genetic diseases presenting in the 1st month of life might be difficult, however, it is remarkable that over 800 genetic disorders have been catalogued in the *Online Mendelian Inheritance in Man* presenting in the newborn period (www.omim.org). Hence, a molecular diagnosis could play a significant role in not only assessing the recurrence risk for families, but also on providing appropriate medical care and health intervention for the newborn. Understanding the basics of the multitude of genetic tests that are currently in place is therefore critical for the healthcare providers, and requires that they be familiar with the fundamental genetic concepts to assess children suspected to have inherited disorders (Lalani, 2016).

There are now thousands of single-gene disorders that are well characterized, with several being recognized in the neonatal period, such as cystic fibrosis, phenylketonuria, spinal muscular atrophy, congenital adrenal hyperplasia, Stickler syndrome, CHARGE syndrome, osteogenesis imperfecta, RubinsteineTaybi syndrome, and Noonan syndrome (Lalani, 2016). These single-gene disorders, also called monogenic disorders, occur as autosomal dominant, autosomal recessive, or X-linked disease. These disorders are routinely diagnosed by analytes, biochemical assays and/or DNA-based studies.

Most states in the USA have mandatory newborn screening for at least 29 primary conditions and 25 recommended secondary targets (with opt-out policies for parents), following the recommendation by a newborn screening expert group convened by the American College of Medical Genetics (ACMG NSEG 2006)

While the application of cytogenetics and molecular cytogenetics has been pivotal in the evaluation of newborns with suspected genetic diseases, DNA-based sequencing studies have been equally important with groundbreaking and innovative utility in newborn evaluation.

Mendelian disorders, such as spinal muscular atrophy, congenital muscular dystrophy, congenital sensorineural hearing loss, and polycystic kidney disease in newborns, have traditionally been evaluated by single-gene DNA sequencing studies or gene-panel evaluation. The emerging newer technologies like the next-generation sequencing (NGS) are now increasingly being utilized in neonatal intensive care setting for rapid genetic diagnosis (Reardon, 2014 and Bhattacharjee et al., 2015). Collectively, the 180,000 exons (termed exome) only account for about 1.5% of the human genome, but they contribute to 80 to 85% of all the known disease-causative variants. Several studies have demonstrated the utility of whole exome sequencing (WES) in critically ill neonates with genetic disorders, providing prompt diagnoses for personalized care (Lalani et al., 2014 and Willig et al. 2015).

7.3 Challenges for Implementing Ngs To Clinical Setting:

In the past, comprehensive sequencing of large genomic areas, such as whole genome and exome sequencing, was prohibitive for most clinical laboratories because of the associated cost and complexity. In the recent years, several factors, such as improvement in NGS technologies, appearance of more manageable and affordable bench-top sequencers, onset of several target capture technologies and decrease in the cost of the computing power, have resulted in widespread acceptance of these technologies. In addition, genome sequencing is an integral part of precision medicine which has generated immense interest and governmental backing in recent years (Burki et al., 2015).

Although sequencing the genome to detect genetic aberrations for theranostic purposes is the hallmark of targeted therapy or precision medicine (Singh et al., 2016), it poses some challenges for implementation of NGS in clinical diagnostic laboratories. The Advantages and challenges of implementing clinical NGS Testing in a clinical molecular diagnostic laboratory are summarized in Table 2 (Singh et al., 2016)

The discovery of genetic aberrations and their establishment as prognostic and predictive markers of diseases has been greatly enhanced and enabled by NGS. However the implementation of NGS assays developed in a research setting often need extensive validation and substantial modification for use in the clinical laboratory before they become routine diagnostic tools.

The advantages associated with the NGS in comparison with earlier (first generation) sequencing technologies, are progressively making the NGS platforms a preferred choice in the clinical diagnostic arena. While, more efficient and powerful third-generation technologies, such as Oxford Nanopore, DNA transistor technologies from IBM and electron microscopy-based techniques, are expected to further revolutionize genome sequencing (Singh et al., 2016). It is expected

that these novel technologies would make massive parallel sequencing of the genome on a larger scale more feasible and a routine with a potential to drastically change clinical genomics beyond the current NGS technologies.

Table 2: Advantages and challenges of implementing clinical NGS testing in a clinical molecular diagnostic laboratory

CLINICAL NGS TESTING	
ADVANTAGES	**CHALLENGES**
Simultaneous screening of multiple markers with a single investment of nucleic acid	Through validation of the research use only NGS technology before implementation in the diagnostic laboratory
Multiplexed screening of several samples simultaneously	Careful selection of the gene panel content, target enrichment and sequencing technology is necessary to suit the tumor and sample type, and sample volumes expected in the laboratory
Scalability to accommodate wide range of genomic areas, umber of gene markers and samples	Adding novel gene markers to the validated and implemented gene panels
Compatibility to wide variety of sample types (fresh, frozen, FFPE, fine needle aspirate, smears, cytology)	Work flow, data analysis and clinical reporting complexities
Simultaneous screening of multiple genomic aberrations like single nucleotide variants, multi-nucleotide variants, insertions/deletions, copy number variation and gene fusions	Rapidly developing technology results in frequent upgrades which warrant revalidation before implementation
Highly sensitive and quantitative mutation detection	Still evolving criteria for clinical reporting and reimbursement

Ref: Singh et al., 2016

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