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Molecular Diagnostics, Medical Genetics and Clinical Chemistry Laboratory – The Integrated Diagnostics

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Abstract

Introduction: Molecular diagnostics, lab diagnostics and medical genetics in laboratory medicine are the new gateways for advancement. Slowly and steadily this stream is gaining momentum and reflected upon the wide use of Reverse transcriptase polymerase chain reaction in the diagnosis and management of COVID pandemic. The making of DNA vaccines, point of care diagnostics, telemedicine, miniaturization, noninvasive, cost effective solutions are making health care access and bettering lives of people.

Method: The internet was widely searched using key words, phrases. Various databases were checked and new information related to advancements in molecular diagnostics, innovative strategies, new advancements studied in details and analysed. Deep neural networks connection made with related content, explored the use of nanotechnology and microfluidics in medicine. Artificial intelligence, machine learning, is pervading the way we work and it has taken over the health care industry in a big way.

Results: Regression analysis, predictive models, analysis and synthesis of new ways ahead is the order of the day. Extrapolation of data to forecast the future trends, disease diagnosis with personalised medicine and genetic methodology, genetic engineering like stem cell therapy, chimeric antigen receptor therapy, crisper CAS 9 technology, are marking a new era in the way of life.

Conclusions: Combining various disciplines like computer science, engineering, medical sciences, data analytics, digitalizations are creating more opportunities, making lives easier, hopefully for a bright future.

Keywords: Covid; Molecular; Generation; Sample; Laboratory; Ionization; Technology; Diagnosis

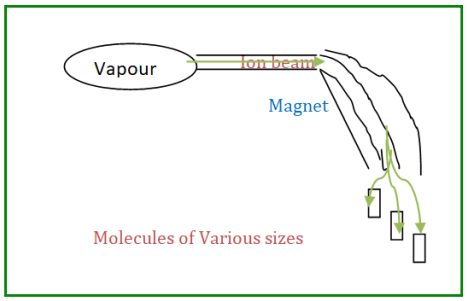
Abbreviations: MALDI: Matrix Assisted Laser Desorption Ionization; MOM: Multiple of Median; POCT: Point of Care Diagnostics; RTPCR: Reverse Transcriptase Polymerase Chain Reaction; LAMP: Loop Mediated Isothermal Amplification; CRISPER CAS: Clustered Regularly Interspaced Palindromic Repeats; ISS: In Situ Sequencing; NMR: Nuclear Magnetic Resonance; HDX: Hydrogen Deuterium Exchange; TSMS: True Single Molecule Sequencing.

Introduction

Mass Spectrometry measures the constituents of protein or nucleic acid depending on the mass to charge ratio. Volatile substance is introduced in an electric field that ionizes the large molecule, then a magnetic field is applied and the ion is deflected at 90 degrees and the time taken for the ion to hit the detector is measured and used to determine the nature of sample present.

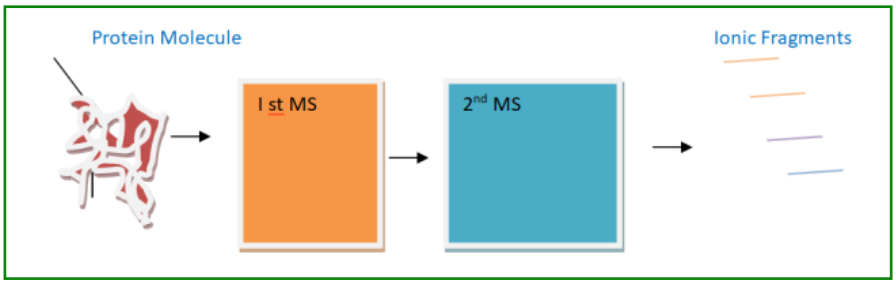
Here the protein or nucleotide molecule is broken into smaller fragments by electrospray ionization that will not destroy the molecule but make it ionized for detection.

Another method of dispersion of molecules is Matrix assisted laser desorption ionization (MALDI) .Here sample is mixed with a light absorbing dye and a source of protons. Then a laser beam is used causing the matter to disperse into a gas phase.



Mass Spectroscopy

Tandem Mass Spectrometry – here two mass spectrometers are used sequentially, one separates peptide on their mass, then in the second MS they collide with argon gas and broken into smaller ions. The parent ion mass and daughter ion mass are detected by their mass spectrum. It can be combined with cheromatographi techniques. USES include protein, drug detection, pesticides, pollutants, screening of inborn errors of metabolism including organic acidurias.



Tandem Mass Spectroscopy

Interpretation of Laboratory Data

The values obtained from a sample and reported in a clinical biochemistry laboratory depend on the assay method, technique and analyzer used. The biological reference interval is a range of values from the population that is healthy. The different range in case of children, adult and old age may vary. Physiological variations can result from gender difference or difference states physiological and time variations. There can be subject based variation like in the same individual at different times ie, intra individual and inter individual variations. The observed value and reference values are written on the same sheet, the test requisition form for comparison and clinical decision making.

Prenatal diagnostics like beta human chorionic gonadotropin, estradiol, vary with the period of gestation. They are reported on reference values obtained on weekly basis of gestation. They are reported in multiple of median (MoM) values. The decision to continue or terminate pregnancy is based on the MoM value which is obtained by dividing the test result by the median of the relevant gestational week. This is a typical example where reliable reference range is crucial for clinical decision making.

Molecular Diagnostics

Molecular Diagnostics is the study of genomic variants for the purpose of detection, diagnosis, prognosis, innovation in treatment and management strategies. It is a complex interplay of medicine, genomics, and laboratory medicine to finally promote personalized medicine, precision medicine and integrated medicine. Molecular Diagnostics was discovered by Mendel.

Next generation sequencing and genome wide association studies, detect single nucleotide polymorphisms, single nucleotide variations, restriction fragment length polymorphisms.

Q PCR has great advantage over PCR in that both amplification and quantification can be done at the same time. There is less chance of contamination as the entire process of amplification plus quantification is done in the same tube.

Molecular Diagnostics are coming in trends for point of care diagnostics (POCT). In the latest development, reverse transcriptase polymerase chain reaction (RTPCR) and loop mediated isothermal amplification (LAMP) are being used in POCT. Integration of wireless data transmission with smartphone based platforms for POCT enable real time disease monitoring and disease detection.

Microfluidics and nanotechnology based systems are coming into vogue. They can be used to target drug delivery system to access remote corners of inaccessible tissues of the body [1].

CRISPER CAS (Clustered Regularly Interspaced Palindromic Repeats) gene editing technology has the potential to alter ones genetic makeup and can be used for treatment and drug discoveries. But it has the potential for oversensitivity, false positives and specificity and ethical concerns regarding gene editing.
Regenerative Medicine uses stem cell therapy, somatic cell

or adult cell therapies, tissue engineering and gene therapy. It applies that the damaged tissue, organ or function can be cured only by a few healthy cells of our own body.Vaccine development and the novel strategies are targeting cancer and infectious diseases. Vaccines being produced today have greater potential for boosting immunity in view of newer pandemics. The m RNA vaccines have already shown quicker response, greater flexibility, quick generation time, and efficacy during COVID pandemic [2].

3D Printing and artificial organ transplantation are new research work arenas in the field of medicine where molecular diagnostics hold great promise. New tissues and organs with semblance to actual functioning of human organs are in process of making either with synthetic polymers or biological tissues. Wearable organs have the potential to prolong life and quality both. Skin grafts, liver, kidney, heart artificial organ transplant can treat many communicable and noncommunicable diseases.3D Printing has made possible artificial orthoses, prosthesis, surgeries with improved outcomes.

Telemedicine such as that over mobile phone, video conferencing, using robotic technologies and molecular diagonostics can access people far and wide at lower costs and better utilization of resources.

The newer technologies by Mass spectrometry and Fourth generation sequencing technologies are operating to identify the sequence of the genome with lower cost and increased productivity and efficiency. The minutest atom or molecular and even smaller quantum mechanics are being used to explore the vast array of promise that still remain unearthed in technology utilization.

The POC devices and biosensors can be potential technologies to enhance the platform of molecular diagnostics. Proteomics, aptamer, peptide based biosensor technology can provide more specificity and sensitivity in covid diagnostics and detecting newer pandemics or outbreaks [1].

Equipment management, management of personnel, resources, training, cost effectiveness and reproducibility are some of the areas need to be focused for optimum implementation of technology [2].
New research on omic technology, epigenomics, proteomics, pharmacogenomics, metabolomic technology. Current technology related deep sequencing and genome wide association studies enhance the study of inherited genetic diseases detection and testing, non invasive prenatal diagnostics. New technology also encompasses hand held and easy to operate point of care tests for molecular testing, biomarker development to enhance personalized medicine. Development of molecular tests for assessing and improving prognosis of patients and regulatory, ethical and payor considerations in molecular diagnostics and advancements in technology [3].

Molecular diagnostics play a central role in detection of infectious pathogens and diseases especially in the covid era. They can detect low levels of pathogen in a short time more accurately thus improving sensitivity, specificity, automation, waits times. The techniques of next generation sequencing, isothermal sequencing, third generation and fourth generation sequencing, gene chip therapy, high throughput sequencing, single cell RNA sequencing method, laser assisted microdissection of cells is a technique to capture cells by visualizing directly under the microscope [4].

Some new techniques employ sequencing of serial consecutive section in different directions and then analysis by computational extraction of spatial expression patterns. In situ sequencing (ISS), ish, spatial transcriptomics employs both in situ and ex situ identification of Some ethical and data confidentiality concerns have to be regulated in field of molecular diagnostics.Mass Spectrometry is able to decipher the structure of proteins when combined with or without other techniques like Nuclear Magnetic Resonance (NMR) Spectroscopy and X ray crystallography, hydrogen/deuterium exchange (HDX), limited proteolysis, and chemical crosslinking (CX), these techniques are used to analyze protein structure and dynamics.

First generation DNA Sequencing method or the Sanger method is used for method validation purposes only as it is costly, uses DNA synthesis technique, using the dideoxyribonucleotides for chain termination of sequences. Next Generation Sequencing Methods have a lot of application and usefulness over Sanger sequencing. A number of genes can be sequenced simultaneously, massive throughput, generating a number of short reads in parallel, high speed and low cost. Sequencing techniques are classified in 2 ways, sequencing by hybridization and sequencing by synthesis. This process works without separating the sequencing reaction into lanes, capillaries or tubes. Billions of genes can be sequenced in slide surface of glass or beads. The reads generated by NGS technique range from 50-300 nucleotides. The reaction mixture contains DNA Polymeras, dNTPs with base specific fluorescent markers and primer. This has wide applications in research, environmental, medical, genetics and agriculture. Steps of DNA sequencing are DNA extraction, library preparation, sequencing, bioinformatics data analysis, clinical implications, and evidence.

3rd generation sequencing techniques include single molecular sequencing and true single molecule sequencing (tSMS). These techniques need less DNA to start with and

require no amplification; they require less time and generate long reads.

4th generation sequencing techniques , also called in situ technology,incorporate nanopore technology where no amplification and repeated cycles are required and sequencing can be done from fixed cells and tissues. Nonpore technology, most popular 4th gen platform allows electrical field to force a molecule through a 2nm diameter. It is ultra fast, whole genome sequence can be done in 15 minutes. Major challenges include managing quality, sequencing workflows, sequencing data handling, and analyzing. Once these hurdles are overcome it will pave the way to personalized medicine.

Conclusion

Molecular diagnostics in combination with novel technologies like next generation sequencing, third generation sequencing, fourth generation sequencing, nanotechnology, artificial intelligence, machine learning recent advances in genetic methodology with the omics approach like metabolomics, genomics, proteomics, and epigenomics will lead the way to develop more cost effective, efficient, resourceful and useful products and services for mankind. The growth is intended for betterment, sustainability and productivity.

The CRISPER (Clustered regularly interspaced short palindromic repeats) CAS technology has paved way for gene editing and drug development to progress medical science. Aptamers are artificially made small oligonucleotide or peptide sequences that target specific DNA or RNA of interest [2].

Nowadays lab diagnosis and testing is increasingly becoming user friendly and available at home or with mobile devices. These are used to conveniently and non invasively monitor and test a range of parameters. Diseases that were previously incurable are increasingly becoming sorted and manageable.

Cell free DNA based blood test and molecular testing is also used to diagnose and cure diseases. Mitochondrial DNA based transfer and prenatal detection and diagnosis of diseases with a hope for cure for diseases such as Down's syndrome by genetic replacement therapy are subject of ongoing research [5-10]. Vaccine development for prevention and increasing immune response to pathogens for various incurable diseases is also part of molecular diagnostics and research.

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