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Association of Clinical Biochemists of India

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Biochem Lab East Boring Canal Road Patna-800 001 (Bihar) kpsacbi@yahoo.co.in

FEBRUARY 2021



MODERATOR

Praveen Sharma Professor Biochemistry AIIMS Jodhpur



Barnali Das Consultant Biochemistry & Immunology Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute, Mumbai

In Quest of Laboratory

Management Reform: Lean-

Six Sigma Holds The Key

Aditi Gupta Lead Consultant Biochemistry Aster Labs, Bengaluru

Demystifying the role of

IQC and EQAS in Clinical

Laboratory Medicine

SPEAKERS

Saantwana Vernekar Founder & Chief Trainer QTEAM, Mumbai



Six Sigma -Requirements and way ahead



Date: 5th February 2021 Time: 3 pm IST; 10.30 am CET Contact: Dr Prasenjit Mitra, AllMS Jodhpur, <u>prasy4u@gmail.com</u>, <u>mitrap@aiimsjodhpur.edu.in</u>

FEBRUARY 26th. 2021 (Exact date & Program to be confirmed)

Registration link (Scan QR code)

ACBI Webinar Undeciphering the Biochemical Conundrum of COVID-19



MODERATOR

Medha Rajappa

Associate Dean (Research), Additional Professor (Biochemistry), JIPMER, Puducherry



Dr. Narayanan

Professor (Pediatrics), JIPMER, Puducherry



Multi-System Inflammatory Syndrome (MIS-C) in Children: Is it a new entity?

SPEAKERS

Dr. Nandeesha Additional Professor (Biochemistry) JIPMER, Puducherry



Laboratory Perspective of COVID-19: A Panoramic View from the Biochemistry

Dr. Ramesh Professor (Biochemistry), JIPMER, Puducherry



Teaching Biochemistry in COVID times: A Medical Educator's Perspective

>>-0-4



We all are in this together Let us do our bit in the fight against COVID-19



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Secretariat Biochem-Lab East Boring Canal Road Patna – 800 001 (Bihar) Email : kpsacbi@yahoo.co.in

Head Office Biochem-Lab East Boring Canal Road Patna – 800 001 (Bihar) Email : <u>kpsacbi@yahoo.co.in</u>

From the Secretary's Desk

Respected Members,

Greetings from ACB Head office.

At the outset, I wish to apologize for the inordinate delay in taking out the second issue of the ACBI News Bulletin.

After the publication of the March 2020 issue, we all were engulfed by the Covid Pandemic bringing life to a complete standstill except for us at the frontline of saving life. All our association activities came to a Full Stop!! It was the Year of THE SPIKE PROTEIN ATTACK!

There was a lot of hectic parlay between the members of the EB regarding the 2020 National Conference. Ultimately, we had to reluctantly move it to December 2021. The dates will shortly be announced. After a lot of hiccups, we were ultimately successful in hosting our very own webinars from December 2020. Previous to this we had webinars & a mini conference under ACBI auspices. We shall be continuing with our webinars throughout 2021. More details are available on our website, www.acbindia.org.

This year we lost three stalwarts of our association, Dr. P.H. Ananthanarayan, Dr. Abhay Pratap and Dr. Arun Raizada, may their soul rest in peace. Dr. Abhay and Dr. Raizada to post-covid complications.

Remember, the Covid vaccine need time to prime our body...

Till then: Wear a Mask.

Maintain social distancing.

Be Covid safe.

Kan I Line

Dr. Rajiv R Sinha General- Secretary, Editor ACBI & Editor-in-Chief

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OBITUARY



Dr. Abhay Pratap, MBBS, MD, CSM, DSc, FACBI

1/07 /1948 - 01/08/2020

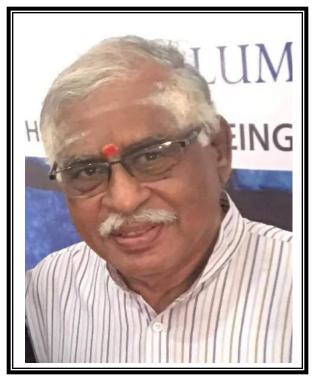
Dr. Abhay Pratap was born on 1st July 1948 in Bihar. He did his MBBS and MD in Biochemistry from Rajendra Medical College, Ranchi now RIIMS.

Dr. Abhay started his career as Biochemists in the Department of Pathology at Bokaro General Hospital, Bokaro Steel Plant. He subsequently became Consultant Biochemists and Joint Director (M & HS) & HOD Pathology at BGH from where he retired in 2019. Has special interest in Automation in Clinical Biochemistry, Quality Analysis, Interpretation and improvement in Biochemistry on which he has given numerous presentations. He was actively involved in running their private laboratory along with his pathologists wife. He leaves behind his Son, Dr. Abhijit Pratap, also a member of ACBI.

He was a life member of the Association and also the Past President of Association of Clinical Biochemist of India, President of the Jharkhand State branch of ACBI. He was an active member of Indian Medical Association and Indian Association of Sports Medicine. Dr Abhay was actively involved in the activities of the association and attended every ACBI National conference. Under his leadership, the Jharkhand branch organized 3 East Zone conferences at Bokaro, which were a resounding success. Members would remember him for his very jovial and mixing nature.

With his passing away the association has lost a very active member. On behalf of the association I extend my condolences to Abhijit and his wife on the passing away of our dear friend, philosopher and guide. **MAY HIS SOUL REST IN PEACE**.

OBITUARY



Dr. Ananthanarayanan P H

20th. September 2020

Dr. Ananthanarayanan P H, Former Director of JIPMER and Retired Professor in Biochemistry, JIPMER, Puducherry, expired on 20 September 2020. He was a great teacher, who always greeted all of us with a smile and helped everyone whose lives he touched. He was an amazing personality with immense talent in music.

He served with distinction and diginity as DGHS, MOHFW, AIIH&PH, Kolkata and at BPKIHD, Dharan, Nepal. He had the distinction of being the first JIPMER alumni to become its Director. He will be remembered for posterity for his teaching and ever-helpful nature. He lives on in his family and students, who will miss him dearly. May God grant strength to his family to bear this loss. **May his soul rest in peace!**

32-0-4

OBITUARY



Dr. Arun Raizada

12/11/1948 - 10/01/2021

Dr. Arun Raizada, did his M.Sc. in Biochemistry from Lucknow University and PhD in Medical Biochemistry from G R Medical College, Gwalior. He started his career as a researcher as Assistant Research Officer, Department of Biochemistry, P.G.I. Chandigarh from 1971 to 1974. Subsequently, he joined Lady Harding Medical College New Delhi as Senior Demonstrator and worked there till 1988. He then moved on to become the Head of Biochemistry at the Escorts Heart Institute, New Delhi. In 2009 he joined as Head, Department of Biochemistry at Medanta – The Medicity. Under his able supervision Medanta got their NABH, NABL & JCI accreditation. Prior to his untimely demise, he was rendering his service as Vice President (Quality), POCT services at Lucknow.

He was the past president of ACBI and Fellow of ACBI (FACBI). He was the organizing secretary of ACBICON 2007 at Indian Habitat Centre, New Delhi. He was actively participating in ACBI meetings and was working in various committees like Congress and Conference Division & Corporate wing. He has represented ACBI at the international associations like IFCC, APFCB and AACC. He was nominated as Director, ICHA by ACBI. He was also a certified technical assessor by NABL. He was the recipient of various prestigious awards and honors, including A. J. Thakur Award for Distinguished Services in Clinical Biochemistry and Laboratory Medicine, Health icon award-2019 for excellence in health care by UP Govt., Bharat Excellence Award 2013 by Friendship Forum of India, Bharat Jyoti Award by India International Friendship Society, Rajiv Gandhi Excellence Award.

The ACBI and Community of biochemists in India mourns on the passing away of **Dr. Arun Raizada**. His presence will be immensely missed. **We pray to the almighty that his soul may rest in peace.**

<u>Notice</u>

We want that all members should actively participate in ACBI activities and be kept informed about the programmes and activities. For this we require your correct addresses and email ID. Please check your details on the ACBI website <u>www.acbindia.org</u> and if any correction is needed, kindly download the **ADDRESS CORRECTION FORM**, fill it up and email the same to <u>kpsacbi@yahoo.co.in</u>.

ADVERTISMENT RATE in ACBI News Bulletin

		One Issue (Rs.)	Two Issues (Rs.)
1	Back Cover (4-colour)	20,000	35,000
2	Back Inside (4-colour)	15,000	25,000
3	Front Inside (4-colour)	15,000	25,000
4	Inside Page (BxW) Full Page	8,000	12,000
5	Inside Page (BxW) Half Page	4,000	6,000
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The Journal of the International Federation of Clinical Chemistry and Laboratory Medicine

Next-generation sequencing approach for the diagnosis of human diseases: open challenges and new opportunities

Chiara Di Resta^{1,2}, Silvia Galbiati², Paola Carrera^{2,3}, Maurizio Ferrari^{1,2,3}

¹ Vita-Salute San Raffaele University, Milan, Italy

² Genomic Unit for the Diagnosis of Human Disorders, Division of Genetics and Cell Biology, IRCCS San Raffaele Hospital, Milan, Italy

³ Laboratory of Clinical Molecular Biology and Cytogenetics, IRCCS San Raffaele Hospital, Milan, Italy

Key words:

Next generation sequencing, genetics, inherited disorders, causative mutations, sequence depth, coverage, incidental findings, variants interpretation, diagnostics, genetic medicine

ABSTRACT: The rapid evolution and widespread use of next generation sequencing (NGS) in clinical laboratories has allowed an incredible progress in the genetic diagnostics of several inherited disorders. However, the new technologies have brought new challenges. In this review we consider the important issue of NGS data analysis, as well as the interpretation of unknown genetic variants and the management of the incidental findings. Moreover, we focus the attention on the new professional figure of bioinformatics and the new role of medical geneticists in clinical management of patients. Furthermore, we consider some of the main clinical applications of NGS, taking into consideration that there will be a growing progress in this field in the forthcoming future.

INTRODUCTION

The next-generation sequencing (NGS) has been introduced in genomic laboratories about 10 years ago. Its impact on technological revolution has important implications in human biology and medicine [1]. After improvements in accuracy, robustness and handling, it became a widely used and an alternative approach to the direct Sanger sequencing [2,3].

The progress of NGS is leading to the increase of discovery of number of genes associated to human inherited disorders and to the elucidation of molecular basis of complex disease [4]. Moreover, since on NGS platforms it is possible to perform a parallel sequencing of different tar-get regions,

NGS is widely used in diagnostics. Recently, the use of NGS in clinical laboratories has became increasingly widespread, used in diagnostics of infectious diseases, immune dis- orders, human hereditary disorders and in non- invasive prenatal diagnosis, and, more recently, in the therapeutic decision making for somatic cancers [5-12]. A great advantage of NGS approach is based on its ability to deliver clinical diagnosis in a short time [3]. Currently, there are several NGS platforms available for routine diagnostic applications. These sequencers allow performing a high-throughput analysis within few days, considerably decreasing costs [13]. These new technologies are different from Sanger sequencing because they are based on a massively parallel analysis and high throughput.

Today two different NGS technologies are mainly used in clinical laboratories: Ion Torrent and Illumina systems [14]. The Ion Torrent Personal Genome Machine (PGM) was launched in 2011, while the widely used Illumina benchtops for diagnostic purpose are MiSeq, marketed in 2011, MiniSeq, launched in 2016, or iSeq100, debuting in the end of 2017. The Ion Torrent exploited the emulsion PCR using native dNTP chemistry that releases hydrogen ions during base incorporation by DNA polymerase and a modified silicon chip detecting the pH modification [15], while Illumina technology is based on the existing Solexa sequencing by synthesis chemistry with the use of very small flow-cells, reduced imaging time and fast sequencing pro- cess [14].

NGS APPROACH IN CLINICAL LABORATORIES

The increase in number of causative genes associated with human inherited disorders is directly associated with the implementation of NGS.

Until now Sanger sequencing has been the gold standard in clinical laboratories for single-gene tests and it serves as the standard methods by which NGS data should be compared and validated [16]. However, Sanger sequencing achieves the diagnostic goal when there is a clear phenotypic indication of a classical Mendelian disorder and the single-gene test approach is preferred. It eliminates the problem of incidental findings that we will discuss later, but it may push the patients into a "diagnostic odyssey", where they could be evaluated by multiple providers, some- times for years, without a genetic diagnosis [13].

Today there is a different scenario, in which genomic technologies can be very useful to detect genetic variations in patients with a high accuracy and an important reduction of costs, thanks to the first-generation sequencing approach. In particular, next-generation sequencing will increasingly be used for clinically heterogeneous inherited disorders, resulting in an increase in number of reported disease-causing genes [6]. Indeed, in the majority of human inherited diseases not merely one gene but a number of genes may interact leading to overlapping pathological phenotypes [2].

NGS approach is tempting when there is a genetic contribution in heterogeneous and complex diseases, such as in cardiomyopathies, in cardiac arrhythmias,

in connective tissue disorders, in mental retardation or autism, where a large number of genes are involved in a large phenotypic spectrum [10,11,17]. In these cases, NGS approaches al- lows to test a large number of genes simultaneously in a cost-effective manner [13]. An important issue is to decide which kind of NGS testing strategy is best suited for each clinical case. Two options are currently available: targeted gene panels or wholeexome sequencing (WES) [13].

Targeted sequencing of selected genes offers a good coverage (mean 300X, depending on platforms and number of analyzed samples) for the entire analyzed panel and specific regions refractory to NGS can be sequenced by Sanger sequencing, in order to cover the gap and to validate the NGS data [18,19]. So far, targeted resequencing has been adopted to develop tests for genetic disorders, such as non- syndromic deafness [20,21], common and heterogeneous diseases, such as hypertension and diabetes [22], or in traditional cytogenetic and Mendelian disorder diagnosis [23,24]. The main limitation of targeted sequencing is the rigidity of testing only a selected number of genes. Since the genetic field is rapidly evolving, new genes may be associated with a clinical phenotype and as such redesigning and revalidation of the panel is needed [13,16].

On the contrary a clear advantage of the use of targeted panel is the reduction of number of incidental findings and/or the number of variants of unknown significance, that will be discuss later in this review.

On the other hand, the benefit of WES is testing a greater number of genes, even if, in practice, complete coverage of all coding exons is infeasible. The WES application may be useful, for example, in negative cases in targeted sequencing or in a rare disease, especially in exploiting trios approach. Indeed, it allowed the identification of genes responsible for the dominant Freeman-Sheldon syndrome, the recessive Miller Syndrome and the dominant Schinzel-Giedion Syndrome [25].

However it is important to keep in mind that about 10% of targeted bases sequenced in WES do not get the 20 read depth [26], required for clinical confidence and interpretation, and approximately only 85% of genes associated to human diseases into the principle database (OMIM) receive the adequate coverage [27].

Poor coverage in WES can due to several fac- tors: probes that are not tiled for particular genes probably not included during assay development or because repetitive sequences prevented inclusion or poorly performing probes owing to GC-richness and low mapping quality [6].

However it is important to consider that both of these approaches can significantly reduce costs and turnaround time for a genetic test [13].

THE MAIN ISSUE OF NGS:

THE INTERPRETATION OF GENETIC DATA FOR A CLINICAL UTILITY

In the NGS process one limiting step is without doubt the complexity of genetic variation interpretation in whole exome, due to the presence of thousands of rare single nucleotide variations without pathogenic effect. Moreover, in the majority of human diseases the pathological phenotype may be caused by a pathogenic rare mutation with a strong effect or it may be caused by a co-presence of multiple genetic variations [28][29].

Reliable interpretation of the multiple and de novo variants identified through NGS will re- quire additional experience and validation be- fore it reaches the clinical stage on a large scale, particularly for diagnosis of complex traits [30]. In the recent past, genetic data did not drive diagnosis but had a primarily confirmatory role. Today the major challenge is to convert pathogenic genetic data into a primary diagnostic tool that can shape clinical decisions and patients management [31].

Actually, the interpretation of genetic variants is based on criteria published by the American college of medical genetics and genomics (ACMG). The ACMG recommends that the vari- ants be allocated to one of the categories re- ported below [32]:

- a. disease causing (class V): the sequence variation is previously reported and recognized as causative of the disorder;
- b. likely disease causing (class IV): the sequence variation is not previously reported as expected to cause the disorder, frequently in a known disease gene;

- variant of unknown clinical significance (VUS; class III): the sequence variation is unknown or expected to be causative of disease and is found to be connected with a clinical presentation;
- d. likely not disease causing (class II): the sequence variation is not previously reported and it is probably not causative of the pathology;
- e. not disease causing (class I): the sequence variation is already reported and documented as neutral variant.
- f. Moreover, most of these classes of variants are subject to supplementary interpretation focusing on literature reported, population frequencies, clinical findings, mutation databases and possibly case-specific research data [31]. The principal human variant databases are useful to annotate both common and pathogenic variants, such as dbSNP, gnomAD or ExAC database (Exome Aggregation Consortium) [33], and to classify variants previously associated with hu- man disorders, such as Human Gene Mutation Database (HGMD) [34] and ClinVar.

The variants of unknown significance (VUS) rep- resent a problem for the interpretative process. Indeed it is known that hundreds of loss of function variants with unknown clinical significance are present in each individual's genome and to- day their prioritization remains a primary challenge [35]. In some cases, the interpretation of VUS can be useful in commencing the segregation analysis in large families including affected members or the identification of the occurrence of de novo variation in the affected patient. Unfortunately, in many cases the interpretation of VUS remains unresolved and its identification cannot be used for the clinical management of patients and families [29,36].

Until now few clear guidelines are published for the VUS interpretation [36]. Today, in order to try to assign a pathological score to VUS, it is important to consider, for example, its allelic frequency in a control population (1000 Genomes or exome sequencing project consortium [ExAC]), the amino acidic conservation, the predicted effect on protein function and the results of published functional assay [37,38].

Up to now in silico prediction algorithms, such as Polyphen, Sift, Mutation Taster or UMD predictor, have been developed and they are widely used for the missense variants interpretation [37]. However, they present some intrinsic caveat and limitations, affecting their specificity and sensitivity, that can lead to possible false-positive and false-negative interpretations [39]. Another existing problem involves the allelic frequency, that is mainly estimated from the 1000 Genome project and ExAC, that represents only a fraction of the worldwide population, so the declared allelic frequency available is not stratified according to the real population groups [29].

Since the problem of the management of VUSs is not yet resolved, it would be fundamental to collect and share VUSs and available clinical data, allowing a progressive and definitive classification of these variants, as deleterious (class V) or neutral ones (class I) [29,30]. Another important challenge of the use of NGS approach in clinical diagnostic is the management of the amount of data generated [40]. Indeed generation, analysis and also storage of NGS data require sophisticated bioinformatics infrastructure [41].

A skilled bioinformatics staff is needed to man- age and analyze NGS data, and so both com- puting infrastructure and manpower impact on costs of NGS applications in clinical diagnostics. Bioinformaticians are to be mandatory in the organization chart of clinical laboratories in the NGS era, where they have to closely collaborate with clinicians and laboratory staff to optimize the panel testing and the NGS data analyses [42]. Bioinformatics has been recently defined as the discipline that develops and applies advanced computational tools to manage and analyze the NGS data. Bioinformatics pipeline developed for NGS are aimed to convert the raw sequencing signals to data, data to information, and information to knowledge [43].

This process can be developed in three different steps - primary, secondary, and tertiary analyses [44]:

- The primary analysis is the process of raw data produced by NGS instruments,
- the secondary analysis is the alignment to a reference sequence and the calling variants and, finally,
- the tertiary analysis is the confirmation or validation of detected variants, providing evidence to facilitate interpretation [41].

All clinical bioinformatics systems require these three steps that should be properly validated and documented. In particular, it requires determination of variant calling sensitivity, specificity, accuracy and precision for all variants reported in the clinical assay [44]. The quality criteria of the performed sequencing test have to be described on the report for clinicians and patients. In particular, it is needed to declare the sensitivity and specificity of the techniques used considering both technical and bioinfor- matics parameters. It is important to report which target region was not sequenced, the number of reads obtained, the quality of the sequence, the limitations of the chosen sequencing method and of the settings of used bioinformatics pipeline [16,45].

ETHICAL CONSIDERATIONS AND MANAGEMENT OF INCIDENTAL FINDINGS

The development and the widespread use of NGS in clinical laboratories are paired with de-bate on the ethics for reporting incidental findings [46,47]. In 2013 the ACMG has highlighted the question of the incidental findings (IF), defining them as "genetic variations" identified by genomic sequencing but not related to the dis- ease being investigated" [48]. According to the European Society of Human Genetics (ESHG) guidelines, the targeted diagnostic testing should be performed minimizing the likelihood of detecting incidental findings, focusing only on genes clinically actionable [49]. It means that genetic testing should aim to analyze the causative genes associated to the primary clinical questions, even if a broader panel of genes or the whole exome sequencing has been performed [49]. It is the role of responsible clinicians requesting the test to disclose an incidental finding to a patient, not the role of the clinical laboratory.

The impact of the IF determines how the genetic finding should be disclosed or not to a patient, also to avoid unwarranted psychological stress. In particular, if it can bring minor consequences or if a clinical intervention is possible, then the variant should be reported.On the contrary, if the variant is associated to a late onset disorder or has major consequences, Counselling and consent will determine if and when the variant can and should be reported to the patient [36]. This implies that genetic tests should be ordered by medical professionals who are capable of performing appropriate Counselling [50]. For that reason, the Counselling and the informed consent are critical steps. There is a difference between recording and reporting a variant, as well as between who receives this information, clinicians or patients, and when. When a variant is reported to a clinician, it does not mean that it will be revealed to patient. Indeed, the clinician should evaluate the impossible clinical implication of this information, based on the clinical history of patient. For example, the impact of an IF in a case without a known family history for a specific disorder is different from the case in which the patient is already aware of a preexisting familial condition.

Another interesting example is the acute neonatal care, in which immediate reporting of all Ifs to patients' families may not be appropriate and the genetic information may be reconsider later in baby's life. Similarly, the report of IFs may be postponed in cases where parents or patients are given a diagnosis linked to poor prognosis or in case of post-mortem genetic testing. Additional contexts in which the reporting of incidental findings may have an influence on the patients management are carrier testing, prenatal diagnosis, pharmacogenetics testing and additional non-diagnostic testing such as medical research (dependent on the study design), forensic testing, parental and genealogical testing. In conclusion, the issue of IFs requires an appropriate pre and post Counselling to correctly inform the patient [16].

The widespread implementation of NGS ap- proach in diagnosis of human pathologies raises the problem of management of IFs and VUSs and it is needed to have clear guidelines for the handling of NGS data in the diagnostics approach (Figure 1).

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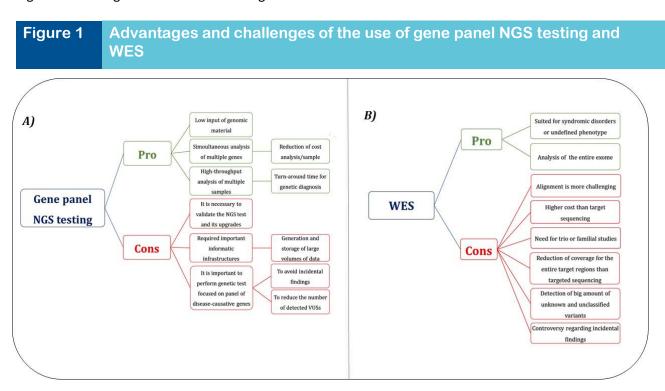
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So far the application of WES in clinical diagnostics presents more open challenges (B) than targeted sequencing (A).

CONCLUSIONS:

Until now Sanger sequencing has been the gold standard in molecular diagnostics and it has been used in clinical testing method for Mendelian disorders, in which most of causative variants are identified in the principal causative genes. Since the rapid and incremental improvements in instrumentations, methodologies and throughput and the significant reduction of costs, the NGS technologies are being integrated into patient care and clinical management. NGS allows sequencing of all genes relevant to a given phenotype starting from a small amount of total DNA. In that way, the limitation factors are no longer the size of the gene or its causative contribution but the actual knowledge of the genetic basis of patient's disease [6]. In the past, clinicians considered genetic tests with a marginal diagnostic value, only if a definitive diagnosis was not yielded or if it had implications on future family planning. Often the positive genetic test results did not influence clinical management of the patient.

However today, with the potentiality of NGS, the parallel sequencing of large multi-genes panel, that may describe a broader range of phenotypes, the clinicians are changing their point of view on the role of the genetics in patients care. Indeed, nowadays the genetic testing may be useful for the evaluation of a clinical case and, if the result were to be positive, it may save time and money in identifying the etiology.

Today physicians often begin their clinical evaluations with the genetic tests. For example, the evaluation of patients with left ventricular hypertrophy begins with genetic testing, given that the genetic diagnosis is achieved in about 80% of hypertrophic cardiomyopathy cases [51].

The results of most targeted genetic tests may be available for clinicians in 2-8 weeks, which is an impressive improvement compared to the time taken for direct Sanger sequencing and the odyssey lived by some patients before to under- stand the cause of their rare disorder [6]. This strategy of approaching the clinical evaluation has also economically beneficial in patients without diagnosis [52].

The euphoria of the widespread use of the NGS applications to the clinical diagnosis is combined with the awareness of emerged challenges, such as the validation of large number of genetic variations detected, that can be IF or VUSs, the use of standardization processes in clinical diagnostics, the management of terabytes of data and variants interpretation.

In the NGS approach, the analysis of data requires the development of a standard pipeline to process sequencing data. The flow chart analysis includes mapping, variant calling and annotation. Today there are various public database, such as dnSNP [53], the 1000 Genome Project [54], ExAC, as well as several internal control databases. Targeted panel sequencing or clinical exome sequencing identifies several variations in each person, but as far there are no clear guidelines to filter variants and to delineate their possible pathological meanings. For this reason, the pathogenic validation may be the limiting step. Because of these considerations, it is important to apply the NGS approach in clinical diagnostics for that disorders of which the main causative genes have been identified. Indeed, in this case the genetic tests can successfully reveal a useful result.

Moreover, another consideration involves the fundamental change of the figure of medical geneticist in the NGS era. Indeed, the NGS applications into diagnostic field can lead to useful results for patient's care with genetic disorders. As such, the geneticists will become a pivotal part of the collaborative team of clinicians and their role will be fundamental for the clinical interpretation of NGS data to guide patient care [25].

Consequently, clinical medical geneticists have to complement their skills with expertise in the clinical interpretation of NGS data.

Moreover we have to keep in mind that the medical geneticist has an important and crucial role also in the pre-test counseling, to deliver reliable information to patients [29]. Indeed it is important to clearly explain to the patient and his family the medical implications of the identification of a genetic alteration, regarding the degree of risk for a disease and also the significance of a possible negative results, both in pretest and in the post test counseling [29].

In meanwhile, the NGS approach becomes a cornerstone for the genetic diagnosis, a more efficient and powerful third-generation technologies are expected to further revolutionize genome sequencing [55]. The three commercially available third-generation DNA sequencing technologies are Pacific Biosciences (Pac Bio), Single Molecule Real Time (SMRT) sequencing, the Illumina Tru-seq Synthetic Long-Read technology, and the Oxford Nanopore Technologies sequencing platform.

Third-generation sequencing was made feasible in part by increasing capacity of existing technologies and improvements in chemistry and it allows to sequence a single nucleic acid molecule, eliminating the DNA amplification step, with a longer and easier mapping of sequencing reads with lower costs [55].

Moreover, the use of longer reads than the secondgeneration allow to overcome the important limitation of NGS in copy number variation analysis (CNV) [56], even if these single-molecule sequencing approaches have to become even more robust for a wider use.

Lastly, few years ago a new technique called Spatial Transcriptomics was developed and gave rise to fourth generation sequencing, also known as single-cell sequencing [55,57]. In this new technology, NGS chemistry is applied to the sequencing of nucleic acid composition directly in fixed cells and tissues providing a throughput analysis, opening great opportunity mainly for the analysis of tumor cells variability in situ [58]. In forthcoming future, it holds exciting prospective for research and new insights regarding genomic diagnostics.

REFERENCES

- 11. Koboldt DC, Steinberg KM, Larson DE, Wilson RK, Mardis ER. The next-generation sequencing revolution and its impact on genomics. Cell. 2013;155: 27–38. doi:10.1016/j.cell.2013.09.006
- 12. Grumbt B , Eck SH , Hinrichsen T , Hirv K . Diagnostic applications of next generation sequencing in immuno genetics and molecular oncology. Transfus Med hemotherapy Off Organ der Dtsch Gesellschaft fur Transfusions medizin und Immunham atologie . 2013;40: 196–206. doi:10.1159/000351267
- Vrijenhoek T, Kraaijeveld K, Elferink M, de Ligt J, Kranendonk E, Santen G, et al. Next-generation sequencing- based genome diagnostics across clinical genetics centers: implementation choices and their effects. Eur J Hum Genet. Nature Publishing Group; 2015;23: 1142–1150. doi:10.1038/ejhg.2014.279
- 14. Coonrod EM, Durtschi JD, Margraf RL, Voelkerding K V. Developing genome and exome sequencing for candidate gene identification in inherited disorders: an integrated technical and bioinformatics approach. Arch Pathol Lab Med. 2013;137: 415–33. doi:10.5858/ arpa.2012-0107-RA
- Peters DG, Yatsenko SA, Surti U, Rajkovic A. Re- cent advances of genomic testing in perinatal medicine. Semin Perinatol. 2015;39: 44–54. doi:10.1053/j. semperi.2014.10.009
- 16. Rehm HL. Disease-targeted sequencing: a corner-stone in the clinic. Nat Rev Genet. 2013;14: 295–300. doi:10.1038/nrg3463
- Thorburn F, Bennett S, Modha S, Murdoch D, Gunson R, Murcia PR. The use of next generation sequencing in the diagnosis and typing of respiratory infections. J Clin Virol. 2015;69: 96–100. doi:10.1016/j.jcv.2015.06.082
- LePichon J-B, Saunders CJ, Soden SE. The Future of Next-Generation Sequencing in Neurology. JAMA Neurol. 2015; doi:10.1001/jamaneurol.2015.1076
- Gorokhova S, Biancalana V, Lévy N, Laporte J, Bartoli M, Krahn M. Clinical massively parallel sequencing for the diagnosis of myopathies. Rev Neurol (Paris). 171: 558–71. doi:10.1016/j.neurol.2015.02.019
- Harripaul R, Noor A, Ayub M, Vincent JB. The Use of Next-Generation Sequencing for Research and Diagnostics for Intellectual Disability. Cold Spring Harb Perspect Med. Cold Spring Harbor Laboratory Press; 2017;7: a026864. doi:10.1101/cshperspect.a026864

- 1.Di Resta C, Pietrelli A, Sala S, Della Bella P, De Bellis G, Ferrari M, et al. High-throughput genetic charac- terization of a cohort of Brugada syndrome patients. Hum Mol Genet. 2015;24: 5828–5835. doi:10.1093/hmg/ddv302
- 2. Carrera P, Di Resta C, Volonteri C, Castiglioni E, Bonfiglio S, Lazarevic D, et al. Exome sequencing and pathway analysis for identification of genetic variability relevant for bronchopulmonary dysplasia (BPD) in preterm newborns: A pilot study. Clin Chim Acta. 2015;451: 39–45. doi:10.1016/j.cca.2015.01.001
- 3. Williams ES, Hegde M. Implementing genomic medi- cine in pathology. Adv Anat Pathol. 2013;20: 238–44. doi:10.1097/PAP.0b013e3182977199
- 4. Quail M, Smith ME, Coupland P, Otto TD, Harris SR, Connor TR, et al. A tale of three next generation sequencing platforms: comparison of Ion torrent, pacific biosciences and illumina MiSeq sequencers. BMC Genomics. BioMed Central; 2012;13: 341. doi:10.1186/1471-2164-13-341
- 5. Merriman B, Rothberg JM. Progress in ion torrent semiconductor chip based sequencing. Electrophoresis. 2012;33: 3397–417. doi:10.1002/elps.201200424
- Rehm HL, Bale SJ, Bayrak-Toydemir P, Berg JS, Brown KK, Deignan JL, et al. ACMG clinical laboratory standards for next-generation sequencing. Genet Med. 2013;15: 733– 747. doi:10.1038/gim.2013.92
- 7. Lin X, Tang W, Ahmad S, Lu J, Colby CC, Zhu J, et al. Applications of targeted gene capture and next-generation sequencing technologies in studies of human deafness and other genetic disabilities. Hear Res. 2012;288: 67–76. doi:10.1016/j.heares.2012.01.004
- Aziz N, Zhao Q, Bry L, Driscoll DK, Funke B, Gibson JS, et al. College of American Pathologists' Laboratory Standards for Next-Generation Sequencing Clinical Tests. Arch Pathol Lab Med. 2015;139: 481–493. doi:10.5858/ arpa.2014-0250-CP
- Johnston JJ, Rubinstein WS, Facio FM, Ng D, Singh LN, Teer JK, et al. Secondary variants in individuals undergoing exome sequencing: screening of 572 individuals identifies high-penetrance mutations in cancer-susceptibility genes. Am J Hum Genet. 2012;91: 97–108. doi:10.1016/j. ajhg.2012.05.021
- Vona B, Nanda I, Hofrichter MAH, Shehata-Dieler W, Haaf T. Non-syndromic hearing loss gene identification: A brief history and glimpse into the future. Mol Cell Probes. Academic Press; 2015;29: 260–270. doi:10.1016/J. MCP.2015.03.008

- 21 Brownstein Z, Abu-Rayyan A, Karfunkel-Doron D, Si- rigu S, Davidov B, Shohat M, et al. Novel myosin mutations for hereditary hearing loss revealed by targeted genomic capture and massively parallel sequencing. Eur J Hum Genet. 2014;22: 768–75. doi:10.1038/ejhg.2013.232
- 22 Szopa M, Ludwig-Gałęzowska A, Radkowski P, Skupień J, Zapała B, Płatek T, et al. Genetic testing for monogenic diabetes using targeted next-generation sequencing in patients with maturity-onset diabetes of the young. Pol Arch Med Wewn. 2015;125: 845–51. Available: http:// www.ncbi.nlm.nih.gov/pubmed/26552609
- 23 Cook JR, Kelley TW. The impact of molecular cytogenetics and next generation sequencing in hematopathology: accomplishments and challenges. Pathology. Elsevier; 2014;46: S22. doi:10.1097/01.PAT.0000454125.58964.86
- 24 Ma ESK, Wan TSK, Au CH, Ho DN, Ma SY, Ng MHL, et al. Next-generation sequencing and molecular cytoge- netic characterization of ETV6-LYN fusion due to chromosomes 1, 8 and 12 rearrangement in acute myeloid leukemia. Cancer Genet. 2017;218–219: 15–19. doi:10.1016/j. cancergen.2017.09.001
- 25 Boycott KM, Vanstone MR, Bulman DE, MacKenzie AE. Rare-disease genetics in the era of next-generation sequencing: discovery to translation. Nat Rev Genet. 2013;14: 681–91. doi:10.1038/nrg3555
- 26 Yao R, Zhang C, Yu T, Li N, Hu X, Wang X, et al. Evaluation of three read-depth based CNV detection tools using whole-exome sequencing data. Mol Cytogenet. BioMed Central; 2017;10: 30. doi:10.1186/s13039-017-0333-5
- Singh RR, Luthra R, Routbort MJ, Patel KP, Medeiros LJ. Implementation of next generation sequencing in clin- ical molecular diagnostic laboratories: advantages, challenges and potential. Expert Rev Precis Med Drug Dev. Taylor & Francis; 2016;1: 109–120. doi:10.1080/238089 93.2015.1120401
- 28 Sommariva E, Pappone C, Martinelli Boneschi F, Di Resta C, Rosaria Carbone M, Salvi E, et al. Genetics can contribute to the prognosis of Brugada syndrome: a pilot model for risk stratification. Eur J Hum Genet. 2013;21: 911–7. doi:10.1038/ejhg.2012.289
- 29 Frebourg T. The challenge for the next generation of medical geneticists. Hum Mutat. 2014;35: 909–11. doi:10.1002/humu.22592
- 30 Matthijs G, Souche E, Alders M, Corveleyn A, Eck S, Feenstra I, et al. Guidelines for diagnostic next-generation sequencing. Eur J Hum Genet. Nature Publishing Group; 2016;24: 2–5. doi:10.1038/ejhg.2015.226
- Katsanis SH, Katsanis N. Molecular genetic testing and the future of clinical genomics. Nat Rev Genet. 2013;14: 415–26. doi:10.1038/nrg3493

- 32. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17: 405–24. doi:10.1038/gim.2015.30
- 33. Song W, Gardner SA, Hovhannisyan H, Natalizio A, Weymouth KS, Chen W, et al. Exploring the landscape of pathogenic genetic variation in the ExAC population data-base: insights of relevance to variant classification. Genet Med. 2016;18: 850–854. doi:10.1038/gim.2015.180
- Stenson PD, Mort M, Ball E V, Howells K, Phillips AD, Thomas NS, et al. The Human Gene Mutation Database: 2008 update. Genome Med. 2009;1: 13. doi:10.1186/ gm13
- Cooper GM, Shendure J. Needles in stacks of needles: finding disease-causal variants in a wealth of genomic data. Nat Rev Genet. 2011;12: 628–40. doi:10.1038/nrg3046
- Hegde M, Bale S, Bayrak-Toydemir P, Gibson J, Bone Jeng LJ, Joseph L, et al. Reporting Incidental Findings in Genomic Scale Clinical Sequencing—A Clinical Laboratory Perspective. J Mol Diagnostics. 2015;17: 107–117. doi:10.1016/j.jmoldx.2014.10.004
- Di Resta C, Manzoni M, Zoni Berisso M, Siciliano G, Benedetti S, Ferrari M. Evaluation of damaging effects of splicing mutations: Validation of an in vitro method for diagnostic laboratories. Clin Chim Acta. 2014;436C: 276– 282. doi:10.1016/j.cca.2014.05.026
- Thompson BA, Spurdle AB, Plazzer J-P, Greenblatt MS, Akagi K, Al-Mulla F, et al. Application of a 5-tiered scheme for standardized classification of 2,360 unique mismatch repair gene variants in the InSiGHT locusspecific data- base. Nat Genet. 2014;46: 107–15. doi:10.1038/ng.2854
- Adzhubei IA, Schmidt S, Peshkin L, Ramensky VE, Gerasimova A, Bork P, et al. A method and server for predicting damaging missense mutations. Nat Methods. 2010;7: 248–9. doi:10.1038/nmeth0410-248
- 40. Stein LD. The case for cloud computing in genome informatics. Genome Biol. 2010;11: 207. doi:10.1186/gb-2010-11-5-207
- Pabinger S, Dander A, Fischer M, Snajder R, Sperk M, Efremova M, et al. A survey of tools for variant analysis of next-generation genome sequencing data. Brief Bioinform. 2014;15: 256–278. doi:10.1093/bib/bbs086

- Moorthie S, Hall A, Wright CF. Informatics and clinical genome sequencing: opening the black box. Genet Med. 2013;15: 165–71. doi:10.1038/gim.2012.116
- 44. Allyse M, Michie M. Not-so-incidental findings: the ACMG recommendations on the reporting of inciden- tal findings in clinical whole genome and whole exome sequencing. Trends Biotechnol. 2013;31: 439–41. doi:10.1016/j.tibtech.2013.04.006
- 45. Wolf SM, Annas GJ, Elias S. Point-counterpoint. Patient autonomy and incidental findings in clinical genomics. Science. 2013;340: 1049–50. doi:10.1126/science.1239119
- McGuire AL, Joffe S, Koenig BA, Biesecker BB, Mc- Cullough LB, Blumenthal-Barby JS, et al. Point-counter- point. Ethics and genomic incidental findings. Science. 2013;340: 1047–8. doi:10.1126/science.1240156
- 47. Green RC, Berg JS, Grody WW, Kalia SS, Korf BR, Martin CL, et al. ACMG recommendations for reporting of inci- dental findings in clinical exome and genome sequencing. Genet Med. 2013;15: 565–74. doi:10.1038/gim.2013.73
- Claustres M, Kožich V, Dequeker E, Fowler B, Hehir- Kwa JY, Miller K, et al. Recommendations for reporting results of diagnostic genetic testing (biochemical, cytogenetic and molecular genetic). Eur J Hum Genet. 2014;22: 160–70. doi:10.1038/ejhg.2013.125
- 49. Hehir-Kwa JY, Claustres M, Hastings RJ, van Raven- swaaij-Arts C, Christenhusz G, Genuardi M, et al. To- wards a European consensus for reporting incidental findings during clinical NGS testing. Eur J Hum Genet. Macmillan Publishers Limited; 2015; doi:10.1038/ ejhg.2015.111
- Teekakirikul P, Kelly MA, Rehm HL, Lakdawala NK, Funke BH. Inherited cardiomyopathies: molecular genetics and clinical genetic testing in the postgenomic era. J Mol Diagn. 2013;15: 158–70. doi:10.1016/j. jmoldx.2012.09.002

- 51. Shashi V, McConkie-Rosell A, Rosell B, Schoch K, Vellore K, McDonald M, et al. The utility of the traditional medical genetics diagnostic evaluation in the context of next-generation sequencing for undiagnosed genetic disorders. Genet Med. 2014;16: 176–82. doi:10.1038/gim.2013.99
- 52. Sherry ST, Ward MH, Kholodov M, Baker J, Phan L, Smigielski EM, et al. dbSNP: the NCBI database of genetic variation. Nucleic Acids Res. 2001;29: 308–11. Available: http://www.pubmedcentral.nih.gov/articlerender.fcgi?a rtid=29783&tool=pmcentrez&rendertype=abstract
- Abecasis GR, Altshuler D, Auton A, Brooks LD, Durbin RM, Gibbs RA, et al. A map of human genome variation from population-scale sequencing. Nature. 2010;467: 1061–73.doi:10.1038/nature09534
- 54. Ståhl PL, Salmén F, Vickovic S, Lundmark A, Navarro JF, Magnusson J, et al. Visualization and analysis of gene expression in tissue sections by spatial transcriptomics. Science. American Association for the Advancement of Science; 2016;353: 78–82. doi:10.1126/science.aaf2403
- 55. Jia W, Qiu K, He M, Song P, Zhou Q, Zhou F, et al. SOAPfuse: an algorithm for identifying fusion transcripts from paired-end RNA-Seq data. Genome Biol. 2013;14: R12.doi:10.1186/gb-2013-14-2-r12
- Ke R, Mignardi M, Hauling T, Nilsson M. Fourth Generation of Next-Generation Sequencing Technologies: Promise and Consequences. Hum Mutat. Wiley-Black- well; 2016;37: 1363–1367. doi:10.1002/humu.23051
- 57. Mignardi M, Nilsson M. Fourth-generation sequencing in the cell and the clinic. Genome Med. BioMed Central; 2014:6: 31. doi:10.1186/GM548



Clinical Chemistry Journal Club

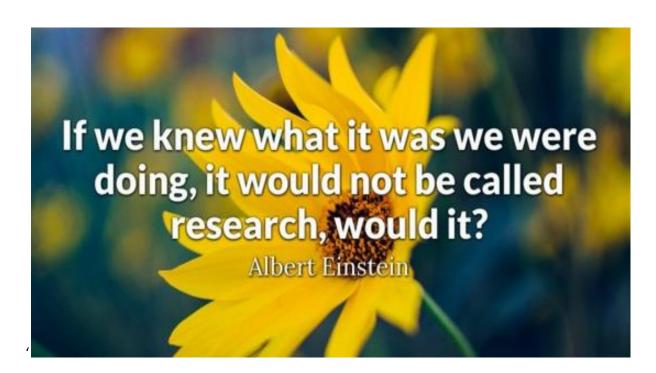


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CLINICAL BIOCHEMISTS REVIEW



Dear APFCB member society,

I am writing to you with information regarding the latest issue of the Clinical Biochemist Reviews which has recently been published.

Latest Issue

Vitamin D Metabolism and Guidelines for Vitamin D Supplementation

Review Article Volume: 2020, 41 (iii) : 103-26 Author: Indra Ramasamy

<u>Clinical and Laboratory Aspects of Insulin Autoantibody-Mediated Glycaemic Dysregulation and</u> <u>Hyperinsulinaemic Hypoglycaemia: Insulin Autoimmune Syndrome and Exogenous Insulin Antibody Syndrome</u>

Review Article Volume: 2020, 41 (iii) : 93-102 Author: Tony Huynh

Considerations for Group Testing: A Practical Approach for the Clinical Laboratory

Review Article Volume: 2020, 41 (iii) : 79-92 Author: Jun G Tan, Aznan Omar, Wendy BY Lee, Moh S Wong

Proceedings of the Australasian Association of Clinical Biochemistry and Laboratory Medicine's 2020 Virtual Scientific Conference

Supplement Volume: 2020, 41 (iii) : S1-S26

The Clinical Biochemist Reviews is an official journal of the APFCB and free full text content is available through <u>PubMed</u> one month following publication. I would appreciate you making this information available to your members.

Best wishes

Dr Kevin Carpenter FFSc (RCPA), FHGSA Chief Executive Officer AUSTRALASIAN ASSOCIATION FOR CLINICAL BIOCHEMISTRY AND LABORATORY MEDICINE P: (02) 9669 6600 | M: 0427 152 501 | Visit our website <u>www.aacb.asn.au</u>, Virtual <u>CPC 2021</u>|February 2021



Clinical Chemistry Journal Club Join Us: 🗜 🍸 in

Thank you for participating in the *Clinical Chemistry* Journal Club.

This month's Editor selection:

Is It Time to Remove Total Calcium from the Basic and Comprehensive Metabolic Panels? Assessing the Effects of American Medical Association-Approved Chemical Test Panels on Laboratory Utilization

B.M. Katzman, S.C. Bryant, B.S. Karon

Journal Club Slides

Join us on Facebook for an online discussion of the article. Questions from the Journal Club slides will be posted on Clinical Chemistry's Facebook page. Simply register with Facebook and like Clinical Chemistry to join the discussion.

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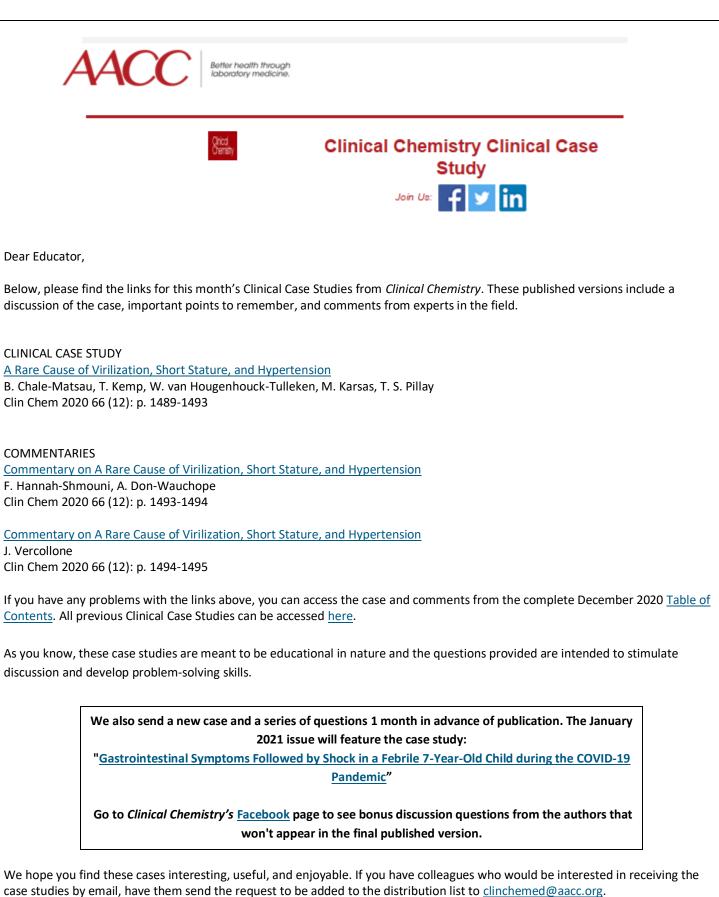
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We welcome the submission of interesting case studies. Instructions can be found here.

Best wishes, Gary L. Horowitz, MD, Roy W.A. Peake, PhD Clinical Case Study Co-Editors

ACBI- CMC VELLORE EQAS ANNUAL REPORT 2019 - 2020

DEPARTMENT OF CLINICAL BIOCHEMISTRY CMC - EQAS

(UNDER THE AGEIS OF ACBI)

ANNUAL REPORT 2019 - 2020

Greetings from CMC, Vellore.

It is my privilege to submit the report of the ACBI - CMC EQAS, Clinical Biochemistry, for the period from 2019 to 2020. This year is the 42nd year of the ACBI-CMC EQAS – Clinical biochemistry programme and I am happy to mention that the vision and mission for which this programme has evolved 42 years ago, with 58 laboratories in the year 1978, has been gracefully taken forward to help the Indian labs – very small, small, medium, large, from private sector, Government hospital labs and PHC's. With increasing awareness of the importance of Quality control and External quality control in medical labs in India, the participating labs have increased in the last few years and as of the year 2020 we have 9500 lab participants registered in 8 different programmes, 7 of these are accredited according to the ISO 17043:2010 standards. There were approximately 2000 new registrations for the year 2020.

		2016	2017	2018	2019	2020
1	Chemistry I	2860	2962	3122	3493	3704
2	Chemistry II	1716	1501	2581	3809	3394
	Chemistry 111	-	-	-	-	2126
3	Thyroid& Cortisol	731	831	938	1145	1299
4	Reproductive Hormones	328	407	447	562	635
5	HbA1c	716	871	1012	1213	1400
6	Markers for Downs screening	54	65	62	76	93
7	Urine Chemistry	220	230	264	288	305
8	Tumor Markers	-	-	-	106	155

Registration Fee for the year 2020

There was no increase in the registration fee since 4 years after the last increase in 2017. For the year 2021, the registration fee for some programmes have been increased due to various expenses incurred such as purchasing of new lyophiliser, cold room facility, additional support staff and increase in the price of reagents and consumables. However, some participating laboratories expressed their inability to pay the revised amount owing to the Covid -19 crisis and on their request a concession in the registration fee was granted.

The circular and brochure for the 2021 cycle were sent to all participating labs during the month of September 2020. The number of participants with online registration has increased gradually from 13.2 % in 2016, to 65% for the year 2020.

NABL Audit:

The NABL PT On-Site surveillance was conducted in Feb 2020 and continuation of accreditation in accordance with ISO/ IEC 17043 :2010 was granted.

New Equipment

To cope with the increasing work load, few new equipments were newly added.

> New lyophilizer (15000 vials capacity), Additional walk in cold room, Additional Standby chiller unit.

Improvements in our EQAS programme:

- > January 2020 Chemistry III programme introduced for only TN Govt. labs (2126 PHC's)
- > 2020 trial run for Urine chemistry using neat urine in different dilutions and bulking agent for proper efficient cake formation of lyophilized material.
- March 2020 Tumor Markers programme accredited by NABL
- Sept 2020 NABL SYMBOL and CMC emblem inserted in certificates .(as required by NABL)

>Nov 2020 - NABL SYMBOL and CMC emblem inserted in monthly and yearly summary report

Additions and changes in the web site : Monthly & Yearly summary report modifications:

> January 2020 - New method and instrument wise configurations were introduced.

Analysis of results for all parameters for all programmes was based on the mean, SD and CV % of the respective groups. The scoring system used is SDI as according to ISO 13528:2015, statistical methods for use in Proficiency testing. The analysis based on analyser groups showed the actual performance of the participating labs in that particular group, which reflected on the improvement in the CMC EQAS analysis.

Conferences and workshops:

Owing to COVID -19 crisis in India and the lockdown, we were unable to hold any workshops or attend any this year. Dr.Pamela Christudoss was invited as a faculty for the workshop on Quality control, conducted by the Paramedical Association of India at Madurai, Kumbakonam, for Lab technicians in Jan 2020.

Participants' feedback for the year 2019

The feedback form was made more user friendly with only few required questions. The filling of the form online was made compulsory for the participants before uploading their January 2020 results. The response was 100 %.

Challenges faced during COVID -19 Pandemic year 2020

Sample dispatch : Due to lockdown and transport restrictions, the second batch of EQAS sample distribution was carried out in a phased manner ,i.e state wise with the help of the local Vellore Head postal dept. Although the samples were dispatched late, we were able to send them to containment zones during the month of May 2020.

Uploading of results: Extension of result submission dates was provided for the participants for uploading EQAS results for the months of April until September, extending 6 – 8 weeks beyond the usual closing date. Messages by SMS, circulars, emails were constantly sent to our participants. We are happy to mention that we were able to receive 80% - 85 % of result submission as compared to the 88-90% precovid times.

Future Plans:

To include Urine Chemistry in the scope for Accreditation in the following year .

Pilot study for:

- Cardiac markers : CK, CKMB, TROP T , NT PROBNP ,
- Trace metals ; Cu , Zn

I take this opportunity to thank the ACBI Executive committee for the encouragement and support received all through these years. I also thank the participants for their feedback which has helped us improve our service. A word of appreciation to our technical staff Mr. Manigandan, Mr. Saravanan, Mr. Ramesh who are involved with the large work load, to make the program run smoothly and to Mr. Sampath for the clerical help and to the other support staff. I am thankful to the administration of CMC, Vellore for their constant support all these years.

Above all I thank God Almighty for this great opportunity given, to be associated with CMC EQAS.

Dr. Pamela Christudoss CMC EQAS Coordinator Professor & HOD Department of Clinical Biochemistry CMC, Vellore

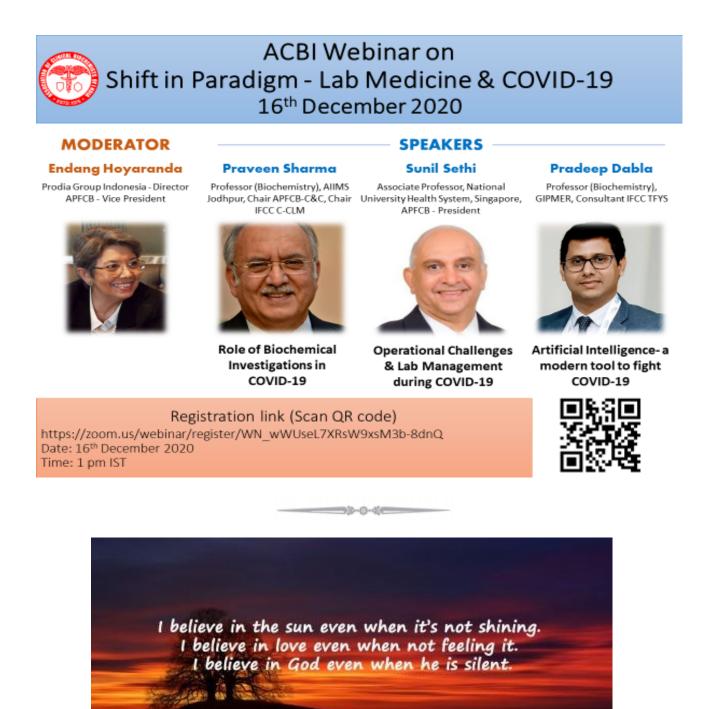
When it rains look for rainbows, when it's dark look for stars

93-0-4C

Covid-hit

NEWS FROM AROUND THE ACOUNTRY

Dear Members, with all physical conferences & CME's on hold, we have had many virtual Seminars (Webinars) organized by various members and organizations. ACBI also provided auspices to SNIBE to host webinars on topics relevant to us. Below are some webinar souvenirs !!



(Anonymous inscription left in the wall of a German internment camp)





AND LABORATORY MEDICINE





Serological markers in treatment and management of COVID-19

Aug. 18th, 2020 (Tuesday) India Time 4:00-6:00 pm (GMT+5.5/IST) Italy Time 12:30-2:30 pm (CEST)

To register for the webinar Please scan the QR code Or use following page for registration http://online.bizconfstreaming.com/webcast/Snibe20200818.html



Co-morbidities associated with COVID-19

Prof. Praveen Sharma (Moderator)



- PhD (Med), FACBI, FAMS, FAACC
- Professor, Dept of Biochemistry AIIMS Jodhpur
- Former Head, Department of Biochemistry, Dean (Research)
- Controller of Examinations, All India Institute of Medical Sciences, Jodhpur-342005 (India)
- President ACBI (2003-2004 and 2014-2015)
- President, InSLAR (2017 to date)
- Chair, IFCC-CCLM (2020 to date)
- Editor-in-Chief, IJCB (2006 to date)
- Chairman, APFCB Congress and Conferences (2019 to date)
- Former Chairman, APFCB Communication committee (2010-2019)
- Chief Editor, APFCB News (2010-2019)
- Director, NRCLPI, Jodhpur (2014 to date)
- Assessor (NABL)
- International Lead Assessor (AERSSC)

Case Discussion and Role of Routine Laboratory Parameters in COVID-19 Patients

Prof. Dr. Barnali Das



- MD, DNB, PGDHHM
- Consultant in Laboratory division of Kokilaben Dhirubhai Ambani Hospital & Medical Research Institute, Mumbai
- Executive Member, Scientific Division, International Federation of Clinical Chemistry & Laboratory Medicine (IFCC)
- Chair of American Association of Clinical Chemistry (AACC) India Section
- Member of the IFCC Committee for Standardization of Thyroid Function Tests (IFCC S-CTFT), 2011-2017
- Tests (IFCC S-CTFT), 2011-2017
- College of American Pathologist (CAP) Inspector & NABL Assessor

Serology screening in COVID-19 pandemic: opportunities and pitfalls



Prof. Sergio Bernardini

- MD, PhD
- Chair, Emerging Technologies Division of IFCC
- Full Professor in Clinical Biochemistry in University of Rome Tor Vergata, Italy

www.snibe.com



ТΗ ANNUAL CME



Department of Biochemistry Sir Ganga Ram Hospital, New Delhi, India cordially invites you to an online CME on

CARDIOVASCULAR RISK STRATIFICATION IN PATIENTS AND HEALTHY POPULATION **ROLE OF LABORATORY MEDICINE**

AGENDA 1:45 PM – 4:35 PM









 Member in HISICON Member in IAMM

· Infection Control Officer at Women's Center and Medserve, Coimbatore

Consultant Clinical Microbiologist at Microbiological Laboratory, Coimbatore



ACBI Webinar on Non-alcoholic fatty liver disease: An under recognized cause with emerging importance 6th January 2021

MODERATOR

Subir Kumar Das

Professor & Head Department of Biochemistry COMJNMH, Kalyani



Kalyan Goswami

Professor & Head Department of Biochemistry AIIMS Kalyani



Dyslipidemia in NAFLD

SPEAKERS

Nihar Ranjan Mishra

Associate Professor Department of Pediatrics AIIMS Kalyani



NAFLD in Children: Pediatrician Perspective Jayeeta Bhowmick

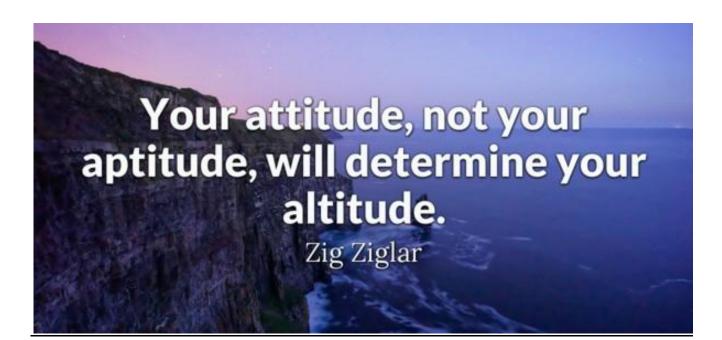
Associate Professor & Head Department of Medicine AIIMS Kalyani



NAFLD: Comprehensive approach



Registration link (Scan QR code) https://zoom.us/webinar/register/WN_06JIuRQuSa2mgppNA2dxXA Date: 6th January 2021 Time: 3 pm (IST)



-0-4

ACBI BENEVOLENT FUND

AN APPEAL

The Executive Council and GB were concerned to know the fact that one of our very senior members is suffering due to lack of money for his treatment and upkeep. For such situation many organizations have created 'Benevolent' fund to assist their members in dire need. We should also have compassion when any of our members are in need of help. Therefore the G.B. has decided to create a Fund to help our needy members and has sanctioned Rs. 50,000 from ACBI account for this fund. The IJCB Board has also decided to contribute Rs. 25,000. Many members have agreed to send money for the fund. Dr. B.C. Harinath has contributed Rs. 17000 which includes the money he got as recipient of ACBI-A.J. Thakur award for Distinguished Clinical Biochemist. Some have sent Rs. 1000 / 2000 /3000 as their contribution.

I solicit your support and **appeal** you to send money for this noble work as much as you like. The money be sent to the Treasurer, Association of clinical Biochemists of India, Biochem-Lab, East Boring Canal Road, Patna - 800001 by bank draft in the name of "ACBI Benevolent Fund" payable at Patna. The names of Donors are published in News Bulletin.

Dr. L. M. SRIVASTAVA

President

LIST OF DONORS TO ACBI-BENEVOLENT FUND

As on 01. 01. 2021

1	Association of Clinical Biochemists of India	50,000
2	Dr. B. C. Harinath, Prof. & Director, JBTDR Centre, Wardha	16,000
3	Dr. S. P. Dandekar, Prof. & Head, Department of Biochemistry, Seth G. S. Medical College,	1,000
	Mumbai	
4	Dr. Sujata W., Biochemistry Deptt., PGI ,Chandigarh	1,000
5	Dr. K. P. Sinha, Retd. Professor of Biochemistry, Patna Medical College, & Advisor	1,000
6	Dr B N Tiwary – Patna	1,000
7	Dr Uday Kumar – Patna	1,000
8	Dr Anand Saran – Patna	1,000
9	Anonymous Donor – Mumbai	5,000
10	Dr Rajiv R Sinha – Patna	1,000
11	Dr. Harbans Lal – Rohtak	2,000
12	Dr. S. J. Makhija	1,000
13	Dr. T. F. Ashavaid – Mumbai	3,000
14	Dr T. Malati – Hyderbad	5,000
15	Dr. Praveen Sharma – Jaipur	4,000
16	Dr. K. L. Mahadevappa – Karnataka	1,000
17	Dr. P. S. Murthy – Bangalore	5,000
18	Dr. Geeta Ebrahim	1,000
19	Dr. M.V. Kodliwadmath – Bangalore	1,000
20	Dr. Harsh Vardhan Singh – Delhi	10,000
21	Dr. M. B. Rao – Mumbai	3,000
22	Dr Praveen Sharma, Jodhpur	30,000
23	Dr. Tester F. Ashavaid, Mumbai	10,000
24	Dr. Manorma Swain, Cuttack	3,000
25	Dr. K. S. Gopinath – Bangalore	15,000
26	Dr. Jayshree Bhattacharjee – Delhi	10,000
27	Dr. K. K. Srivastava – Delhi	10,000
28	Dr. Subir Kumar Das – Kalyani	10,000

ASSOCIATION OF CLINICAL BIOCHEMISTS OF INDIA <u>MEMBERSHIP APPLICATION FORM</u>

INICAL BIO	WIEWIDERSIIIF AFFLICATION FUR	
of CLE	(Please write in Capital or Type)	
COLUMN CONTRACTOR)	Please Affix Stamp-size Photograph
1. Category of N	Membership Applied (tick the choice): Life/Associate Life/Annual/Sessional	
2. Name Dr/Mr.	/Mrs./Ms. :	
	Family Name	First name
3. Sex :		Nationality:
6. Academic Qu	alifications with Year: (attach Photocopies)	
7. Designation	:	
8. OFFICIAL A	DDRESS:	
1. Department	:	
2. Institution	:	
3. Address	:	
4. City	: 5. Pincode :	
6. State	:	
7. Telephone (w	rith area code):	
8. Fax (with area	a code):	
10. Mobile:		
11. RESIDENT	IAL ADDRESS:	
1. Address:		
2. City:		
4. State:	5. Telephone (with area code):	

8. Mobile:	
9. Address for Communication: Official OR Residential (p	lease tick the choice)
10. Professional Experience (briefly) on separate page:	
Teaching/Research/Diagnostic:Years	
11. Field of expertise/ Areas of Interest :(1)12. Publications, if any:Attach	ach a list giving details of publications.
13. Membership of other professional bodies, if any:	
14. Any other relevant information (brief): (on separate page) 15. D.D. No
16.Date: 17. Bank:	Branch :
Amount Rs: (Enclose the crossed D.D. for Clinical Biochemists of India" payable at Patna)	an appropriate amount drawn in favour of "Association of
	y the Applicant ical Biochemists of India. If admitted as a member, I shall
Signature of the Applicant Date	Place
Recommendation by a memb I have verified the information given in these applications eligibility requirement for becoming a member of ACBI. that membership of the ACBI. Name & Signature of the Member ACBI Membership No:	Place er of ACBI (This is essential) that are true to the best of my knowledge. He/She fulfils trecommend that
Recommendation by a membro I have verified the information given in these applications eligibility requirement for becoming a member of ACBI. that membership of the ACBI. Name & Signature of the Member. ACBI Membership No: (Disclated I) I have no objection / I object* if my address and full details a	Place er of ACBI (This is essential) that are true to the best of my knowledge. He/She fulfils t recommend that

ADMISSIBILITY RULES

ELIGIBILITY CRITERIA : Membership of the Association is open to teachers & research scientists in the discipline of Biochemistry, Clinical Biochemistry, Immunology, Pathology, Endocrinology, Nutrition, Medicine and other allied subjects in a medical institution and also to persons holding M.B.B.S., M.Sc. (Biochemistry or Clinical Biochemistry) and are engaged in research or practice of clinical Biochemistry in hospital or in private laboratory.

ASSOCIATE MEMBERSHIP: Those graduates who do not fit in the above criteria, but have an interest in Clinical Biochemistry are eligible to become Associate Members.

CORPORATE MEMBERSHIP: A company dealing in biochemical and instruments for biochemistry laboratories can become corporate members.

SESSIONAL MEMBERSHIP: Those persons who are not members but want to attend ACBI National Conference and attend and/or present papers have to become Sessional Member. This membership will be valid for that conference only. If he/she fulfils all eligibility criteria for membership and again pays the next years Annual membership fees, they will be admitted as Annual Member of ACBI.

MEMBERSHIP FEE: (a) Annual Member – Rs. 600/- annually , (b) Life Member – Rs.5130/- (Rs.5000/- once + Rs.30/for L.M.certificate posting + 100/- I Card (or Rs. 1800/- annually for 3 consecutive years.) (c) For persons residing in other countries – US \$200/- (d) ASSOCIATE LIFE MEMBERS - Rs.5130/- (Rs.5000/- once + Rs.30/- for L.M.certificate posting + 100/- I Card, (e) Corporate Member : Rs. 25,000/- one time payment. (f) Sessional Member – Rs. 600/- (g) IFCC subscription (optional) - Rs. 1500/- once.

Prescribed fee should be paid by BANK DRAFT (Preferably on SBI) only payable to "ASSOCIATION OF CLINICAL BIOCHEMISTS OF INDIA" at PATNA. NO CHEQUE PLEASE. Our Bank – SBI, Patna Main Branch, West Gandhi Maidan, Patna. Bihar. The completed application (along with enclosures) & draft should be sent to Dr. Rajiv R. Sinha, General Secretary, ACBI, Biochem-Lab, East Boring Canal Road, Patna – 800 001, preferably by registered post.

PHOTOGRAPH: Please affix a passport-size photo on the form.

PROFORMA

Members Identity Card

Please affix Stamp size

Photograph.

(Do not staple or pin)

Please type or write in CAPITAL Letters.

- 1. Name:
- 2. Qualification:

3. Membership Type : LIFE / ASSOCIATE LIFE / CORPORATE / HONORARY

(will be filled up at Head office)

4. ACBI Membership Number:

(will be filled up at Head office).

- 5. Work Place (City):
- 6. State:
- 7. Date of joining ACBI: (will be filled up at Head Office)

<u>NEW MEMBERS</u> : Filled up form to be posted along with the Membership application form. ID card charge is included in LIFE/ASSOCIATE LIFE/CORPORATE membership fees.

ALREADY A LIFE/CORPORATE MEMBER : Kindly fill up the form, paste one photo and send along with DD of Rs.100/-.

Please Note: Photo Identity card of ACBI is mandatory for members to attend the Annual Conferences, all meetings and also for exercising their voting rights. The charge for the ID card is <u>Rs.100</u>/-. Payment to be made by Demand Draft to "Association of Clinical Biochemists of India" payable at "PATNA".



Laboratory Medicine; Stepping Forward to the New Era

Laboratory Medicine Congress & Exhibition 2021 & G2nd ANNUAL MEETING

September 30–October 2, 2021 Songdo ConvensiA, Incheon, Korea

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