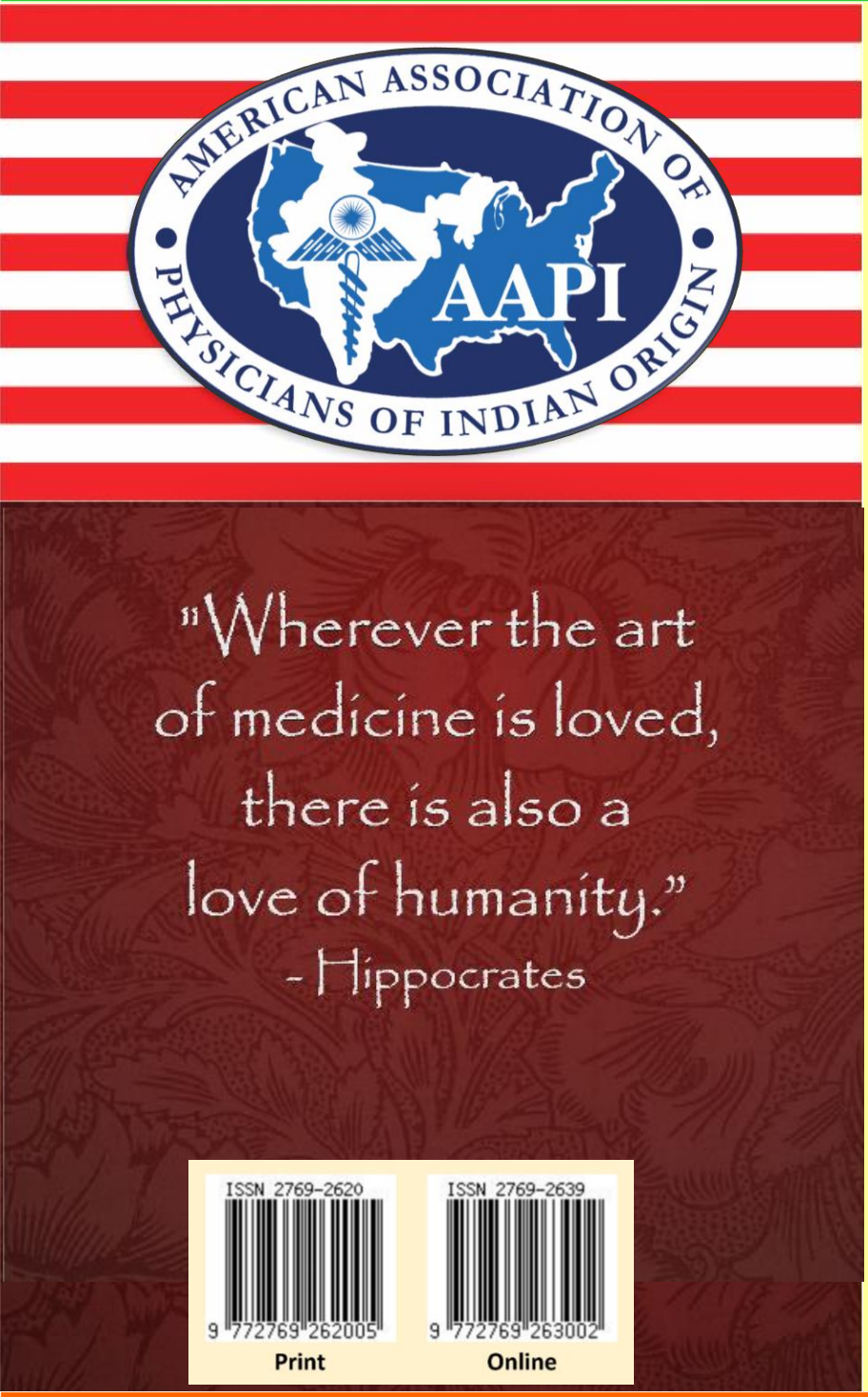
JAAPI

Journal of the American Association of Physicians of Indian Origin

Vol. 2 No. (3) Winter 2022



ISSN 2769-2620
9 772769 262005
Print

ISSN 2769-2639
9 772769 263002
Online

In this Issue...

This Winter Issue of JAAPI is Dedicated to

Sir C. V. Raman

Nobel Prize in Physics 1930

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About 100 years ago Sir C. V. Raman made a groundbreaking discovery of Raman Effect, which then impacted physical sciences only. But today Raman Spectroscopy is revisiting and penetrating biomedical sciences and clinical diagnosis at sub-molecular level and thus strengthening Precision Medicine. Sir C.V. Raman's discovery was far ahead of his time.

JAAPI: Winter 2022 Issue, Vol 2 No. (3)

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JAAPI is a Publication of the

American Association of Physicians of Indian Origin (AAPI)

600 Enterprise Dr., Suite 108, Oak Brook, IL 60523

https://www.aapiusa.org/jaapi/

Pioneers in Medicine and Healthcare

Sir Chandrasekhara Venkata Raman

Winner: 1930 Nobel Prize in Physics

A Scientist Far Ahead of His Time

Photo: Nobel Lectures, Physics 1922-1944, Elsevier Publishing Co., Amsterdam
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In the history of science, we often find that the study of some natural phenomenon has been the starting point in the development of a new branch of knowledge. – Sir C. V. Raman

Generally, the progression of science and medicine moves at a steady pace. However, now and then the discovery of a groundbreaking phenomenon or invention of a marvelous technology accelerates the progress forward tremendously by either opening a new world or markedly enhancing our ability to move fast tearing down the barriers. We have seen such discoveries or inventions, like – X-rays, genetic code, microscope, penicillin, insulin, hybridoma technology, restriction endonucleotidases, genetic engineering, PCR, and sequencing of human genome, CRISPR/Cas9, among others. With most of these discoveries or inventions, we learned of their significance or applications in opening new avenues thus markedly expanding our knowledge and ability. However, none made a second or third resurrection with hitherto unknown applications. In this respect, Raman Effect or Raman Spectroscopy, which was discovered a century ago, stands unique. Within a few years after its discovery, Raman Spectroscopy penetrated virtually into every aspect of physical and material sciences, chemistry, astrophysics, and other fields. Biology and medicine were not touched. But recently, Raman Spectroscopy is making rapid strides into biomedical sciences and clinical diagnosis at sub-molecular level, and thus strengthening Precision Medicine. Sir C. V. Raman could not imagine that one day his groundbreaking invention will impact biomedical sciences and clinical diagnosis so deeply. It took so long as supporting sciences and technologies must develop to understand the impact of Raman Spectroscopy in medicine and healthcare. **Thus, Sir C. V. Raman, a Nobel Laureate in Physics, became an unwitting Pioneer in Medicine and Healthcare.**

Sir C. V. Raman has been a household name in India and was known worldwide in the scientific field. He was unique, as he was one of the few in sciences or medicine who won a Nobel Prize without a Ph.D. or M.D. degree. Raman obtained his B.A. degree from the University of Madras with gold medals in physics and English. While still a student, Raman published his first paper in the British journal *Philosophical Magazine*. Later he earned M.A. degree from Madras University with the highest distinction. Following his family tradition, Raman took a job as Assistant Accountant General in Kolkata. But it was his freelance research work carried out at the Indian Association for the Cultivation of Science (IACS) that helped him to establish as a scientist within a short period. Working at IACS during his free time, Raman published several outstanding papers in prestigious journals. The impact was so strong by 1915, when Raman was 27 years old, the University of Calcutta assigned research scholars to work under his supervision at the IACS. By 1919, Raman guided more than a dozen students working at the IACS part time on freelance basis, while doing his breadwinning job as Assistant Accountant General. Following that, Raman was chosen by the University of Calcutta as Palit Professor of Physics, despite strong objection by some members of the Senate of the university, as he had no Ph.D. qualification. Raman reluctantly resigned from his accounting job with the government, which was paying twice as compared to the new professor position. Later, the University of Calcutta conferred honorary Doctorate in Science (D.Sc.) on Raman.

In 1919, Raman started his research work on scattering of light. He was keen to investigate how seawater acquires blue color. Using simple optical equipment, pocket-sized spectroscope, and a Nicol prism, Raman studied the sea water. After making several discoveries on scattering of light and publishing high impact papers, on February 16, 1928, Raman and A. S. Krishnan, his Research Associate, sent a manuscript to the *Nature* titled *A New Type of Secondary Radiation*, which was published on March 31st. Raman and Krishnan spent hardly 200 rupees on this work. But this fetched Nobel Prize to

Raman in 1930. During the intervening two years period, quite a few European physicists reported successful reproduction of Raman Effect, the benchmark of good science. Peter Pringsheim at the University of Berlin was able to reproduce Raman's data as early as in June 1928 and called it *Ramaneffekt* (Raman Effect) and *Linien des Ramaneffects* (Raman Lines) in his articles published soon after that. These made Raman so confident that he was destined to receive the Nobel Prize, in June 1930 he booked a ticket to Sweden in advance, although the Nobel Prize winners were not announced until November. As he expected, in 1930 Raman won the Nobel Prize in Physics "for his work on scattering of light and for the discovery of the effect named after him". The Nobel Committee cited Raman's work: *When light meets particles that are smaller than the light's wavelength, the light spreads in different directions. This occurs, for example, when light packets—photons—encounter molecules in a gas. In 1928 Venkata Raman discovered that a small portion of the scattered light acquires other wavelengths than that of the original light. This is because some of the incoming photons' energy can be transferred to a molecule, giving it a higher level of energy. Among other things, the phenomenon is used to analyze different types of material.* Raman Effect was one of the earliest proofs of the quantum nature of light. While awarding Hughes Medal to Raman, Earnest Rutherford, President of the Royal Society, said that Raman effect was among the best three or four discoveries in experimental physics in the previous decade.

Raman also did research work on acoustics and Indian musical instruments, X-rays, crystals, and diamonds. Besides the Nobel Prize, he received several prestigious awards, including Bharat Ratna from the Government of India. He was elected as a Fellow of the Royal Society (FRS) and was knighted in 1929. Raman was the first Indian Director of the Indian Institute of Science (IISc) in Bangalore. He founded the Indian Academy of Sciences and started publishing the academy's journal *Proceedings of the Indian Academy of Sciences*.

Raman Spectroscopy in Biomedical Sciences and Clinical Diagnosis and Therapy: In recent years, several scientific publications reported the application of Raman Spectroscopy in medical field. Raman Spectroscopy per se, and its modified versions, such as Surface-Enhanced Raman Spectroscopy (SERS), Spatially Offset Raman Spectroscopy (SORS), Coherent Anti-Stokes Raman Spectroscopy (CARS), and Stimulated Raman Loss (SRL) along with other powerful technologies, such as Atomic Force Microscopy (AFM) and machine learning are making rapid strides into various areas of biomedical sciences and clinical diagnosis and therapy. This could not be imagined until a couple of decades ago. What is interesting, by positioning itself at sub-molecular level, Raman Spectroscopy ushering us into the arena of Sub-molecular Diagnosis, which greatly empowers us to move into Precision Medicine. In other words, Raman Effect was discovered more than 60 years before the advent of Evidence-based Medicine, which is in the process of being replaced by Precision Medicine now. **Thus, Raman's groundbreaking discovery was about a century ahead in time.** In the following key aspects of Raman Spectroscopy in Biomedical Sciences and Clinical Diagnosis and Therapy are listed with references to the sources.

Biomedical Sciences: Raman Spectroscopy has been useful in monitoring blood glucose in a non-invasive manner (1); therapeutic drug monitoring and determination of metabolites (2); analysis of biomolecules in biomedical fluids (3); and analysis of pharmaceutical solids (4). Raman Spectroscopy can also be used for studying biochemical composition and analysis, and imaging of living microglial cells (2). Raman Spectroscopy and Surface-enhanced Raman Spectroscopy (SERS) are powerful vibrational spectroscopy techniques being developed for highly sensitive pathogen identification in complex clinical samples (5). Raman Spectroscopy can also determine the atherosclerotic plaque composition (6). Detection of multi-resistant clinical strains of *E. coli* is made possible by Raman Spectroscopy (7). Measurement of methemoglobin concentration (8) is another application of Raman Spectroscopy. Raman Spectroscopy on blood samples of patients with end-stage liver disease provides many insights into the disease (9). Raman Spectroscopy is helping in assessment of composition of bone (10), in serum-based diagnosis of asthma (11), and biomedical analysis of alterations in red blood cells at molecular level (12).

Clinical Diagnosis and Therapy: Raman Spectroscopy has emerged as a non-invasive and versatile diagnostic technique. This is due to unique advantage of Raman Spectroscopy over other currently available technologies, namely the ability to provide molecule-specific information with ultrahigh sensitivity at near-physiological conditions. At the same time, Raman Spectroscopy does not need extensive sample preparation, and is not affected by water molecules in the samples. Application of Raman Spectroscopy for in vivo medical diagnosis is often termed as Optical Biopsy technique due to its

characteristics (13, 14). Combined with atomic force microscopy (AFM), Raman Spectroscopy has emerged as a multi-functional and powerful toolkit for probing nano structural, biomechanical, and physicochemical properties of biomedical samples. These find applications to investigate pharmacotherapy, surgical evaluation, and medical therapy in conditions such as progressive keratoconus, skin rejuvenation, healing of Achilles tendinitis, orthodontic treatment, and toothbrushing time to minimize the loss of teeth after exposure to acidic drinks (15). Raman Spectroscopy is making strides into disease detection and sensing, especially in cancers. Raman Spectroscopy is providing molecular diagnostics in precancerous changes in tumors (16). Coherent anti-Stokes Raman (CARS) microscopy and stimulated Raman loss (SRL) microscopy, which are orders of magnitude more efficient than Raman Spectroscopy are enabling us to acquire high quality chemically specific images in seconds (17, 18). The development of spatially offset Raman Spectroscopy (SORS) and renaissance of Raman Spectroscopy are permitting non-invasive deep diagnosis of bone diseases and cancer (19). The combination of Raman Spectroscopy with machine learning holds promises for developing an accurate, inexpensive, fast diagnostic tool in a non-invasive manner (20). Applications of Raman Spectroscopy in prostate cancer include biopsy analysis, assessment of surgical margins and monitoring of treatment efficacy (21). Raman Spectroscopy allows rapid diagnosis of nasopharyngeal cancer (22); head and neck cancers (23); hepatocellular carcinoma (24); gastric cancer (25); bladder cancer (26, 29); colorectal cancers (27); cervical cancers (28); lung-cancer (30); breast cancer (31); dysplastic and malignant oral lesions (32); and cutaneous melanoma (33). Raman Spectroscopy is helping differentiation of adenomatous from hyperplastic polyps (36). It is also functions as a potential diagnostic tool for oral diseases (34) and in rheumatology (35). Finally, Raman Spectroscopy is helping in studying prognosis of macular degeneration (37).

Regenerative Medicine: In the arena of regenerative medicine, Raman Spectroscopy is helping us in monitoring skeletal muscle cells and skeletal regeneration (38), and other aspects of regenerative medicine too (39, 40)

Neurodegeneration: Raman Spectroscopy is emerging as a tool in neurodegenerative disease research and diagnosis (41). Raman Spectroscopy helping to diagnose Alzheimer's disease and dementia with Lewy Bodies in blood (42), or by cerebrospinal fluid analysis (43). It is also helping in the diagnosis of Huntington's disease (44).

Thus, it is a question of time when Raman Spectroscopy and technologies derived from it belong to medicine and healthcare and will be used routinely, as part of the Precision Medicine.

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Contributed by: Bellamkonda K. Kishore, M.D., Editor-in-Chief of JAAPI

Invited Editorial

Kidney Disease: The Silent Killer that Needs Our Voice

Agnes B. Fogo, M.D.
President, International Society of Nephrology (ISN)

Chronic kidney disease (CKD) is the 11th leading cause of death globally. Kidney disease is also increasing rapidly as a cause of death and is now the 6th fastest-growing cause of death (1). The high rate of existing kidney disease and its accelerating rise pose significant healthcare challenges for governments, particularly in low and middle-income countries. Current estimates are that 1.2 million deaths globally per year are due to kidney disease (2).

In addition to direct deleterious effects on the kidney, kidney diseases also increase a wide range of cardiovascular diseases, due to complex crosstalk (3-5). Despite the ongoing increase in mortality rates, kidney disease is still a "silent killer". This crisis related to kidney disease does not dominate either political or public discourse. The International Society of Nephrology (ISN) is the only kidney professional society in official relations with the World Health Organization (WHO). In this role, the ISN urges for increased prioritization of kidney-related advocacy. We have proposed the addition of kidney-relevant diagnostics and treatment to the list of policy options and cost-effective interventions WHO's Member States should prioritize. In addition to WHO's guidance to prevent and control well-recognized non-communicable disease (NCD), these added priorities will significantly and positively impact not only kidney health but health in other organ systems, including a wide range of cardiovascular diseases. Details of these proposals are listed in the latest round of consultations in Appendix 3 of the WHO Global NCD Action Plan for 2013-2030 (6).

As specifically noted in a 2016 Global Burden of Disease (GBD) report, omitting chronic kidney disease, an NCD that is "comparably prevalent" to other high-priority NCDs, should be properly addressed (7). Notably, **850 million people worldwide are now estimated to have some form of kidney disease** (8). As shown in the 2016 GBD report, kidney-related disability-adjusted life years (DALYs) represented about 65% of all diabetes DALYs and more than most individual cancers. Between 2.3 and 7.1 million people with kidney failure die prematurely because of a lack of access to dialysis and transplantation. Most of these deaths occur in countries where infrastructure and resources are insufficient and catastrophic payments are required for life-sustaining interventions (9). Even with access to dialysis or transplantation, mortality is increased in those with end-stage kidney disease. Thus, overall, it is estimated that globally between 5 and 10 million people die prematurely related to kidney disease (10).

Kidney disease is also an important contributor to **increased morbidity and mortality from other diseases,** including cardiovascular disease. For example, chronic kidney disease may be a stronger risk factor for coronary events than diabetes. When the two conditions co-exist (which occurs in a third of patients with diabetes), the risk of cardiovascular events and overall mortality is much increased (11). Further, kidney disease is an important complication in various conditions such as diabetes, hypertension, and obesity. Various kidney injuries can also develop secondarily in some infections such as HIV, malaria, tuberculosis and hepatitis B and C. During the recent COVID-19 pandemic, acute kidney injury was an important complication increasing mortality, beyond the severe respiratory disease caused by COVID-19 (12). In addition, those with preexisting chronic kidney disease have a worse outcome when also infected with various pathogens.

Treatment of kidney failure with chronic dialysis or transplantation imposes high and disproportionate costs on health systems, many of which cannot afford to provide universal access and healthcare coverage for these treatments. Many of the adverse consequences of kidney disease are, however, preventable. For example, integrating chronic kidney disease screening and management strategies into national NCD programs can reduce the burden and cost of chronic kidney disease care, reduce the cumulative incidence of kidney failure, and improve overall life expectancy, especially in developing countries (13). The 2016 Global Burden of Disease report also outlined the high burden of non-diabetes, non-hypertension-related chronic kidney disease in low-income countries. These data further support initiatives to specifically

address kidney disease in screening programs, beyond blood pressure and diabetes checks (14). These could include dipstick testing for proteinuria and measurement of serum creatinine to calculate an estimated glomerular filtration rate (eGFR). While national policies and strategies for NCDs, in general, are common in many countries, specific policies directed toward screening, prevention, and treatment of kidney disease are often lacking (15). We suggest that such policies could be reviewed, and the benefits of adding additional screening for kidney disease considered. The specific strategies will depend on local health burdens, local specific kidney disease prevalence and resources.

The ISN has as one of its main missions the goal to forge new partnerships and collaborations to bridge the gaps in kidney care. These include active participation in developing future generations in the World Health Organization's Youth Council (16), where a member of ISN's Young Nephrologists Committee (YNC) (17) will serve for a term of two years. We are also continuing to bring kidney health to the forefront of public discourse with the 2023 World Kidney Day (18) campaign. World Kidney Day has been held yearly since its inception in 2006 as a joint initiative of the ISN and the International Federation of Kidney Foundations. We now aim to expand awareness of kidney disease and build on such initiatives as outlined above with WHO and World Kidney Day to have kidney disease awareness and increased screening and capacity to recognize and treat all regions at all times. Unsurprisingly, and as recent years have sadly shown to all of us, in the face of emergencies, people living with kidney disease are among the most vulnerable in the population due to their ongoing requirements for consistently coordinated care. Kidney disease is a high-priority NCD that now requires urgent consideration by both health care stakeholders and political leaders. Initiatives led by WHO and other agencies for sustainable development goals agenda are important and provide a platform for raising awareness of NCD health care and monitoring needs. At the next UN High Level meetings on universal health coverage in 2023 and on NCDs in 2024, important guidance will emerge to lead us all in striving for better and sustainable health worldwide. We now call for kidney disease to emerge from the silent shadows in such global undertakings and become an integral part of the global policy response.

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Professor Agnes Borge Fogo completed her medical and pathology training at the Vanderbilt University, Nashville, TN, USA. Her main research interests are focused on progression of chronic kidney disease and crosstalk between tubules and glomeruli, funded by the NIH and other sources. She has created an online Atlas of Renal Pathology with the American Journal of Kidney Diseases (AJKD), and the National Kidney Foundation (NKF), and two renal pathology books. She received the Robert G. Narins award from the American Society of Nephrology (ASN), and the Roscoe R. Robinson award from the International Society of Nephrology (ISN) for her contributions in teaching. She has been a councilor of the ISN, served as Chair of its Renal Pathology Committee, with focus on developing educational tools related to kidney biopsy interpretation. She started her 2-year term as the President of the ISN at the 2021 World Congress of Nephrology (WCN) meeting. She is currently the John L. Shapiro Professor of Pathology, Microbiology and Immunology, Professor of Medicine and Pediatrics and Director of the Renal/Electron Microscopy Laboratory, at Vanderbilt University Medical Center.

ISN
INTERNATIONAL SOCIETY OF NEPHROLOGY

The ISN is a global professional association dedicated to advancing kidney health worldwide, through education, grants, research, and advocacy. Established in 1960, the ISN has promoted and worked toward a future where all people have equitable access to sustainable kidney health. The ISN embraces the principles of diversity and believes that inclusivity fosters the creativity, innovation, and excellence needed to achieve the mission of advancing kidney health worldwide.

From the Editorial Desk

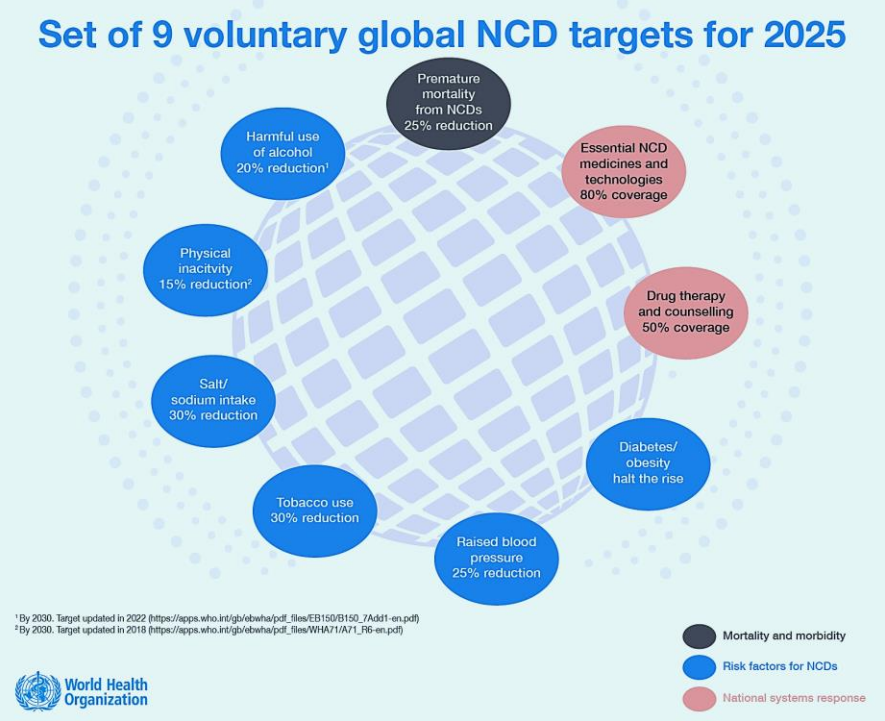
Reducing the Burden of Non-Communicable Diseases

Sharmila Makhija, M.D., MBA
Associate Editor-in-Chief of JAAPI

Noncommunicable diseases (NCDs), including heart disease, stroke, cancer, diabetes, and chronic lung disease, are collectively responsible for 74% of all deaths worldwide. More than three-quarters of all NCD deaths, and 86% of the 17 million people who died prematurely, or before reaching 70 years of age, occur in low- and middle-income countries. – World Health Organization

Non-communicable diseases (NCD) are defined as chronic medical conditions that are not transmissible from person to person, require long term management and are often a result of genetic, physiological, environmental, or behavioral factors. The World Health Organization reports that globally, NCDs contribute to 74% of all deaths every year, equivalent to 41 million people, with the vast majority of cases seen in low- and middle-income countries. The four main groups of non-communicable diseases are cardiovascular, cancer, chronic respiratory diseases, and diabetes. Together they account for over 80% of all NCD deaths (1).

Well-established modifiable risk factors include the effects of alcohol and tobacco use, unhealthy diets, and physical inactivity. Risk factors that include an unhealthy diet coupled with physical inactivity can often lead to hypertension, obesity, metabolic syndrome and diabetes, all known co-morbidities for cardiovascular disease, the leading NCD. Strategies have focused on modifying diet and lifestyle behaviors to manage the rising rates of NCDs. (1-3). Because of increases in risk factors and aging population in India, the prevalence of NCDs has escalated, contributing to over 60% of all deaths in the country and is predicted to continue this trajectory (4). In June 2022, the World Health Organization proposed a set of 9 voluntary NCD targets for 2025 to reduce their global prevalence as shown in the following.



Yet evolving research has revealed that maternal and infant nutrition and metabolism may play a significant role in the eventual development of NCDs. When fetuses are exposed to a limited nutrient supply, structural and metabolic changes can lead to heart disease and diabetes in adulthood (3, 5, 6). Initially seen in undernourished and low-birth weight infants, with additional research these same changes were seen in macrosomic or large babies as well. For example, it has been shown that maternal folate deficiency leads to obesity and cardiometabolic risk in the offspring (7), and high sodium intake in the first 6 months after birth may lead to higher blood pressure by sensitizing the kidneys during postnatal period (8). The concept of fetal programming has developed further with significant DNA chemical changes discovered. As the embryo is most vulnerable during the periconceptional period, this may be the ideal time to focus our efforts on preventing the development of future NCDs (9).

As our scientific understanding of the intrinsic and extrinsic risk factors of NCDs continue to mature, we should be cognizant of focusing efforts in a more direct and effective way to have the most impact on managing these sets of chronic diseases. In the United States, the American Board of Internal Medicine is offering board certification in Lifestyle Medicine. In addition to the current protocols in place addressing lifestyle changes, spreading awareness among healthcare providers in maternal and infant nutrition is imperative. This could include educating our medical and nursing students, residents, and practicing providers in identifying high risk reproductive age women and providing these women with clear guidance on proper nutrition, for themselves and their children, and its impact on their child's future risk of developing a chronic disease. We likely need this in other specialties and to consider starting this training earlier as part of the medical school curriculum. It is time for doctors to receive formal education and training in nutrition.

In the recently held AAPI Global Healthcare Summit 2023 in Visakhapatnam, India, the JAAPI-sponsored symposium on the on NCDs in India highlighted the importance of the role of maternal and infant nutrition in the development of NCDs in adulthood. Experts in the field explored the evolving epidemiological findings, scientific evidence, and public health resources with proposed remedial measures so a new way of addressing NCDs in India at the national, regional, and local levels will emerge based on science and evidence-based medicine.

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JAAPI

Journal of the American Association of Physicians of Indian Origin

ISSN: 2769-2620 (Print) & 2769-2639 (Online)

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- **Clinical Studies:** Clinical studies can be observational or retrospective analysis of data or prospective randomized studies. All clinical studies should be conducted under the regulations and guidelines, documenting informed consent, protection of research subjects, inclusion of minorities etc., as per the guidelines of the US Public Health Service. Rigorous statistical analysis should be followed. Raw data should be provided for analysis if required. These articles can be up to 5,000 words, excluding title page, abstract, tables, legends, and references. Maximum number of figures or tables are 7 combined. Additional figures or tables should be justifiable for the study. Supplemental Information (SI) is allowed for deposition.
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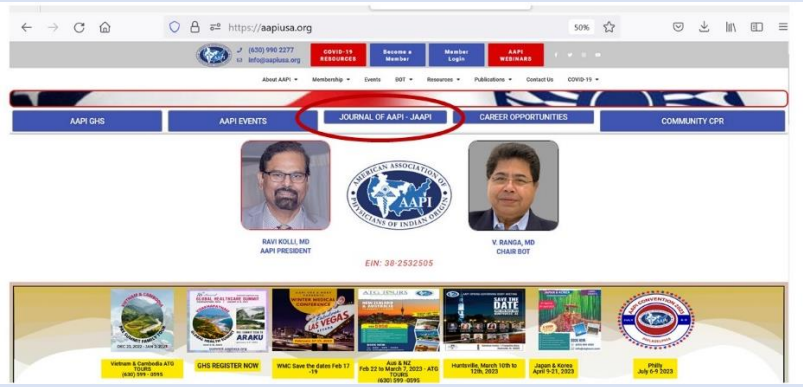

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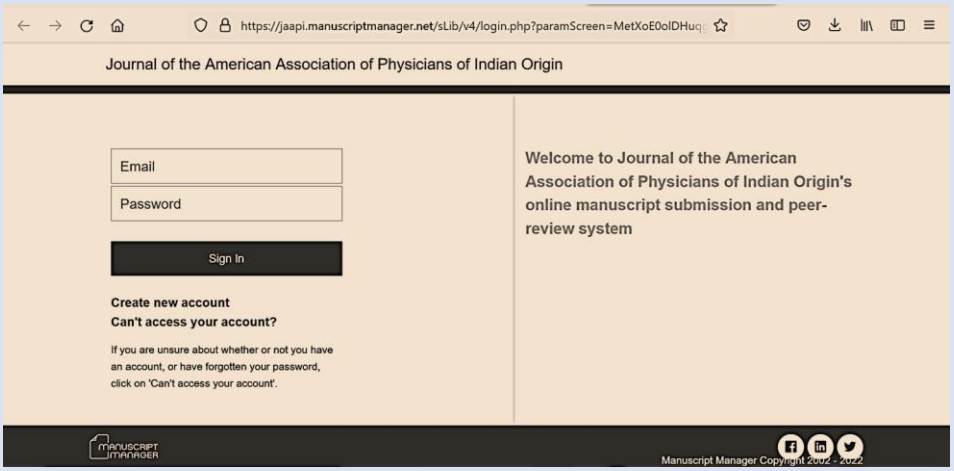

Prospective authors should create a new account as per the instructions. This will remain as portal of entry to authors throughout the review process and beyond. Once inside, authors can configure their profiles, and peruse the profiles of the members of the Editorial Board and send messages to them or receive messages within the system without the need for using emails.

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for the
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Starting from 2022, each year JAAPI will give 3 awards for the Best Original Research Articles submitted by YPS/MSRF Members as the first authors and accepted for publication in JAAPI after peer-review process.

The Awards include the following cash prizes and a citation on a plaque.

Winner – One Award $1,000
Runners – Two Awards $500 each

Membership in YPS/MSRF is mandatory at the time of submission of the Original Research Articles.

A panel of judges drawn from the Editorial Board will decide the winners.

Only Original Research Articles are eligible for entry, not Reviews or Case Reports etc. The criteria and details of the process will be published in the JAAPI web page.

Call for Articles on
Asian American Healthcare Issues

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It has been well documented that Asian Americans, especially the South Asians, have higher prevalence of cardiovascular diseases and face higher cardiometabolic risk. This is attributed to several factors, including genetics. On May 10, 2022, the Newsroom of the American Heart Association pointed out that "one-size-fits all" is flawed for assessing cardiovascular diseases risk among Asian Americans. In view of the above, starting from Spring 2022 Edition, JAAPI has a section dedicated to **Asian American Healthcare Issues.** We welcome articles on all aspects of Asian American or South Asian healthcare under this section.

In-Depth Review

Hepatitis B Reactivation in the Era of Chronic Immunosuppression

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Received: *August 11, 2022*
Accepted: *December 7, 2022*

Citation:
Colvin et al, JAAPI 2(3): 22-34, 2022

Abbreviations Used: AASLD – American Associate for the Study of Liver Diseases; AGA – American Gastroenterological Association; APASL – Asian Pacific Association for the Study of Liver; ccDNA – covalently-closed DNA; CCL – chronic lymphocytic leukemia; EASL – European Association for the Study of Liver; HBcAg – hepatitis B core antigen; HBeAg – hepatitis B e-antigen; HBsAg – hepatitis B surface antigen; HBV – hepatitis virus B; IVDU – intravenous drug use; IBD – inflammatory bowel disease; JAK – Janus kinase; NCCN – National Comprehensive Cancer Network; rcDNA – relaxed-circular DNA

Abstract: The rates of acute Hepatitis B virus (HBV) infection have drastically declined in the United States over the past several decades. Infection numbers declined largely due to access to vaccination, although there is concern for rising cases with the opioid crisis. However, increased use of immunosuppressive medications leaves patients with previous HBV exposure at rising risk for reactivation. The fields of cancer/malignancy, rheumatologic-inflammatory diseases, solid organ transplantation, bone marrow transplantation, and inflammatory bowel disease (IBD) are developing new treatments at a rapid pace. Studies assessing awareness of HBV reactivation management shows that continued education is vital. The purpose of this article is to heighten awareness of HBV reactivation in the setting of chronic immunosuppression and immunotherapy use. In this article, we will review the pathophysiology of HBV infection and reactivation along with diagnostic criteria for HBV reactivation. We aim to provide information to stratify patients based on risk factors for HBV reactivation and evaluate many of the most prescribed immunosuppressants through an in-depth literature search. We will discuss the decision for patients to either receive prophylactic anti-viral treatment or monitor through frequent clinic visits and laboratory observations. Guidelines for prophylactic treatment or laboratory monitoring differ depending on several risk factors and differ amongst the AASLD, EASL, and AGA. Lastly, the paper will cover treatment of HBV reactivation including medications and length of therapy. In conclusion, there is a clear indication for anti-viral prophylaxis in patients with active HBV infection undergoing treatment with immunosuppressive regimens. However, more research is required for patients with occult infection.

Key Words: HBV reactivation, Liver, Hepatitis, Immunosuppression, Immunotherapy, Screening, Prophylaxis, Guidelines, Management

Introduction: With the advent of vaccination, infection with Hepatitis B virus (HBV) has become a preventable disease. However, access to care may limit those who can be vaccinated and thus risk exposure and/or transmission of HBV. HBV is spread by way of semen, blood, or other body fluids (1, 2). The majority of HBV is currently transmitted by intravenous drug use (IVDU) or sexual contact, but transmission via mother-baby or vertical transmission remains an ongoing issue in some regions (1, 2). If transmission occurs after birth, particularly as an adult, the risk of developing chronic HBV is low, approximately 5%. However, the risk of developing chronic HBV when transmissions occur as a child is approximately 90% (2).

The most recent data from both census data in the United States of America and foreign-born migration estimate around 2.2 million people in the USA are infected with HBV (1, 3, 4). The rate of acute HBV has declined since the vaccination became commercially available in 1982. Cases went from 9.6 cases per 100,000 population in 1982 to 1.1 cases per 100,000 population in 2015 (1, 5). The opioid crisis in the US has become an avenue for new cases to emerge, and three states showed new cases increase over 100% due to IVDU (1, 3).

New drug developments in immunotherapy and immunosuppression also present challenges to HBV-infected patients, increasing the risk of HBV reactivation. In the fields of cancer/malignancy, rheumatologic-inflammatory diseases, solid organ transplantation, bone marrow transplantation, and inflammatory bowel disease (IBD) these therapies are developing at a rapid pace. By targeting the immune system, these therapies treat the primary disease, but unfortunately risk worsening other previously controlled diseases, such as HBV infection. This article heightens awareness of HBV reactivation in the setting of chronic immunosuppression and immunotherapy use. We aim to provide information to stratify patients based on risk factors for HBV reactivation, evaluate medications that may lead to HBV reactivation, and discuss best practices for prevention and treatment of HBV reactivation.

A. Pathophysiology of Infection and Reactivation:

Infection: HBV is part of the Hepadnaviridae family, and the infecting virion is made of a capsid with a surrounding envelope (6). The entire HBV genome is made of an open circular DNA with four reading frames (6). Following transmission, HBV travels through the bloodstream before eventually arriving to the hepatocytes (7). The entry of HBV into hepatocytes involves hepatitis B surface antigen (HBsAg) and interaction with surface proteins on the hepatocyte (6). The virus exists in two forms, relaxed-circular DNA (rcDNA) and covalently closed DNA (ccDNA) (6). Following entry into the hepatocyte, the viral capsid is released into the cytoplasm before being transported to the nucleus as rcDNA. In the nucleus, rcDNA is converted to ccDNA, which is necessary for protein production and viral replication. (7). ccDNA also contributes to the production of core antigen (HBcAg) that eventually leads to host production of core Ab (HBcAb). HBV is not cytopathic/pathological by its own activity, rather it's the body's immune response to the virus that causes inflammation. The body attempts to control viral replication by production of hepatitis B surface antibody (HBsAb) and loss of detectable HBsAg. The immune response can be quite strong in the acute setting leading to massive hepatic necrosis with loss of hepatic function or mild with little response leading to chronic HBV.

Stages of Chronic Infection: The European Association for the Study of the Liver (EASL) proposed updated nomenclature for chronic HBV disease in 2017. Their nomenclature divides chronic HBV into 5 phases depending on the presence of HBeAg, HBV DNA levels, alanine aminotransferase (ALT) levels, and liver inflammation. The patients with chronic HBV will be HBc antibody positive (8). The following stages have been identified (8).

- Phase 1 is characterized by HBeAg positive status, high levels of HBV DNA, non-elevated ALT levels, and minimal evidence of liver inflammation or fibrosis.
- Phase 2 is characterized by HBeAg positive status, high levels of HBV DNA, elevated ALT levels, moderate-severe inflammation, and fibrosis.
- Phase 3 is characterized by absence of HBeAg, presence of serum antibodies to HBeAg, undetectable or low HBV DNA levels, normal ALT levels, and minimal inflammation or fibrosis.
- Phase 4 is characterized by absence of HBeAg, presence of serum antibodies to HBeAg, moderate to high HBV DNA levels, fluctuating or persistently elevated ALT levels, inflammation, and fibrosis.
- Phase 5 is characterized by HBsAg negative status, normal ALT levels, serum HBV DNA can be negative or elevated, and minimal liver inflammation. Detection of HBsAg is dependent on sensitivity of the assay used for detection.

Table 1: Overview of the different phases of hepatitis B virus infection

	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
Disease Status	ACTIVE				OCCULT
Terminology	Immune tolerant	Activation	Carrier	Reactivation	Occult
HBsAg	+	+	+	+	-/+
HBeAg	+	+	-	-	-
HBV DNA	++	++	Low / Undetectable	+	Undetectable
ALT level	Normal	Elevated	Normal	Elevated	Normal
Liver inflammation	Minimal	Present	Minimal	Present	Minimal

Table based on EASL nomenclature (8)

Reactivation-Phase 4: HBV reactivation can occur in patients with HBsAg positive and negative serologies and can be spontaneous or following treatment with immunosuppressive regimens (7). For patients with HBsAg negative serology, HBV DNA can persist in the liver in the form of ccDNA despite undetectable serum HBV DNA (6). Proposed mechanisms of reactivation include weakening of the anti-HBV immune response, increases in viral replication, and other mechanisms which remain less clear. A weakened immune response, as is present in patient's on immunosuppressants, may result in unchecked HBV replication. Additionally, some drugs including cortico-steroids, induce increased HBV replication (7). Thus, following treatment with immunosuppressive regimen, there will be a significant increase in viral replication. Reactivation can be classified into 3 distinct Subtypes: i) increase in viral replication, ii) liver injury, and iii) recovery (9). Reactivation appears similar to initial infection with substantial increase in HBV DNA followed by liver injury that results from a delayed immune reaction (7, 9).

B. Diagnosing HBV Reactivation:

In 2018, the American Association for the Study of Liver Diseases (AASLD) provided updated guidelines for diagnosis of HBV reactivation (2). The criteria for HBV reactivation differs between patients that are HBsAg positive/anti-HBc positive and patients that are HBsAg negative/anti-HBc positive. In the HBsAg positive/anti-HBc positive group, HBV reactivation is defined as (i) >100 fold increase in HBV DNA compared to baseline level, (ii) HBV DNA >1000 IU/mL in a patient with previously undetectable level, or (iii) HBV DNA >10,000 IU/mL if no baseline level is available.[2] For patients that are HBsAg negative/anti-HBc positive, HBV reactivation is defined as (i) detectable HBV DNA or (ii) reappearance of HBsAg (2).

Table 2: Comparing the diagnostic criteria for HBV reactivation between patients that are HBsAg positive and HBsAg negative.

HBsAg+ patients	HBsAg-/anti-HBc+ patients
i) >100-fold increase in HBV DNA compared to baseline. ii) HBV DNA > 1000 IU/mL in patient with previously undetectable level. iii) HBV DNA > 10,000 IU if no baseline level is available.	i) Detectable HBV DNA ii) Reappearance of HBsAg

C. Awareness of HBV Reactivation in Oncology and Rheumatology

Oncology: Immunosuppressive regimens including chemotherapy are associated with increased risk for HBV reactivation. In 2013, a questionnaire among physicians licensed to prescribe chemotherapy in Turkey, revealed only 59% of surveyed physicians stated that they always performed pretreatment screening for HBV reactivation, and 51.8% of physicians stated they would observe for HBV reactivation with liver function studies (10). Likewise, another study found that 20% of practicing oncologists never performed HBV screening before initiation of chemotherapy (11). Thus, NCCN Prevention and Treatment of Cancer-Related Infections Panel now recommends pretreatment screening for all oncology patients before chemotherapy initiation (12).

Rheumatology: Immunosuppressive and immunothera-peutic regimens have become increasingly more prevalent in the treatment of many rheumatologic diseases. While HBV reactivation has been recognized in rheumatologic patients undergoing immunosuppressive therapies, screening practices may not be sufficient in preventing HBV reactivation in patients with resolved HBV. In a 2010 study assessing screening practices of rheumatologists, nearly 50% of practitioners screened with HBsAg alone (13).

More recently, there appears to be increasing awareness in the field. In 2019, the Turkish Society of Rheumatology released a questionnaire to assess screening practices for practitioners who prescribe immunotherapeutic. Among the 48 respondents, all 48 recommended screening with HBsAg prior to initiating treatment, and 40/48 respondents also said they would screen with anti-HBc (14). Additionally, 2018 Meta-analyses found that HBV reactivation rates in rheumatic patients undergoing therapy have been steadily decreasing over the past 10 years (15).

D. Risk Factors for HBV Reactivation

The risk of HBV reactivation can be defined as high risk (representing HBV reactivation rate greater than 10%), moderate risk (1-10%), and low risk (less than 1%) and is affected by a multitude of causes including host, virologic, and immunosuppressive factors (16).

Host Factors: Host factors associated with increased risk for HBV reactivation include male sex and malignancy type (diffuse large B-cell lymphoma) (17, 18). Male sex has been associated with increased rates of HBV reactivation although the mechanism remains unclear. Patients with lymphoma undergoing chemotherapy have been observed to have increased rates of HBV reactivation, particularly diffuse large B-cell lymphoma (16). It remains unclear if this can be attributed to more immunosuppressive regimens in this cohort or if there is intrinsic risk for reactivation with lymphoma.

Viral Factors: Viral factors associated with HBV reactivation include positive HBsAg status, detectable HBV-DNA quantification and diminished HBsAb titers. HBsAg status has been widely recognized as a risk factor for HBV reactivation. The AASLD, American Gastroenterological Association (AGA), and EASL differentiate the use of prophylaxis based upon HBsAg status, and HBsAg should be screened for in all patients before undergoing immunosuppressive therapy (2, 18, 19). Patients positive for HBsAg undergoing chemotherapy have been noted to have HBV reactivation rates greater than 40% (17). A meta-analysis demonstrated that chronic HBV carriers receiving chemotherapy for solid tumors had reactivation rates ranging from 4-68%, while patients with occult infection had reactivation rates ranging from 0.3-9% (20).

Patients with detectable but non quantifiable HBV DNA have also been found to be at increased risk for reactivation when compared to patients with undetectable DNA. In a retrospective study assessing HBV reactivation in patients with B-cell lymphoma, 83% of patients with detectable but non quantifiable HBV DNA had HBV reactivation (18).

Patients with diminished HBsAb titers have been associated with increased risk for HBV reactivation. A recent study by Kotake et al showed that patients with titers <10.0 mIU/mL were at significantly increased risk for reactivation (21). In lymphoma patients undergoing treatment with rituximab, there was a 33.9% increased risk for reactivation for patients with negative HBsAb titers (22). This increased risk is likely attributed to a decreased immune response from the host.

Immunosuppressive Medication Factors:

Anti-CD20 Agents:

Rituximab: Rituximab is a monoclonal antibody directed against the CD20 antigen on B-lymphocytes. It is indicated for the treatment of CLL, non-Hodgkin lymphoma, rheumatoid arthritis, and other rheumatologic conditions. Rituximab has been heavily associated with HBV reactivation and is considered high risk for active chronic HBV as well as those with occult disease. Previous studies have noted HBV reactivation rates for active chronic HBV patients to range from 38-72% (23, 24). In a meta-analysis evaluating HBV reactivation in non-Hodgkin lymphoma (NHL) patients treated with rituximab, the cumulative incidence of HBV reactivation was noted to be 11.9% (46/387). This effect was noted in the occult cohort with the relative risk being 5.5 (p=0.0007) (25). Another meta-analysis evaluated occult patients with lymphoma treated with rituximab revealed HBV reactivation rates of 9.0% with a reactivation rate of 17.0% in prospective studies (26). Due to high risk of HBV reactivation, all patients with active and occult HBV treated with rituximab should receive anti-viral prophylaxis.

Ibritumomab: Ibritumomab is a monoclonal antibody directed against CD20 and induces apoptosis against B-lymphocytes. It is used in the treatment of non-Hodgkin lymphoma. Relatively little information is available regarding ibritumomab and HBV reactivation compared to other drugs within this class. However, one case report detailed HBV reactivation in a patient with active HBV and non-Hodgkin lymphoma. The patient was noted to have transaminitis and increased HBV DNA four weeks after initiating treatment with ibritumomab. The patient then underwent treatment with lamuvidine with normalization of liver enzymes within two weeks (27). Ibritumomab should be treated as high risk for HBV reactivation for both active and occult disease.

Obinutuzumab: Obinutuzumab is a monoclonal antibody that binds to CD20 molecules present on B-lymphocytes causing cytotoxicity and phagocytosis that is both antibody and complement mediated. It is indicated in the treatment of chronic lymphocytic leukemia and follicular lymphoma. In the phase III GOYA and GALLUM studies, the use of rituximab or Obinutuzumab based chemotherapy was studied in patients with B-cell non-Hodgkin's lymphoma. The protocol allowed for the use of

prophylactic anti-HBV nucelos(t)ide therapy at the discretion of the investigator. Patients with active HBV were excluded from the study although 232 patients with occult HBV were included. None of these patients received prophylactic anti-HBV nucleos(t)ide therapy (NAT). Of the 232, 27 (10.8%) developed HBV reactivation, with 17 of the patients receiving Obinutuzumab. Differences in reactivation rates between Obinutuzumab and rituximab were not statistically significant in this study (28). Much like rituximab, patients with active or occult HBV are at high risk for HBV reactivation and should receive anti-viral prophylaxis when treated with Obinutuzumab.

Ofatumumab: Ofatumumab is a monoclonal antibody that binds the CD20 molecule, expressed on B-lymphocytes. This results in lysis and toxicity in cells that overexpress CD20. Ofatumumab is indicated to treat chronic lymphocytic leukemia and relapsing multiple sclerosis. Clinical trials of ofatumumab excluded patients with chronic Hepatitis B (29), and to date, there are no incidents of associated HBV reactivation. However, ofatumumab should be treated as high risk considering the similar mechanism of action to rituximab.

IL-6 Receptor Antagonist Agents:

Tocilizumab: Tocilizumab is an interleukin-6 (IL-6) receptor antagonist and limits inflammatory responses by reducing cytokine and acute phase reactant production. It is indicated for multiple rheumatologic diseases including rheumatoid arthritis, giant cell arteritis, systemic juvenile polyarticular arthritis, and polyarticular juvenile idiopathic arthritis. One prospective study evaluated the safety of tocilizumab in patients with active or occult HBV. They observed HBV reactivation in 3/7 patients with active HBV infection while no patients with occult infection developed HBV reactivation (30). Another retrospective study evaluated fifteen patients with occult Hepatitis B undergoing treatment with tocilizumab for rheumatoid arthritis. Patients with active HBV were excluded from the study. There were no incidences of HBV reactivation in their cohort (31). Based on the limited data, patients with active HBV should be treated as moderate-high risk when undergoing treatment with tocilizumab and should receive anti-viral prophylaxis. Meanwhile, there is limited information regarding the safety of tocilizumab in patients with occult HBV, and caution should be used until further studies clarify its risk.

Sarilumab: Sarilumab is an IL-6 receptor antagonist and limits inflammatory responses. It is approved to treat rheumatoid arthritis. To date, there were no recorded incidences of HBV reactivation in patients with chronic or occult disease. Due to similar mechanism as tocilizumab, Sarilumab should be treated similarly to tocilizumab with moderate-high risk for reactivation in patients with active HBV.

Other Monoclonal Antibody Agents:

Ustekinumab: Ustekinumab is a human monoclonal antibody that binds and inhibits interleukin-12(IL-12) and IL-23, which are proinflammatory cytokines. IL-12, 23 inhibition prevents natural killer cell activation and T-cell activation and differentiation. Ustekinumab is frequently used in the treatment of psoriasis as well as IBD. One prospective study evaluated the safety of ustekinumab in 54 patients with HBV. They treated 10 patients with active HBV infection with 2 receiving viral prophylaxis. There were two incidences of HBV reactivation in patients that did not receive anti-viral prophylaxis. No patients with occult HBV infection received anti-viral prophylaxis, and there was one incidence of HBV reactivation in this group (32). Another retrospective study evaluated the safety of ustekinumab in patients with either active hepatitis B or occult infection. Only 10 patients were included in the study with 5 having active infection and 5 with occult infection. Four of the 5 with active infection received anti-viral prophylaxis, and none developed HBV reactivation. Additionally, no patients with occult HBV developed reactivation (33). Patients with active HBV infection should be treated as moderate risk when undergoing Ustekinumab therapy and receive anti-viral prophylaxis. Risk of HBV reactivation is uncertain in patients with occult HBV infection, and the AASLD states anti-viral prophylaxis or lab monitoring can be used in this group.

Vedolizumab: Vedolizumab is a humanized monoclonal antibody that binds alpha 4 beta 7 integrin thus blocking the interaction between the integrin and mucosal addressin cell adhesion molecule-1 (MAdCAM-1). This inhibition prevents migration of memory T-cell into inflamed parenchyma. Vedolizumab is used in the treatment of IBD. There is little information regarding HBV reactivation in patients treated with vedolizumab, and in clinical trials (GEMINI I, II, and III), there were no incidences of HBV reactivation (34). Risk of HBV reactivation is uncertain in this population. However, vedolizumab is a potent inhibitor of T-cell function and should therefore have the potential for HBV reactivation. Patients with active HBV should receive anti-viral prophylaxis, and depending on the clinical situation, occult patients can either receive anti-viral prophylaxis or be carefully monitored.

Anti-Tumor Necrosis Factor-Alpha (Anti-TNF):

Infliximab: Infliximab is a chimeric monoclonal antibody that binds tumor necrosis factor alpha inhibiting proinflammatory cytokines and leukocyte migration. It is indicated for ankylosing spondylitis, plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, and IBD. An observational study evaluated 80 patients treated with infliximab at their institution over a 4-year period. Three patients were noted to have active HBV infection at the time of infliximab infusion, and 2/3 developed HBV reactivation. The third patient received anti-viral prophylaxis with lamivudine (35). Another study pooled several retrospective and prospective studies to evaluate safety of anti-TNF use in patients with HBV exposure. They observed reactivation in 15/122 patients with active HBV infection with two of those patients undergoing treatment with infliximab (36). Additionally, there is risk for HBV reactivation in patients with occult disease, as seen in small studies and case reports (37-38).

Adalimumab: Adalimumab is a recombinant monoclonal antibody that binds tumor necrosis factor alpha inhibiting proinflammatory cytokines and leukocyte migration. Indications are similar to infliximab, but it is also used to treat hidradenitis suppurativa and juvenile idiopathic arthritis. In the above-mentioned meta-analysis, adalimumab showed a pooled prevalence of HBV reactivation to be 4.6%, although there was no listed analysis of active infection or occult disease (39). One retrospective study evaluated the use of adalimumab in patients with occult HBV infection and reported HBV reactivation in 3/19 (15.8%) of these patients (38). Another cohort study evaluated the use of adalimumab in 7 patients with occult HBV infection, and there was no incidence of HBV reactivation in this group (40).

Certolizumab: Certolizumab is a pegylated humanized antibody Fab' fragment of tumor necrosis factor that neutralizes TNF-alpha activity. Its indicated uses include ankylosing spondylitis, Crohn disease, plaque psoriasis, psoriatic arthritis, and rheumatoid arthritis. There is little information regarding the safety profile of certolizumab in patients with HBV exposure compared to adalimumab and infliximab. There was one incidence of HBV reactivation in the certolizumab clinical trial, and two additional incidences found through the pharmacovigilance database. There was no information given about HBsAg status of these patients or how HBV reactivation was diagnosed (41).

Golimumab: Golimumab is a human monoclonal antibody that binds to tumor necrosis factor alpha helping to reduce proinflammatory cytokines. It is indicated for treatment of ankylosing spondylitis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis. There were no incidences of HBV reactivation in patients treated with golimumab published to date but should be treated similarly to the rest of the anti-TNF medications.

JAK-2 Inhibitors:

Tofacitinib: Tofacitinib inhibits several JAK (Janus Kinase) isoforms, most notably JAK 1 and 3, leading to modulation of IL-6 and IFN signaling (42). It is indicated to treat rheumatoid arthritis, ulcerative colitis, psoriatic arthritis, and polyarticular juvenile idiopathic arthritis. One retrospective study evaluated the use of tofacitinib in 116 Taiwanese patients with rheumatoid arthritis. In their cohort, there were 6 with active HBV infection and 75 patients with occult infection. Of the six patients with active infection, four did not receive anti-viral prophylaxis with two patients developing HBV reactivation. There was no HBV reactivation in the occult infection group (43). Another case series evaluated 8 patients with occult infection treated with tofacitinib. There were no incidences of HBV reactivation in their cohort although two patients received anti-viral prophylaxis and two patients were lost to follow up (44). Tofacitinib can likely be treated as moderate risk for patients with active HBV infection and should be treated with anti-viral prophylaxis. Patients with occult HBV infection are likely low risk and can be closely monitored.

Baricitinib: Baricitinib is a selective, reversible inhibitor of JAK 1,2 that disrupts activation of proinflammatory cytokines. It is indicated in the treatment of moderate to severe rheumatoid arthritis. There is little clinical data regarding the use of Baricitinib in chronic HBV carriers as this group was excluded from previous clinical trials. In the phase III clinical trial, there were 215 patients with occult infection. Of the 215 patients, eight (3.7%) had quantifiable HBV DNA results (>29 IU/mL), of which four (1.8%) were diagnosed with HBV reactivation using the definition of HBV DNA>100 IU/mL. Antiviral therapy was administered in only 3/8 of the patients with quantifiable HBV DNA (45). Baricitinib can be treated similarly to tofacitinib regarding prophylaxis vs lab monitoring.

Upadacitinib: Upadacitinib is a selective JAK-1 inhibitor that diminishes proliferation and survival of immune cells, T cell differentiation, and macrophage activation. It is indicated for moderate to severe rheumatoid arthritis. There were no published cases of upadacitinib associated HBV reactivation and should be treated similarly to the other medications in this class.

B-Lymphocyte Stimulator Inhibitor (BLys):

Belimumab: Belimumab inhibits B-lymphocyte stimulator, which is an essential modulator of B-cell survival and differentiation. It is primarily used in the treatment of systemic lupus erythematous (SLE). There is no formal recommendation for using belimumab in chronic carriers or patients with resolved/occult HBV. There are no recorded incidents of HBV reactivation with belimumab use, and there is limited information on its risks. A randomized phase III clinical trial assessed the efficacy of belimumab in patients with SLE. Patients with active HBV infection were excluded from the study, but 78 patients with occult infection were included. There was no incidence of HBV reactivation seen in their study (46). There is uncertain risk in patients with active HBV infection, while those with occult HBV are likely low risk and can be closely monitored.

Bruton Tyrosine Kinase-Inhibitor (BTK):

Ibrutinib: Ibrutinib irreversibly inhibits BTK, disrupting B-cell antigen receptor signaling as well as B-cell adhesion and migration. Ibrutinib's indicated uses include mantle lymphoma, chronic lymphocytic leukemia, and Waldenstrom's macroglobulinemia. There are several case reports showing HBV reactivation in patients with active and occult HBV infection (47, 48). One institution recently treated 38 CLL patients with ibrutinib as single therapy. Seven of their patients were noted to have occult HBV infection. There was no evidence of HBV reactivation in their limited cohort, and none of their patients received HBV prophylaxis (49). There is likely low-moderate risk for HBV reactivation in occult HBV carriers, but continued caution is advised until evidence of its safety is proven. Last, there is an ongoing phase III clinical trial in China evaluating safety of ibrutinib use in patients with active HBV and occult HBV infections. Prior trials have excluded patients with active HBV infection, and this trial should help shape future recommendations regarding this patient group (50).

T Cell Modulators:

Abatacept: Abatacept is an immunosuppressant typically used in the treatment of severe rheumatoid arthritis. Abatacept downregulates T-cell function by preventing binding to antigen presenting cells, thus preventing activation. A retrospective analysis evaluated abatacept use in 8 patients with active HBV infection. Four patients received anti-viral prophylaxis without incidence of HBV reactivation. The other 4 patients that did not receive anti-viral prophylaxis all developed HBV reactivation (51). Another retrospective study evaluated the safety of abatacept in 72 patients with active or occult HBV infection. Their study followed 4 patients with active HBV infection with the remaining 68 patients having occult infection. No patients developed HBV reactivation after 24 months of follow up (52). There is a case report of one incidence of HBV reactivation in a patient with an occult infection (53). Based on current information, patients with active infection are moderate-high risk and should receive anti-viral prophylaxis. Patients with occult infection are likely low risk and can receive prophylaxis vs lab monitoring depending on the clinical situation.

Other Immunosuppressive Drugs:

Leflunomide: Leflunomide inhibits pyrimidine synthesis, resulting in antiproliferative and anti-inflammatory processes. It is indicated for treatment of rheumatoid arthritis in adults. In vitro studies have shown that leflunomide can increase HBV replication and expression (54). Additionally, an observational study exhibited patients with active HBV infection carry substantial risk for reactivation while undergoing treatment with low dose leflunomide. Their study followed 17 patients with active HBV infection and 36 patients with occult HBV infection for 24 weeks of treatment. In the active HBV infection group, they observed increases in HBV-DNA levels in 8 patients and HBV reactivation in 5 patients. There was no incidence of reactivation in the occult HBV infection group (55). Patients with active HBV appear to be moderate risk and should receive anti-viral prophylaxis. Patients with occult infection are likely low risk and can be monitored closely.

Methotrexate: Methotrexate is a folate antimetabolite that interferes with DNA synthesis, repair, and replication. It is indicated to treat psoriasis, rheumatoid arthritis, and polyarticular juvenile idiopathic arthritis. In the literature, there are two incidences of HBV reactivation in patients with occult disease (56, 57). In a retrospective study that evaluated the use of methotrexate in 173 patients with rheumatologic disease, including 65 patients with occult

HBV infection. There was no incidence of reactivation in their cohort (58). Patients with both acute and occult HBV infection are likely low risk for HBV reactivation and can be closely monitored instead of empirically treated with anti-viral prophylaxis.

Azathioprine: Azathioprine prevents DNA replication and inhibits purine synthesis, thus preventing proliferation of B and T lymphocytes. Its indicated uses include rheumatoid arthritis and rejection prevention following organ transplantation. There is limited information showing HBV reactivation in patients undergoing treatment with azathioprine as single therapy. One case study reported HBV reactivation in a patient with dermatomyositis and occult HBV infection. This patient underwent treatment with prednisone and azathioprine and reactivated after six months of therapy (59). Similarly to methotrexate, patients with both acute and occult HBV are low risk for HBV reactivation and can likely be safely monitored instead of receiving anti-viral prophylaxis.

Calcineurin Inhibitors: Tacrolimus and cyclosporine are immunosuppressive agents that inhibit phosphatase calcineurin thus blocking T-cell proliferation. These medications are often used in conjunction with other immunosuppressants to prevent post-transplant organ rejection. A case control study evaluating the risk of HBV reactivation with anti-rheumatic drugs reported 5 cases of tacrolimus induced HBV reactivation although there is no information given regarding pretreatment screening, HBsAg status, or how reactivation was diagnosed (60). A 2003 retrospective study assessed the risk of HBV reactivation in 49 patients with occult infection receiving tacrolimus or cyclosporine following organ transplantation and documented no evidence of HBV reactivation (61). There is uncertain risk of HBV reactivation in patients with acute HBV and should be treated with anti-viral prophylaxis. Patients with occult infection are likely low risk and can be closely monitored.

B and T Lymphocyte Inhibitors: Mycophenolate mofetil and mycophenolic acid are immunosuppressants frequently used to prevent allograft rejection and used in the treatment of autoimmune diseases and liver transplant recipients. These drugs prevent lymphocyte production by inhibiting IMDPH (inosine monophosphate dehydrogenase), an essential step in DNA replication of T and B cells. In vitro studies have demonstrated that mycophenolic acid could enhance HBV replication and expression (54). However, there were no published incidences of mycophenolate causing HBV reactivation as single therapy, and no studies evaluated its risk for HBV reactivation. One prospective study compared mycophenolate mofetil (0.5-1.0 mg BID) and low dose prednisone (0.5 mg/kg daily) vs standard dose prednisone (1 mg/kg daily) in treatment of HBsAg carriers with nephrotic syndrome. Their study showed significantly reduced incidence of HBV reactivation in the combined therapy group of mycophenolate mofetil and low dose prednisone (62). There is insufficient evidence to provide recommendations regarding prophylaxis or reactivation risk in patients with active or occult HBV infection.

mTOR Inhibitors: Everolimus and sirolimus inhibit the mammalian target of rapamycin (mTOR). Everolimus is frequently used as an immunosuppressant following organ transplantation and in treatment of malignancy, namely renal cell carcinoma (RCC). There are three reported cases of everolimus associated HBV reactivation (63-65) and one case of sirolimus associated HBV reactivation (66). For everolimus, two reports detail patients with active HBV infection and with RCC that saw significant serum transaminitis and increased levels of HBV DNA. However, confounding factors were present as the patients received multiple immunosuppressive regimens several months before HBV reactivation, and reactivation can occur as late as one year after discontinuing treatment (16). Overall, there is uncertain risk of HBV reactivation with mTOR inhibitors. They should be treated similarly to other immunosuppressive regimens with anti-viral prophylaxis in patients with active infection and close monitoring in the patients with occult infection.

E. Medication Prophylaxis vs Lab Monitoring

Screening: Prior to initiation of immunosuppressive or cytotoxic therapies, patients should be screened for HBV exposure. The AASLD, EASL, AGA, and APASL all recommend screening with HBsAg and anti-HBc antibodies (2, 8, 19, 67). However, the APASL recommends additional screening with anti-HBs and an assessment of liver fibrosis (67). Anti-HBc antibody titers are assays that could have future applications in the identification of patients at increased risk for HBV reactivation (68).

Prophylaxis vs Labs Monitoring: There are several proposed guidelines to determine the use of anti-viral prophylaxis versus lab monitoring. The AASLD and EASL practice guidelines recommend anti-viral prophylaxis for patients with active HBV infection undergoing immunosuppressive therapies as well as prophylaxis in patients with occult infection being treated with B-cell

depleting agents (2, 8). The AGA recommends that all patients designated as moderate-to-high risk for HBV reactivation (see table below) should empirically be treated with anti-viral prophylaxis (19). Similar to the AGA, the APASL recommends stratifying patients based upon HBsAg status and medication risks. Both patients with acute HBV with moderate-high risk and occult patients with high risk are recommended to receive anti-viral prophylaxis. However, their recommendations also include that all patients with advanced fibrosis or cirrhosis should be treated with prophylaxis regardless of risk status (67).

Table 3: AGA stratification of immunosuppressive medications risk for causing HBVr

High Risk Medications: Risk >10%	
HBsAg+ patients	**HBsAg- patients**
Anti-CD20 (rituximab, ofatutumab) Anthracyclines (doxorubicin, epirubicin) Moderate or high dose corticosteroids	Anti-CD20 (rituximab, ofatutumab)
Moderate Risk Medications: Risk 1-10%	
HBsAg+ patients	**HBsAg- patients**
Anti-TNFa inhibitors Cytokine or integrin inhibitors Tyrosine Kinase Inhibitors Low Dose Corticosteroids	Anthracyclines (doxorubicin, epirubicin) Moderate or High Dose Corticosteroids Tyrosine Kinase Inhibitors Cytokine or integrin inhibitors Anti-TNFa inhibitors
Low Risk Medications: Risk <1%	
HBsAg+ patients	**HBsAg- patients**
Azathioprine, 6-mercaptopurine, methotrexate Intra-articular steroids Corticosteroids <1 week duration	Azathioprine, 6-mercaptopurine, methotrexate Intra-articular steroids Corticosteroids <1 week duration Low dose corticosteroids

Table Based on Reddy et al (19)

For patients receiving prophylactic anti-viral therapy, recommended agents include entecavir, tenofovir alafenamide, and tenofovir disoproxil fumarate (TDF) (69). These medications are well tolerated and dosed once daily (entecavir 0.5mg daily, tenofovir alafenamide 25 mg daily, and TDF 300 mg daily). There are limited data regarding anti-viral prophylaxis in pediatric populations with no evidence of previous trials on literature review. Previously, lamivudine was considered a first line agent in preventing HBV reactivation. However, it has fallen out of favor secondary to increased rates of viral resistance with long term use (70). One randomized clinical trial evaluated the efficacy of lamivudine vs entecavir as prophylactic anti-viral therapy in diffuse large B-cell lymphoma patients treated with R-CHOP chemotherapy. Their study showed entecavir as superior to lamivudine in preventing HBV reactivation (93.4% vs 70%), HBV related hepatitis (100% vs 86.7%), and chemotherapy disruption (98.4% vs 81.7%) (71). No studies have evaluated the efficacy of entecavir vs tenofovir for anti-viral prophylaxis to date. The AASLD, EASL, and AGA collectively agree that anti-viral treatment should be started six weeks prior to initiation of immunosuppressive therapy and continue for at least six months after cessation of immunosuppressive therapy. Anti-viral treatment should be extended to 12 months after cessation when treated with B-cell depleting agents (2, 8, 19). The APASL panel differs slightly with recommendations to consider discontinuing prophylaxis 6 months after completion of immunosuppressants in HBsAg+ patients without fibrosis/cirrhosis and low-level HBV DNA (< 2000 IU/mL) with the guidance of a hepatologist. Discontinuation of anti-viral prophylaxis should be considered after 6 months in patients with occult disease (67).

The AASLD recommends lab monitoring and on-demand anti-viral therapy for patients with occult infection being treated with immunosuppressive regimens, excluding B-cell depleting agents. This includes testing ALT, HBV DNA, and HBsAg every 1-3 months until 12 months post treatment (69). The EASL guidelines recommend monitoring in patients with occult infection with undetectable HBV DNA using ALT and HBV DNA every 1-3 months depending on immunosuppressive therapies and comorbidities (8). The AGA recommends lab monitoring in patients determined to be low risk (see table above) (19). Last, the APASL recommends lab monitoring with ALT every month in acute HBV/low risk, occult HBV/moderate risk, occult HBV/low risk patients if there is no underlying advanced fibrosis or cirrhosis (67).

Prior studies evaluating prophylactic anti-viral therapy have shown significant benefit for patients with active HBV infection undergoing immunosuppressive therapies. A meta-analysis evaluating lamivudine as prophylaxis in patients treated with chemotherapy observed a risk reduction of 79% for HBV reactivation and HBV related hepatitis (72). In 2013, a prospective study evaluated efficacies of prophylaxis versus on-demand anti-viral therapy in lymphoma patients with occult HBV infection treated with rituximab-based chemotherapy. This study observed significant decreases in HBV reactivation in patients that received prophylactic entecavir (73). There is less evidence for anti-viral prophylaxis in patients with occult infection undergoing other immunosuppressive therapies.

HBV Reactivation Management: Treatment is recommended for all patients that develop HBV reactivation with the goal to prevent progression to severe hepatitis, hepatic failure, or death (74, 75). Similar to anti-viral prophylaxis, first line agents include entecavir, tenofovir alafenamide, and TDF.[2] Dosing for HBVr treatment is the same as prophylactic dosing and is listed below.

Entecavir dosing for treatment of HBV is recommended as 0.5 mg daily for patients with compensated liver disease or nucleoside naïve patients. Patients previously treated with lamivudine should avoid entecavir however as there is an association with higher viral resistance rates in this population (75, 76). Entecavir dosing should also be increased to 1.0 mg daily for all patients with decompensated cirrhosis. Of note, entecavir is renally cleared and should be adjusted based upon creatinine clearance (77). Entecavir dosing in the pediatric population is weight based and studied in patients age 2-16 (78).

Tenofovir alafenamide is dosed as 25 mg daily for treatment of HBV. Tenofovir alafenamide should be avoided in certain populations including decompensated cirrhotic, pregnant women, and patients with creatinine clearance less than 15 mL/min. It is renally cleared but does not require dose adjustment unless creatinine clearance falls below 15 mL/minute (77). Tenofovir alafenamide is also available for treatment of HBV in the pediatric population with a recommended dose of 25 mg daily in patients aged 12 and older (79).

TDF is dosed as 300 mg daily for treatment of HBV. TDF is not preferred when compared to tenofovir alafenamide due to risk of proximal tubular injury in the kidney, progression of chronic kidney disease, and bone toxicity. However, TDF is the agent of choice in treating pregnant females as entecavir and tenofovir alafenamide have not been extensively studied in this population. It is renally cleared and dosing depends on the patient's creatinine clearance (77). TDF has been studied in the pediatric population and approved for treatment of HBV in children greater than 2 years and weight greater than 10 kg. Treatment is weight based and is 8 mg/kg dosed once daily (80).

There are no data indicating superiority of one treatment over the other. There is limited information regarding the duration of treatment following HBV reactivation. Possible endpoints of treatment could consist of normalization of ALT and viral load suppression (81). For patients that develop HBV reactivation secondary to immunosuppression, decisions to discontinue the immunosuppressive therapy can be made after weighing the risks and benefits. Patients with only mild reactivation can likely continue treatment (82). Patients with more severe HBV reactivation should discontinue immunosuppression until ALT/HBV DNA levels normalize.

Conclusion: Acute HBV infection has become less prevalent in the United States, but rates of reactivation are rising with the increasing use of immunosuppressive regimens. Implementation of screening and management guidelines has led to better outcomes, but continued education is vital. There is a clear indication for anti-viral prophylaxis in patients with active HBV infection undergoing treatment with immunosuppressive regimens. However, more research is required for patients with occult infection.

Disclosure: Authors declare no competing interests.

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Communication on Healthcare Quality Improvement

Clinical Audit in Personalized Predictive Preventive Health Screening: A Key Element of Continuous Quality Improvement

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Received: *November 12, 2022*
Accepted: *December 25, 2022*

Citation:
Venkatesh et al, JAAPI 2(3): 35-38, 2022

Abstract: A pivotal element of continuously evaluating and improving the various facets of patient-centric care is clinical or medical audits of practices or processes. Clinical or medical audits are a transparent, non-judgmental, systematic, and critical analysis, evaluation, and documentation of various domains of patient care against well-defined (desired) standards. These clinical care domains include availability, structure, process, outcome, competence, or management intervention, to identify changes needed to steer continuous improvement in healthcare quality. A key component of Apollo Hospitals ProHealth - an AI-powered personalized, predictive preventive health screening program, is the periodic audit of guest report medical summaries to assess and grade physician adherence to pre-set criteria for completing them. These audits aim to maintain high-quality clinical reviews and care continuum recommendations. This report highlights the steps and parameters we use for clinician audits, including scoring and grading, and recommendations for ensuring sustained quality improvement for patient-centric care.

Key Words: Audit, Physician, Medical Summary, Grade, Score, Peer Review, Quality Improvement

What is a Clinical or Medical Audit? Evaluating and improving the various facets of patient-centric care quality is the cornerstone of the healthcare paradigm. One element of this continuous quality improvement process is clinical or medical audits of practices or processes. "Audit", originally a Latin word encompassing active listening, investigation, inspection, and interrogation, is widely used across diverse settings with the objective that procedures adhere to well-defined, structured, and consistent standards. Clinical or medical audits are a transparent, non-judgemental, systematic, and critical analysis, evaluation and documentation of various domains of patient care against well-defined (desired) standards. These clinical care domains include availability, structure, process, outcome, competence, or management intervention. The goal is to identify changes needed to steer continuous improvement in healthcare quality (1-3).

General Steps Involved in Planning and Validating a Clinical Audit (1-3):

- **Identify a relevant topic** that impacts health care processes, outcomes, resources, costs, or risk, with data (prospective or retrospective) on performance indicators or improvements that are not difficult to collect and analyze.
- **Define and design aims and objectives:** These could include the implementation of new processes (e.g., referrals, laboratory protocols, non-pharmacological procedures, etc.) or the improvement of current strategies already in place (e.g., standard operating procedures for vaccinations).
- **Formulate methodology** by defining any or more of the following:

i. Indicators (can be expressed as absolute numbers, averages, rates, or percentages)

ii. Criteria (evidence-based parameters measuring acceptability and appropriateness of health care quality), or

iii. Reference standards of care for each criterion (usually expressed as a percentage).
Consensus among experts and literature or guidelines can drive this process. Identify the reference population or sample for randomization.

- **Allocate the necessary staff and resources** for the project, assigning specific responsibilities.
- **Collect qualitative or quantitative data.**
  - **Sources** can be medical records, questionnaires, interviews, laboratory, or imaging evaluations, etc.
  - **Highlight any inadequacies of data management** during the preliminary phase of data collection itself.
  - **Protect the privacy** of data; all information must be anonymous.
- **Analyze collected data with pre-set indicators or criteria and formulate strategies to sustain quality improvement or implement change.** Prepare a written report for the audit participants and delineate insights and real-time feedback.
- **Periodically monitor and formally document implemented strategies and assess maintenance of quality improvements.**
  - If clinical adherence or improvement is sub-optimal, introduce structured and systematic changes to planned strategies.
  - Establish a monitoring framework to sustain quality improvements if observed clinical outcomes are impactful.

International clinical studies indicate that resource-effective and personalized audit and feedback interventions can:

- Improve physician adherence to clinical practice guidelines (4).
- Improve physician performance on chronic disease screening and management-related ambulatory quality measures (5)
- Reduce low-value testing (6)

Clinician Audit as Part of ProHealth, Apollo Hospital's Personalized and Predictive Artificial Intelligence (AI)-Powered Preventive Health Screening Program

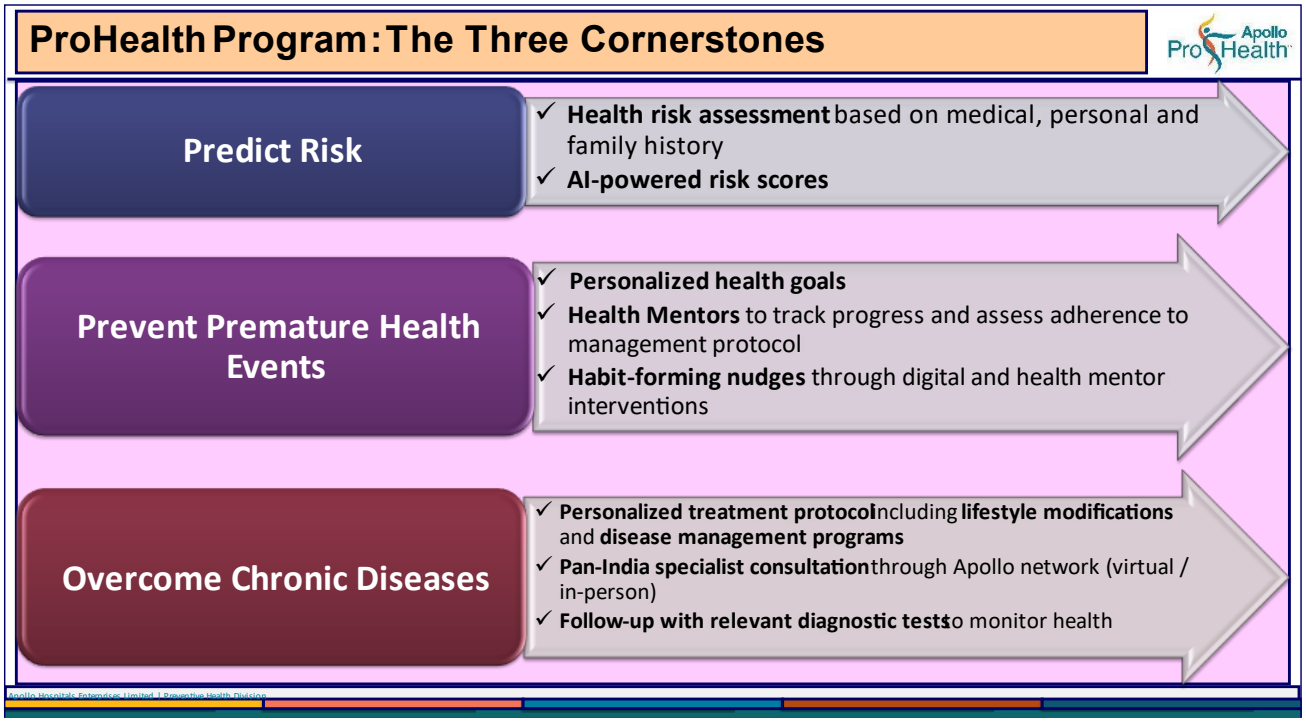
Apollo Hospitals Group's ProHealth, an AI-powered personalized, predictive preventive health screening program designed from 30 million health check assessments, has three pillars: Health risk assessment, including AI-powered risk scoring; preventing premature health events; and overcoming chronic diseases with a systematic and structured care continuum (**Figure 1**).

Our ProHealth physician panel currently comprises 134 internal medicine consultants across 40 units in India. Following diagnostic and imaging tests, a ProHealth guest will receive a personalized dynamic guest report, which includes the following components:

- **Medical history** and **physical examination** results
- Results from the **screening investigations**
- **Risk scores** for cardiovascular disease, pre-diabetes, and chronic pulmonary disease (*Liver and kidney disease risk scoring-based algorithms are under clinical development).*
- **A Medical Summary**, which includes:

1. Physician's impression regarding the guest's overall health
2. A personalized management protocol, including follow-up assessments and consultations (in person or virtual)
3. Recommendations for referrals if any
4. Vaccination counselling

Figure 1. The three cornerstones of the ProHealth Program



A key ProHealth process is the periodic audit of guest report medical summaries to assess and grade physician adherence to pre-set criteria for completing them (Apollo Hospitals Preventive Health. ProHealth 2021. Data on File.). These audits aim to maintain high-quality clinical reviews and care continuum recommendations. To the best of our knowledge, Apollo ProHealth is currently the only team conducting this format of clinical audits at a national level. Here are the steps of the process:

- From our panel of 134 physicians, our clinical audit team randomly selects a batch of 20 medical summaries. We blind patient and physician names and general information to ensure data privacy.
- Two physicians are randomly selected to submit a peer review of each other's medical summaries (digital or paper-based) based on clarity and succinctness of documentation. The physicians submit their audit reports to the Apollo Hospitals Group central preventive health screening clinical audit team via messaging, email, or paper.
- The Preventive Health Medical Director reviews the physician audit sheet and provides additional recommendations if needed.
- The audit team collates the two sets of recommendations (Physician + Medical Director) into a single scoring sheet to calculate the compliance percentage based on the following parameters (**Table 1**).

Table 1. Scoring medical summary completeness based on parameters.

Parameter	Denominator	Score Received	Compliance (%)
Diagnostic correlation and use of standard terminology	2		
Examination	1		
Recommendations for additional tests, if needed	1		
Disease monitoring and follow-up	1		
Referral to an appropriate specialist, if needed	1		
Advice on diet	1		
Advice on exercise	1		
Advice on lifestyle modifications	1		
Advice on vaccination recommendations	1		
TOTAL	**10**		

- We grade the physicians based on their cumulative score on this 10-point scale (**Table 2**):

Table 2. Physician clinical audit grade based on score.

Score	Nomenclature	Grade
8-10	Stellar	A
6-8	Adept	B
≤6	Sub-Optimal	C

- For physicians receiving grades B and C, we are conducting a five-summary clinical audit and calculating the mean score regarding compliance with the medical summary systematic completion process. For these physicians, we are implementing strategies such as induction and refresher training modules on ProHealth processes and best practices (for example, samples of well-documented medical reports and summaries) to improve the quality of completing medical summaries. Clear and comprehensive medical review summaries can help guests adhere to structured, evidence-based care continuums and enhance their clinical outcomes, including improving and maintaining wellness.

- **Completion of medical summaries is a pre-requisite to initiation of the care continuum health mentorship.** Health mentors assess guest adherence to the management protocol and track their progress. Depending on the severity of their condition, guests receive disease-state awareness-related messages on various topics, such as clinical importance and frequency of diagnostic testing, stages of disease progression, the role of imaging modalities, etc.

Summary and Conclusions: Clinical or medical audits are a systematic and critical analysis of various domains of patient care, such as structure, process, outcome, competence, or management intervention against well-defined (desired) standards. The end goal of a clinical audit is identifying changes needed for continuous improvement in healthcare quality. The ProHealth clinical audit team periodically assesses physician adherence to completing guest report medical summaries based on pre-set criteria. This audit aims to maintain high-quality clinical review documentation and care continuum recommend-dations. We provide education and training regarding ProHealth processes and best practices to document, monitor and sustain quality improvement.

Disclosure: Authors declare no competing interests.

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Perspectives

The Biopsychosocial Approach to Medicine: Using Creative Problem Solving to Improve Diagnosis

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Received: October 7, 2022
Accepted: February 3, 2023

Citation:
Gatewood & Firestien, JAAPI 2(3): 39-47, 2022

Abstract: Misdiagnosis resulting in inappropriate treatment is a significant problem in medical care. Often, this is because the approach most frequently employed is reductionist and myopic, focusing only on the biologic symptoms of a patient. By moving to a more comprehensive biopsychosocial approach for diagnosis, clinicians can dramatically increase the effectiveness of their diagnoses, resulting in improved patient care and lives saved. Creative Problem-Solving (CPS), a research-validated process designed to enhance both individual and team creativity, is effective in operationalizing a biopsychosocial diagnosis and treatment. In addition to focusing on the importance of a biopsychosocial diagnosis approach, this paper will detail problem clarification techniques within the CPS process that can increase accuracy of patient diagnosis and treatment.

Key Words: Misdiagnosis, Biological (approach), Biopsychosocial (approach), Creative Problem Solving, Medical Problem Solving

Introduction: It is estimated that 12 million Americans are misdiagnosed annually. Misdiagnosis can lead to significant consequences and contributes to 40,000-80,000 deaths annually in the United States (1). The most common cause of medical malpractice is misdiagnosis accounting for more than a third paid malpractice lawsuit (2). There are a variety of reasons for serious, even fatal medical errors. In medicine, when we depend on a purely biological approach to diagnosis, we often neither define nor treat the real problem. This single-minded approach fails to consider the psychologic and social determinants of a patient's illness.

Patients are more than just skeletons filled with organs and covered by muscle, tendons, ligaments, and skin. For that reason, it is crucial to transition our traditional biologic (reductionist) approach to a broader biopsychosocial approach when faced with diagnosing and treating our patients' problems. The biopsychosocial model of care, first introduced by George Engel in 1977, considers not only the physiologic pathology (bio) but also the psychological and social (psychosocial) factors in order to fully understand a patient's medical condition (3). This approach is considered essential in understanding the complexities of health and illness and in arriving at a correct diagnosis as well as a comprehensive treatment plan (Figure 1).

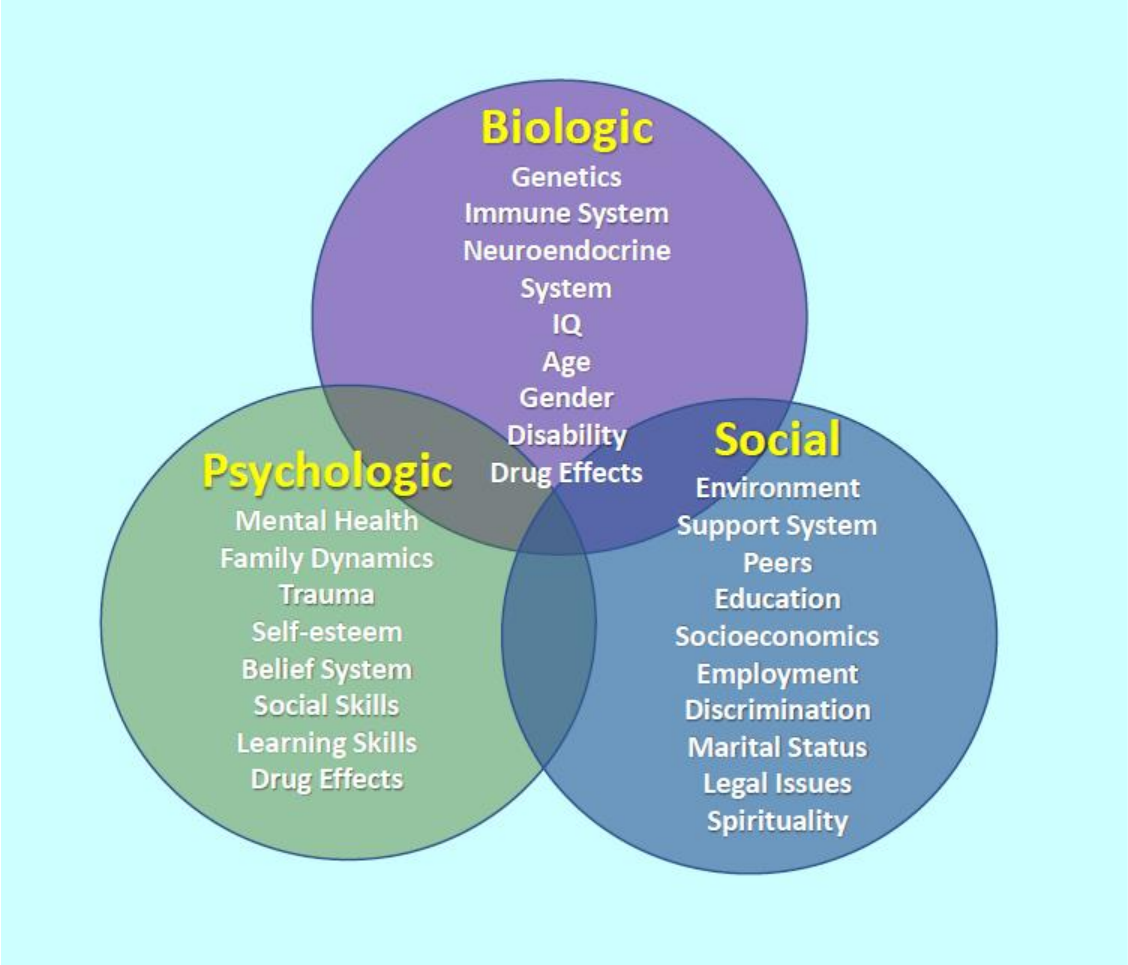

Figure 1. Biopsychosocial Model Gatewood, R.P. (2022), printed with permission.

The Importance of the Biopsychosocial Approach: Consider the case of Linda, a standardized patient in Dr. Robert Gatewood's Clinical Practice in Medicine seminar class (CPM-1) at the SUNY Buffalo School of Medicine. After a brief "icebreaker" about the unusually warm weather, the students began by eliciting Linda's chief concern which was acute epigastric pain. It had begun during the night and had not gone away. She had experienced the same discomfort intermittently over the past five to six years, but unlike her other episodes, it was not promptly relieved with an antacid. Linda had no recent reflux symptoms, nausea, vomiting, change in bowel habits, melena or bright red blood in her stool. Her appetite and weight had been unchanged. There was no radiation of her discomfort. Linda volunteered that she was concerned not only because the pain did not go away right away but because her father had suffered from gastric cancer.

Upon further review of her past medical history, she reported osteoarthritis with intermittent knee arthralgias; otherwise, she had no other chronic diseases. Her only surgery was a Caesarean section. Linda took no medications on a regular basis but recently had been taking ibuprofen (800 mg) twice a day because of a flareup of her knee pains. She had no allergies. She did not smoke or use illicit drugs but had an alcoholic drink most evenings.

The students in Dr. Gatewood's class obtained Linda's social history before proceeding to the abdominal exam. They asked questions about Linda's life, not just her symptoms. Linda explained that she was a widow and lived alone. Her only son lived on the East Coast, and she had no family in Buffalo, New York, where she lived. She was working full-time as a bank manager and over the past few months her bank had been in the midst of a merger.

Recently, bank management had informed Linda she would have to lay off several of her longtime employees. The thought of telling her employees with whom she had close relationships they no longer had jobs at the bank was

causing her considerable stress and anxiety. As a result, she became much less active at home in the evening. She spent most of her time ruminating on the couch and drinking much more alcohol than usual. About this time Linda experienced an increase in her knee pain for which she took ibuprofen hoping to relieve her discomfort.

Linda seemed eager to share her recent struggles with the class. The students and Dr. Gatewood expressed how difficult this must be for her and promised to help with her concerns. To help do that, several students conducted a thorough abdominal exam. The group practiced the standard techniques, including listening for bowel sounds and abdominal bruits, palpating the abdomen, assessing the liver and spleen, and testing for direct and rebound tenderness. Afterwards, the students and Dr. Gatewood informed Linda that except for epigastric tenderness, her abdominal examination was unremarkable.

The class ended the examination by reassuring Linda that everything pointed to recurrent gastritis, most likely precipitated by her recent use of ibuprofen and increased intake of alcohol. They recommended a short course of omeprazole, along with switching ibuprofen to acetaminophen and reducing alcohol intake, reassuring Linda that her symptoms should resolve completely within a few days.

But they were wrong. Dr. Gatewood woke up that night around 2:00 a.m. "*I found myself thinking about Linda. I realized I had missed an opportunity to use her case as an example of the importance of taking a biopsychosocial approach when defining and treating a patient's "real" problem. Here is the email I sent to the CPM-1 team later that morning:*

Hi all, I woke up in the middle of the night thinking about our standardized patient, Linda. While we were concentrating on history taking and the abdominal exam, we did not complete her diagnosis and treatment from a biopsychosocial standpoint. Reflecting on her case, I would propose the following sequence of events:

Linda was notified that her bank, where she works as a manager, was coming under new management due to a merger. Linda was told that she would have to lay off some of her longtime employees. She was also likely to be concerned about her own future and longevity with the bank (SOCIAL). This led to Linda's feelings of stress, anxiety and, perhaps, other emotions such as depression and anger (PSYCHOSOCIAL). As Rachel Zoffness, a Health and Pain Psychologist at the University of California at San Francisco tells medical students, negative emotions turn the pain volume up in patients with chronic pain.(4) In Linda's case, her negative feelings led to a worsening of her chronic arthralgias (BIOPSYCHO).

This biopsychosocial cascade of events led Linda to take an NSAID (non-steroidal anti-inflammatory drug) regularly and to increase her alcohol intake as a coping mechanism. As a result, Linda experienced a recurrence of her gastritis precipitated by an alcohol-induced increase in gastric acid production and by the increased use of NSAIDs which block COX1 (cyclooxygenase-1) enzymes which play an important role in protecting the lining of the stomach, reducing Linda's resistance to the irritating effects of acid on her stomach mucosa (BIOLOGIC). (5, 6)

Therefore, Linda's diagnosis should not be solely acute gastritis secondary to alcohol and NSAID use. This purely biologic, or reductionist, diagnosis does not address the true root cause.

The crux of Linda's problem is her job situation and the related negative emotions. Likewise, limiting her management to omeprazole and discontinuation of alcohol and NSAIDs leaves Linda partially treated. By adopting a biopsychosocial approach, we would consider adding to Linda's treatment plan short-term counseling to improve Linda's coping skills through talk therapy, cognitive behavioral therapy, and a stepwise program to help her return to normal activities and regular exercise. This more comprehensive approach is critical for Linda's psychological well-being, arthritis, dependency on alcohol, and her gastritis. Omeprazole and Tylenol would serve only as a temporary bridge until Linda is feeling better from a biopsychosocial standpoint."

Traditionally physicians have been trained in the biological approach, however by taking a more biopsychosocial approach, physicians can significantly enhance their diagnosis and treatment capabilities. The goal of this new approach is to identify the patient's real problem to allow for a more accurate and comprehensive treatment plan. One of the emerging methods to help do this is **Creative Problem-Solving**. That is where we will now turn our discussion.

Think Outside the Biological: You have certainly heard the phrase, "think outside the box." It is a common reminder, when working on a problem, to think beyond the usual ideas to create new associations that generate creative ideas. Try this phrase on for size: "think outside the

biological." In medicine, it means to think beyond the usual boundaries of what a healthcare practitioner might *think* the biological cause of an illness is. Because there might be something other than a traditional diagnosis causing the illness.

Let's revisit the case presented to the students in Dr. Gatewood's class. But this time we'll review the case and "think outside the biological." When we look closely, the discovery of the real problem came when the students did two things: (i) they asked questions, (ii) they took time to dig deeper. Dedicating time to ask questions also created an environment for the patient to feel more comfortable. As a result, the patient may have volunteered additional information that might not have been a direct answer to a specific question.

Clarifying the Problem is a Process: Ask Creative Questions:

When individuals and groups solve problems, there are several things to consider. First, there is the *content* of the problem – *what* is the problem all about? What are the details? What do we know about the problem right now? In our medical case above, most of the narrative regarding Linda's illness was devoted to the *content*.

The second part of solving problems is the *process*. This is *how* we solve the problem. It is the *method* we use for solving problems. One such method is the scientific method, in which a problem is identified, relevant data is gathered, a hypothesis is formulated, and the hypothesis is empirically tested.

Another method is Creative Problem-Solving or CPS. It is the most widely researched, used and validated method for creative problem solving in use today.

In an experimental study that examined the effects of Creative Problem-Solving training on communication behaviors in groups, students trained in CPS exhibited more positive group behavior as evidenced by more participation, more smiling, more laughter and significantly less criticism when solving a problem (7).

In a related study that examined the quality and quantity of ideas generated by groups trained in CPS, the trained groups outperformed control groups on both quantity and quality of ideas generated (8).

The long-term impact of a six-day graduate course in Creative Problem-Solving was found to have a positive effect on participants ability to solve real-life problems. This study measured treatment effect up to one year after the course was completed (9).

Several meta-analyses of programs designed to teach creative thinking have concluded that creativity training works for a variety of individuals, groups and professions (10). Additional studies have found that the most effective structured program for enhancing creativity is Creative Problem-Solving (11).

Studies conducted in industrial, organizational and educational settings have also shown the efficacy of training in Creative Problem-Solving to positively affect organizational gains (12).

Originated in the early 1950s by Alex Osborn, the inventor of the brainstorming technique, CPS was further developed by another creativity pioneer, Sidney Parnes in the 1960s and 70s. Creative Problem-Solving (CPS) is a **simple, repeatable process for defining a problem, then generating solutions and action steps targeted and focused on results.** The CPS process defines exactly how to approach a problem that might appear impossible to solve. And CPS can be applied to almost any challenging or ambiguous situation that confronts us.

One of the most recent developments in the Creative Problem-Solving process is put forward by one of the authors - Dr. Firestien. It is called 21st Century Creative Problem-Solving and it is illustrated below.

Figure 2- Twenty First Creative Problem-Solving model.
From: Firestien, RL. (13), printed with permission.

As shown, the first stage of the process focuses on clarifying the problem. In this paper we will only focus on the Clarifying the Problem stage of the process. Further, we will focus on just one tool in the Clarifying stage. That tool is "creative questions".

Ask Creative Questions: Questions are more relevant than answers. Questions are bigger than answers. *"One good question can give rise to several layers of answers, can inspire decade-long searches for solutions, can generate whole new fields of inquiry, and can prompt changes in entrenched thinking. Answers, on the other hand, often end the process" (14).*

Not all questions are the same. There are three types of questions:

Fact-finding questions: Questions that ask for information. Once you have the information you have answered the questions. For example: *How long have you been experiencing pain? How many hours a day do you sleep on average? Do you smoke cigarettes?*

Judgment or decision questions: *Should I be drinking less alcohol? Should I be exercising more often?* Judgment questions involve value judgments that ask for a yes or no answer.

Creative questions: Questions posed in such a way they instruct the brain to go and look for creative answers, for multiple answers, for answers beyond the obvious; answers with a greater potential to solve the real problem. *What might be all the things you think may be contributing to your abdominal pain?*

Creative questions are the path to finding the best problem to solve. They are the beginning of a successful diagnosis. They open our thinking to search for more information.

Creating Creative Questions: So how do you turn a question into a "creative question"? There is actually a format. Creative questions begin with phrases that open your thinking.

When generating creative questions, we begin the question with these phrases:

"What might be all the ways…"
"How to…"
"How might we…"
"In what ways might I…"

Questions framed in this way provoke our minds to search for ideas. Creative questions tell the brain to consider what "*might*" be. It is built right into the construction of the question. In other words, "Let's go find some answers." And because we're using the word *might*, these can be any answers. "We haven't made any decisions yet. Look for options."

In addition to using the phrases outlined, Creative Problem-Solving follows guidelines. Here are the guidelines for generating creative questions.

Defer judgment. Don't judge your creative questions while you are generating them.

Strive for quantity. The more creative questions, you have, the greater your chance of identifying the real problem.

Seek wild and unusual questions. The reason you are stymied with this problem is because the usual approaches haven't worked. Go for the unconventional.

Combine and build on other questions. Let one creative question inspire another creative question inspire another.

The problem you see is the problem you solve. To solve the best problem, you need to see lots of questions.

For example, in our case with Linda, the students might have generated creative questions like:

"What might be all the things in your present routine which affect, or are affected by, your stomach pain?"

"What might be all the reasons your stomach may have started to hurt?"

"What might be all the reasons you are worried about your stomach pain?"

"What might be all the possible reasons for experiencing more knee pain?"

"How might your daily activities affect your feeling of well-being?"

"What might be all the reasons for drinking more alcohol?"

"What might be any other concerns or worries you have, aside from your stomach pain?"

Table 1 below shows the traditional approach to diagnosis, (OLDCAARTS) and lists examples of creative questions that could also be used in the diagnostic process.

Table 1: OLDCAARTS and Creative Questions

OLDCAARTS	CREATIVE QUESTIONS
Onset: • When did your symptoms start? • Have you had these symptoms before? • Were there any precipitating factors?	• What do you think might have contributed to your problems/symptoms?
Location: • Where are your symptoms located? • Do they radiate anywhere?	• What might be some things at home that could be contributing to your symptoms? At work? In your neighborhood?
Duration: • How long do your symptoms last?	• What might be changes that occurred in your life lately? How did those changes make you feel?
Character: • How would you describe your symptoms (sharp, dull, aching, burning, etc.)?	• What feelings are you experiencing in relation to your health? What do you think you might have?
Associated Factors: • Do you have any additional associated symptoms?	• How are you doing financially? Any concerns? Are you worried about any medical bills or cost, such as for medications?
Aggravating Factors: • Is there anything that makes your symptoms worse?	• What things in your life would you like to change? What prior experiences have you had in your life that might amplify your symptoms? How are things at home?
Relieving Factors: • Is there anything that helps relieve your symptoms?	• What are some activities that make you feel better?
Temporal Factors: • Do your symptoms tend to occur any particular time during the day or the night? • Are they intermittent or continuous?	• What are some of the things that are happening in your life when you experience pain? What have you been coping with lately? In what ways have your symptoms affected your sleep, eating pattern activities and interest in things?
Severity: • On a scale of one to ten how severe do your symptoms get?	• What do you most fear about your symptoms? What are some of the things you are concerned about?

<u>Don't rush it: Take the time to identify the real problem</u>. One of the biggest concerns in medicine today is that not enough physician time is dedicated to direct patient interaction when addressing their symptoms and concerns. Patients are squeezed into a limited time slot, typically an average of 15 minutes, of which only a portion is used for direct physician–patient interaction. If physicians are forced to see patients in a defined time period, how can they focus their time to get beyond the biological and use the biopsychosocial approach? How can they use the time they have available to ask creative questions so they can see the bigger picture?

There is a famous quote often attributed to Albert Einstein about spending time to define a problem. Einstein was asked: *"If some imminent disaster threatened the world and you had one hour in which you knew you could save it, how would you spend your time?"* Einstein replied, *"I would spend the first 55 minutes identifying the problem and the last five minutes solving it. For* ***the formulation of a problem is often far more essential than its solution,*** *which may be merely a matter of mathematical or experimental skill… To raise new questions, new possibilities, to regard old problems from a new angle, requires creative imagination and marks real advance in Science" (15).*

Most physicians don't have an hour to diagnose a patient's condition. But it doesn't take an hour to significantly increase the probability of discovering the true cause of the patient's condition. We just need a few tools. One tool is creative questions themselves; the other is the time to ask those creative questions. Years after Einstein supposedly spoke those words about identifying the problem, researchers are replicating his advice in a variety of studies. Here is one that impacts directly on this topic.

It only takes a few minutes to redefine the problem. In a controlled study on *problem construction,* researchers found that just five to six minutes defining the problem made a big difference on the quality of ideas generated. In this study, researchers instructed half of the study participants to restate the problem in a variety of ways before working. The other half of participants were instructed to read the problem and immediately solve it. The results: Those individuals who restated the problem in a variety of ways produced more original and higher quality solutions than those participants who went right to work. The researchers had not placed a limit on the time the group had to generate new problem statements. Researchers instructed participants to, "Take your time. There are no time limits." When observed, however, the subjects took only about *5-6 minutes* to generate a list of problem statements, from which they selected a problem and generated ideas to solve it (16).

The subjects in that group had no formal or structured training on how to formulate problems. Yet, just the encouragement from the researchers and a few minutes of talking amongst the group about the problem yielded superior results. Imagine if these subjects had formal instructions and practice on how to redefine problems or knew how to ask creative questions. This is precisely the work being conducted at the University at Buffalo School of Medicine.

Using a broad biopsychosocial approach and creative questioning in Linda's case, revealed that her "real" problem was much deeper than simply acute gastritis. Only by delving into Linda's life was the emotional turmoil she was experiencing as a bank manager revealed. This was what led to her increased knee pain and inactivity, her increased alcohol intake, and her need for ibuprofen. Therefore, her treatment required not only an H2 blocker, discontinuation of ibuprofen and a reduction in her alcohol intake, but also counseling and support to help her better cope with her stressful situation at the bank.

If her initial evaluation had stopped at acute gastritis simply due to the use of NSAIDs and increased alcohol intake, her treatment would have been incomplete. This is much like pulling a weed at the surface and leaving the roots in place. Eventually the weed will grow back. This is far less likely to occur when combining Creative Problem-Solving and a biopsychosocial approach to identify a patient's real underlying problem before determining the optimal treatment.

Summary: Creative Problem-Solving, a systematic process to take on new challenges and develop innovative solutions that create productive change, can be used to effectively operationalize the biopsychosocial approach to diagnosis and patient care. In addition to taking the time to clearly define the problem to be solved, using creative questions can significantly enhance the clinician's ability to successfully diagnose and treat patients. The result: better diagnoses and more lives saved.

Disclosure: The authors declare no competing interests.

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Viewpoint

An Oral Health Strategy to Advance the Quintuple Aim to Improve Health Equity and Quality

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Received: August 3, 2022
Accepted: December 15, 2022
Citation: Ferguson et al, JAAPI 2(3):48-51, 2022

Abstract: Many chronic conditions share common risk factors, and these risk factors can be seen early in an individual's life trajectory manifesting in poor oral health. Poor health literacy of parents and caregivers, related to the social determinants of health, results in poor oral hygiene practices and poor nutritional choices in infants and children. This accounts for poor oral health manifested starting early in life (infancy) and progressing through childhood, adulthood, and finally old age. Thus, monitoring an individual's oral health status can give physicians insight into the likelihood of patients being at risk for a variety of noncommunicable and metabolic diseases and it would be valuable to incorporate measures of oral health into risk assessments in physicians' clinical practices.

Key Words: Quintuple Aim, Equity, Quality, Oral Health, Healthcare

Prologue: Increasingly, and particularly in the wake of the COVID-19 pandemic, there is growing concern about healthcare equity for vulnerable individuals and communities and an understanding these issues must be addressed to ensure equity regardless of the social demographics of the patients or community. In the February 2022, issue of the Journal of the American Medical Association (JAMA), Dzau, Mae, and O'Kane stated: "It is impossible to deliver equitable health care if it is not high-quality care. In other words, there is no equity without quality, and there is no quality without equity" (1). In 2008, Berwick, Nolan and Whittington proposed the triple aim - improving population health, enhancing the patient experience, and reducing cost - as three goals to improve healthcare (2). A quadruple aim – to address the growing phenomenon of professional burnout - was recognized in 2014 by Bodenheimer and Sinsky (3). In the January 2022 issue of JAMA, Nundy, Cooper and Mate offered the goal of a Quintuple Aim stating: "The pursuit of health equity ought to be elevated as the fifth aim for healthcare improvement, purposefully including with all improvement and innovation efforts a focus on individuals and communities who need them most" (4).

Equity in Healthcare: Healthcare equity is defined as "The state in which everyone has the opportunity to attain full health potential, and no one is disadvantaged from achieving this potential because of social position or any other socially defined circumstance" (5). We increasingly appreciate that Social Determinants of Health (SDoH) are the overarching influencer of an individual's health. Starting even before birth, SDoH describes the conditions, such as economic stability and education access, into which we are born, grow, live, and work. These situations are predictable, and the overarching drivers of the behaviors, habits, and lifestyle choices known to lead to chronic illness, such

as diabetes, high blood pressure, and heart disease (5, 6). These situations and environments set up consumers for chronic health problems: first consumers don't have a process to know and do health and thus, often present "late" to healthcare practitioners with health problems. To achieve breakthroughs in population health, we must focus on the consumer, who are at the intersection of equity and care quality. Protecting health requires knowledge and proactive action by consumers. First to have health, they must know and do health and second, present to healthcare practitioners in "timely" manner to confirm the impact (quality) of their health management. Then, it would be logical to have a system to gather and share these data across the healthcare system (consumers, healthcare practitioners, payers, policy, organizations). This process parallels how healthcare works for illness: consumer presents with symptoms to healthcare practitioners who confirm the symptoms via tests to identify, confirm, and treat disease. This system for health would begin in early childhood and continues across all ages. The impact of SDoH begins in early childhood with child-care; thus, the caregiver's health management for their child or family member is either protecting health or driving the risk for disease. Furthermore, consumers presenting timely to health practitioners provide the opportunity to confirm health management quality and early intervention advancing care quality. Within these two goals of health management and timely presentation to healthcare practitioners, it would be logical to create a process of principles and actions to guide consumers in their proactive pursuit of health. While healthcare practitioners learn a process of "principles" and associated "actions" to guide their professional health care, there is no system to guide consumers in their health management or a partnership with healthcare practitioners. Gathering data from this process would also create quality measures that would benefit primary care. Over time, good health management will be pivotal to improving care management of chronic illness (reduce cost and improve quality) and create opportunities for improving accountability in consumers and healthcare practitioners (7, 8).

At the intersection of equity and care quality is the consumer. Protecting health requires knowledge and proactive action by consumers. This would reduce the predictable and harmful influences of SDoH, which in turn would advance the quality of care. Beginning in childhood, the caregiver's health management results in either protecting health or driving disease risk for themselves and children. Furthermore, consumers presenting timely to health practitioners provide the opportunity to confirm health management quality and for early intervention advancing care quality. Over time, good health management will also be pivotal to improving care of chronic diseases at all levels of the healthcare system. With the two variables of health management and timely presentation to healthcare practitioners, it would be logical to create a process of principles and actions to guide consumers in their proactive pursuit of health across their lifespan.

Much of the focus about chronic health problems and situations that impact health begins with adults as symptoms of chronic illness risk increases or symptoms appear; however, the predictable impact of SDoH that greatly influence equity and quality begins with the health management of very young children. It is critical to realize the same behaviors, habits, and lifestyle choices that influence chronic illness, such as diabetes, high blood pressure, and heart disease begin in early childhood and cause poor oral health (tooth decay and bleeding gums) long before chronic illness manifest. We acknowledge these linkages to be "Oral-Systemic Connections" (7, 9). The 2021 report Oral Health in America: Advances and Challenges details how oral health and general health are interrelated, and that general health conditions can affect oral health, and oral health can affect general health (7). For example, the report indicates that "periodontitis may be a modifiable risk factor for cardiovascular disease" and that "periodontal disease is considered an independent risk factor for cerebral ischemia". Diabetes is a significant risk factor for periodontitis and moderate to severe periodontal disease is a predictor for developing type 2 diabetes. Thus, obtaining consumers' feedback about their health management of their young children, confirmed by feedback from clinicians regarding the child's oral health status would equip healthcare stakeholders a unique window to predict and prevent chronic illness. This process would also connect consumers of all ages in a win-win partnership with the healthcare system and significantly strengthen primary care (2, 10, 11).

At the end, we are talking about accountability and autonomy as consumers are the ultimate drivers of their own health equity and quality of care. Health cannot be guaranteed and does not happen by luck. To improve the healthcare system (consumers, healthcare practitioners, payers, and policy makers), it would be beneficial to have health measures from this process that would be shared across healthcare stakeholders enabling everyone work together (2, 10, 11).

Oral health provides a path to reduce cost, improve quality and advance population health. The innovation for a system's improvement to drive health equity would be provided by payers using web-based technology to engage consumers in their health and clinicians who can confirm the quality of consumer health management. Using an on-line tool, consumers can respond to questions about their behaviors, habits, and lifestyle choices known to be associated with their or their dependent's oral health. A clinician would respond to questions about the consumer's oral health status. The consumers would receive personalized health guidance from their responses and the clinician's responses to the surveys. We call this two-part data with timely feedback to the end users. The key benefit of this process is sharing of health measures across the healthcare system to payers, health providers and policy makers creating a partnership of consumers and the healthcare establishment. This process would enable dentistry and medicine to better collaborate in prevention and early identification of chronic illnesses.

What would be the benefits to healthcare?

1. Consumers would receive continuous and personalized health guidance, empowering them to become more engaged and accountable in their health. Community-based organizations can better support vulnerable groups by advancing autonomy, equity, and justice for their members thus reducing the predictable SDoH impact. This would be significant in locations where access to care is limited such as rural communities.
2. Dental and medical practitioners would have a continuous conversation via information sharing and data exchange about health realizing a significant improvement in collaboration. In addition, this communication could benefit individuals without consistent oral healthcare due to lack of resources and dental insurance by having physicians providing input on the importance of oral health and oral health care.
3. Payers could incentivize consumers and clinicians based upon their participation (reporting) and the outcomes (quality) of their Timely Feedback. This would be particularly appropriate in value based or pay for performance programs.
4. Timely Feedback would improve the electronic health record and reduce the burden reported by practitioners.
5. Policymakers could advance population health and practice standards to become anticipatory, preventive, proactive, and create equity, equality, and justice.

Oral health provides a means of tracking health for consumers and crystal ball for payers and policy. Why? The core obstacle for improved healthcare is a poor relationship of consumers and their health. Effective relationships require four critical components for success: First, a shared vision amongst the participants, second - the feedback drives responsibility and accountability, third - the feedback applies to everyone, and fourth - the feedback starts early and is continuous.

Health is what's essential. COVID-19 has critically challenged our healthcare system to become more resilient in the face of unforeseen threats to population health. Integrating dental and medical care, a movement in the right direction in care management of chronic illness, will not address our healthcare's systemic problems. Gathering and sharing oral health data to a broader spectrum of healthcare stakeholders to improve collaboration would provide logical strategy to advance health and care. This action would bring a systems transformation in healthcare to advance prevention and would better align the medical and dental care communities.

Disclosure: NKA and SDL declared no competing interests. FSF is President/CEO, Health Migration Consulting Inc. (HMCI), a data mining company committed to addressing core problems in the healthcare industry by developing tools and services to

migrate from a platform that focuses on "care" to a platform that focuses on "health." HMCI provides a BLUE STRATEGY to address the core problems in healthcare by educating consumers (patients) to become responsible health managers (partners), providing new data to improve collaboration across healthcare and encouraging integration to improve efficiency and reduce cost.

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JAAPI

JAAPI Symposium at the AAPI Global Healthcare Summit 2023

Maternal and Infant Nutrition in the Development of Non-Communicable Diseases in India

This is Non-Peer Reviewed Section

Maternal and Infant Nutrition in the Development of Non-Communicable Diseases in India

Objective: To present and discuss about the critical role of maternal and infant nutrition in the development of non-communicable diseases (NCDs) in adulthood and its health impact in India.

Concepts and Methods: Non-Communicable Diseases (NCDs) are a large group of chronic diseases which cannot be transmissible from person-to-person. NCDs progress slowly and last long often with comorbid conditions, thus result in huge economic burden to manage. NCDs occur due to complex interactions among genetics, physiology, behavioral and environmental factors. At present, globally NCDs account for 41 million deaths per year or about 71% of all deaths. It is expected to reach 52 million deaths per year by the year 2030. According to the World Health Organization, four NCDs, namely cardiovascular diseases, chronic respiratory diseases, cancers, and diabetes mellitus account for about 82% of all NCD deaths. Other NCDs include, mental health disorders, chronic kidney disease, musculoskeletal diseases, and eye and ear disorders. These also account significantly for the total burden of morbidity associated with NCDs. Within the context of India, NCDs contribute to about 5.87 million (60%) of all deaths. NCDs also account for 44% of disability-adjusted life-years (DALYs) lost in India. Hence, to reduce the total healthcare burden of India and to make lives of the people healthy and more productive, addressing the origin or root cause of NCDs at the national level is very critical. During the past few decades, much attention has been paid to the behavioral or lifestyle and environmental factors in adulthood to prevent or reduce the prevalence of NCDs. However, recent research findings in experimental animals and human subjects strongly point to the nutritional status (abuse or insult) of pregnant mothers and infants or toddlers as potential cause. This has been well established in certain conditions, such overweight or obesity, salt-sensitive hypertension, and lean diabetes, which are prevalent in Asians and African Americans. Thus, the evolving science is dictating a paradigm shift in the way we need to look at the origin of NCDs and tailor our efforts and utilize our limited and/or precious resources to address the problem more effectively or impactfully by hitting the bullseye in the target. Based on this premise, the critical problem to be addressed seems to be nutrition of pregnant mothers, infants, and toddlers. Thus, the overarching theme of this symposium is to explore the evolving epidemiological findings, scientific evidence, and public health resources and then propose remedial measures so that a new way of addressing NCDs at the national, regional, and local levels will emerge based on science and evidence-based medicine.

Overarching Learning Objectives: 1) Defining the prevalence of NCDs and their magnitude in overall morbidity and mortality; 2) Understanding the origin of the seeds of NCDs in utero or early life, and the potential cellular and molecular mechanisms involved in it; 3) Delineating the strategies to prevent the NCDs by addressing the nutritional needs of pregnant mothers, infants, and children.

Time	Topic	Speaker	Moderator
02:00 - 04:00	**Session 3 : JAAPI Symposium - Development of Non-Communicable Diseases in India**		
02:00 – 02:30	Non-Communicable Diseases (NCDs): A Global Health Challenge in the 21st Century	Dr. Soumya Swaminathan, Former Chief Scientist, WHO	Dr. Suresh Karne, *USA*
02:30 – 03:00	Non-Communicable Disease Risk Factors and Their Trends in India	Dr. Suzanne Tanya Nethan, *INDIA*	
03:00 – 03:30	Intergenerational Transmission of NCDs in Developing Countries and in India	Dr. Chittaranjan Yajnik, *INDIA*	
03:30 – 04:00	Role of Infant Nutrition in the Development of Adultonset NCDs	Dr. Ramasubbareddy Dhanireddy, *USA*	

Synopsis of Lecture – JAAPI Symposium at the GHS 2023

Non-Communicable Diseases (NCDs): A Global Health Challenge in the 21st Century

Soumya Swaminathan, M.D., FIAP, FNAS, FIAS
Former Chief Scientist, World Health Organization

Highlights:

- Understanding global NCD problems from the lens of equity.
- Understanding and identifying strategic priorities to tackle NCDs in low- and middle-income communities.
- Understanding and addressing the importance of a multisectoral, whole-of-society approach in tackling NCDs.
- Importance of regular screening, and awareness in the control of NCDs.

The prevalence of non-communicable diseases (NCDs), such as diabetes, hypertension, stroke, heart and kidney diseases, and cancer in India is steadily increasing, taking the lives of people even before they reached old age. India has been identified as the 'diabetes capital of the world'. Many risk factors for NCDs have been described, such as genetic factors, individual behavior, diet (excessive consumption of salt or sugar), environmental pollution, and use of tobacco or alcohol. Of these factors, individual behavior is mostly responsible for the NCDs. Strong regulatory mechanism may also help by curbing some of the contributing factors.

From the point of national healthcare, investing in primary healthcare and screening for the early signs of NCDs is mot effective method. Obviously, early diagnosis and treatment of NCDs have dramatic effect in saving the lives of people. The combination of clinical screening with laboratory technology, such as blood and urine analysis will have strong impact on identifying and treating NCDs and thus reducing their mortality and morbidity. These in turn dictate the need to build laboratory infrastructure at various levels to reach the community and serve people in remote parts of the country.

The use of internet and telehealth and telemedicine can transform the healthcare delivery in not only emerging economies like India, but also developing countries worldwide. Recent COVID-19 pandemic has transformed the healthcare system all over the world with the use of internet as a portal for telemedicine, with physicians helping patients across the continents.

In parallel to the above efforts by healthcare providers and public health officials, efforts by governments to reduce environmental pollution, improving the nutritional status of pregnant mothers, infants and children will markedly reduce the prevalence of NCDs in countries like India.

Disclosure: Author declares no competing interests.

Speaker Profile:

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- Former Coordinator, UNICEF/UNDP/World Bank/Who Special Programme for Research and Training in Tropical Diseases

Synopsis of Lecture – JAAPI Symposium at the GHS 2023

Non-Communicable Disease Risk Factors and Their Trends in India

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Highlights:

- Three nationally representative surveys have provided information on the prevalence of the various non-communicable disease (NCD) risk factors, namely the National Family Health Survey (NFHS), National NCD Monitoring Survey (NNMS), and Global Adult Tobacco Survey (GATS).
- Prevalence of overall tobacco use has decreased from GATS -1 (2009-10) to GATS-2 (2016-17). A decrease in the prevalence was also noted among both males and females.
- Prevalence of alcohol use has also decreased among males whereas no notable change is noted among females, from NFHS-4 (2015-16) to NFHS-5 (2019-21).
- Prevalence of overweight and obesity raised blood glucose and raised blood pressure have increased among both males and females, from NFHS-4 to NFHS-5.

Introduction: Non-communicable diseases (NCDs) are chronic diseases as a result of a combination of genetic, physiological, environmental and behavioral factors. The main types of NCDs are cardiovascular diseases, cancers, chronic respiratory disease, and diabetes. Forty-one million or 74% of all deaths globally per year are attributed to NCDs with 3/4th of these deaths occurring in low- and middle-income countries. In India, 60% of total deaths occur to due to NCDs. The risk factors for NCDs could either be behavioral (alcohol or tobacco use, physical inactivity, low fruit and vegetable consumption, salt and saturated fat intake) or biological (raised blood pressure, blood glucose, or cholesterol, and overweight and obesity).

Surveys for NCD Risk Factors: There are several surveys which deal with one to two NCD indicators such as Global Adult Tobacco Survey (GATS). There are other examples such as District Level Household Survey (DLHS) with information on NCD risk factors limited to only few states. National Family Health Survey (NFHS) and National NCD Monitoring Survey (NNMS) cover many of the NCD indicators. For NFHS, several rounds have been conducted, hence the prevalence trends may be compared at national and state levels. The NNMS does not provide state level estimates and only a single round has been conducted, hence the trends cannot be estimated.

Tobacco Use: Prevalence of tobacco use has decreased by six percentage points from 34.6% in GATS -1 (2009-10) to 28.6% in GATS-2 (2016-17). A decrease in the prevalence was also noted among both males (from 47.9% in GATS-1 to 42.4% in GATS-2) and females (20.3% in GATS-1 to 14.2% in GATS-2). The highest prevalence of tobacco use is reported in Tripura (64.5%), while the lowest prevalence is reported in Goa (9.7%). In the north-eastern and eastern states (except Sikkim), the prevalence of tobacco use among adults is higher than the national average. The three large states of Uttar Pradesh, West Bengal and Maharashtra together account for more than one-third (38%) of the tobacco users in India. In NFHS, between 2015-21, a decline in tobacco use from 44.5% in NFHS-4 to 38% in NFHS-5 was noted among males while a slight increase was noted among females i.e., from 6.8% in NFHS-4 to 8.9% in NFHS-5.

Alcohol Use: In NFHS, between 2015-21, a decline by ten percentage points (i.e. from 29.2% in NFHS-4 to 18.8% in NFHS-5) is seen among males whereas an increase by 0.1% is noted among females. Among males, the highest prevalence is noted in Goa (59%), Arunachal Pradesh (57%), and Telangana (50%) and the lowest in Lakshadweep (1%), while Arunachal Pradesh (18%) and Sikkim (15%) have shown the highest prevalence of female alcohol users.

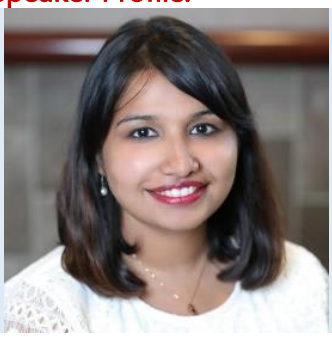
Overweight and Obesity: Prevalence of overweight and obesity has increased by about three to four percentage points among both males and females, from NFHS-4 (2015-16) to NFHS-5 (2019-21), i.e., from 19% in NFHS-4 to 23% in NFHS-5 among males and 21% NFHS-4 to 24% in NFHS-5 among females. Among males, the highest prevalence was noted in Andaman & Nicobar Island (45%), Puducherry (43%) and Lakshadweep (41%), while among females, the highest prevalence was noted in Puducherry (46%), Chandigarh (44%), Delhi, Tamil Nadu & Punjab (41% each), and Kerala & Andaman & Nicobar Islands (38% each).

Raised Blood Glucose: The overall prevalence of raised blood glucose has increased among both males and females i.e., from 11.9% in NFHS-4 to 14.5% in NFHS-5 among males and from 8.6% NFHS-4 to 12.4% in NFHS-5 among females. Among males, the highest prevalence is in Kerala (24%) and Goa (22%) while the lowest is in Ladakh and Jammu & Kashmir (7% each). A similar prevalence pattern is also noted among females with the highest prevalence in Kerala (21%) and lowest in Ladakh (6%).

Raised Blood Pressure: The overall prevalence of hypertension has increased among both males and females i.e., from 13.6% in NFHS-4 to 21.4% in NFHS-5 among males and from 8.8% NFHS-4 to 17.6% in NFHS-5 among females. Among both males and females, the highest prevalence is noted in Sikkim (42% among males, and 35% among females); the lowest prevalence among males is in Dadra & Nagar Haveli and Daman & Diu (15% each).

Disclosure: Authors declare no competing interests.

Speaker Profile:



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Synopsis of Lecture – JAAPI Symposium at the GHS 2023

Intergenerational Transmission of NCDs in Developing Countries and in India

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Highlights:

- The current model of NCDs envisages a non-modifiable genetic susceptibility and transmission, and precipitation by lifestyle factors.
- Research over the past decades has suggested a modifiable epigenetic susceptibility.
- The most important window for epigenetic susceptibility is during preconceptual period, pregnancy, and infancy (1000+ days).
- The new research has contributed to the idea of 'primordial prevention' (before the beginning).
- Health of young girls is crucial for the health of next generation.

Current ideas of etiology of type-2 diabetes suggest that the susceptibility is based on genetic factors and that hyperglycemia is precipitated by obesogenic lifestyle, usually in the adult age. India is one of the world capitals of diabetes. Indians develop diabetes at a younger age and at much lower levels of obesity compared to Europeans. Our research showed that Indians have a thin-fat phenotype compared to the Europeans i.e., they have extra fat (adiposity) for a given BMI (Body Mass Index). The thin-fat phenotype is associated both with insulin resistance and relative insulin deficiency (low disposition index). In the Pune Maternal Nutrition Study (PMNS) we found that this thin-fat phenotype expresses at birth, and is related to maternal factors (small size, undernutrition, excess physical activity etc.). It appears that fetal phenotype and body composition are influenced by 'epigenetic' factors, maternal methyl donor nutrition (vitamin B12, folate), 1-C metabolism and glycemic status.

We have now completed 21 years follow up in the Pune Children's Study (PCS, urban), and we are following up participants in the PMNS (rural) at 24 years of age. In the PCS we found that diabetes related phenotypes (glucose tolerance, insulin resistance disposition index, adiposity, and central adiposity) were influenced by small size at birth and large size in later life.

In the rural PMNS we found a high prevalence of prediabetes (28%, America Diabetes Association criteria) in 18-year-old participants (37% in males, 18% in females). Prediabetic individuals were born short and with a smaller head circumference, had higher fasting plasma glucose from 6 years of age and lower insulin secretion in relation to prevailing insulin resistance. Interestingly, mothers of prediabetic children were less likely to be obese but had higher glucose in the normal range. Childhood adiposity and insulin resistance in these offspring at 6 years of age was predicted by lower maternal circulating vitamin B12 and higher folate concentrations during pregnancy. This led to the Pune Rural Intervention in Young Adolescents (PRIYA) trial which was started in adolescent age to reduce risk of diabesity in their offspring. Children born to mothers who received physiological dose of vitamin B12 have shown better neurocognitive function compared to the placebo group. Diabesity will be evaluated at a later age.

Thus, results of observational and interventional studies in Pune birth cohorts have supported a strong role for maternal nutrition before and during pregnancy in determining future risk of diabesity in the offspring. This is the exciting science of Developmental Origins of Health and Disease (DOHaD). Our results support a 'primordial' prevention (pre-conceptional) to reduce risk of diabesity in the future generations, in addition to improving the lifestyle. Investigation of molecular mechanisms will improve our knowledge and ability to refine our interventions.

Disclosure: Author declares no competing interests.

Relevant Publications by the Author:

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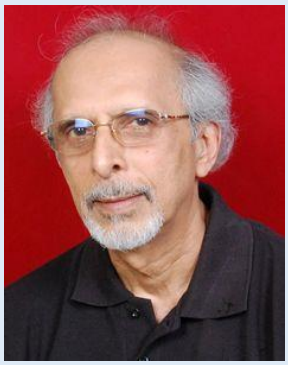
- Chittaranjan S Yajnik. Vitamin B12: An Intergenerational Story. *Nestlé Nutr Inst Workshop Ser*, 93:91–102, 2020
- Chittaranjan S Yajnik and Parag C Yajnik. Fetal adiposity epidemic in the modern world: A thrifty phenotype aggravated by maternal obesity and diabetes, American *Journal of Clinical Nutrition*, 112, 8–10, 2020

Speaker Profile:



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Synopsis of Lecture – JAAPI Symposium at the GHS 2023

Role of Infant Nutrition in the Development of Adult-Onset Non-Communicable Diseases

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Highlights:

- Low birth weight and poor intrauterine growth increase the risk of adult on-set non-communicable diseases.
- Protein intake in infancy and later affects the risk of overweight and obesity.
- Breastfeeding during first two years of life reduces the risk of overweight and obesity later in life.
- Breastfeeding also prevents the cardiac structural abnormalities found in adults born with low birth weight.

As aptly said by Mahatma Gandhi, "*A nation's greatness is measured by how it treats its weakest members*." According to the International Institute for Population Sciences (IIPS), and National Family Health Surveys (NFH), over the decades the under-five mortality, infant mortality and neonatal mortality have shown steady decreases in India, and currently stand at 42, 35 and 25 deaths per 1,000 live births, respectively as per NFHS-5 data. Yet, these numbers are relatively higher as compared to other emerging economies. Much more needs to the done to improve these mortality numbers related to infants and children.

Low birth weight (LBW), birth weight <2500 grams, is an important factor contributing to the neonatal and infant mortality as well as the under-five mortality. The worldwide prevalence of low birthweight is 14.6%, while the corresponding number for India is about 18%; majority of these LBW infants are term and have poor growth in utero and are small for gestational age at birth (SGA). Several conditions result in LBW in India, such as poverty, poor sanitation, poor dietary intake by mothers, deficiency of micronutrients among others. Due to these factors, the developing fetus undergoes physiological responses or adaptation, which lead to long-term outcomes, such as development of type-2 diabetes mellitus (T2DM), hypertension, dyslipidemia, and obesity in adulthood. It has been shown that pre-mature birth, LBW, and SGA at birth increase the risk of adverse metabolic and cardiovascular outcomes in adulthood. LBW is significantly associated with metabolic syndrome and T2DM in adulthood. LBW and premature birth are positively associated with systemic arterial hypertension in adult life. Thus, many of the non-communicable diseases seen in adulthood are programmed during fetal development or at birth.

Models, such as Thrifty Phenotype and Overloaded Adipocyte Hypothesis were developed to explain the modeling of phenotype that occurs before or at the time of birth. Studies have also shown a relationship between gestational age at birth and the risk of heart failure and acute myocardial infarction (AMI) in childhood and young age. Structurally, LBW was associated with later development of more concentric pattern of left ventricular remodeling and poorer left ventricular function. Thus, LBW contributes to greater incidence of AMI and greater left ventricular concentricity and poorer left ventricular function.

Many of the above developmental abnormalities can be prevented by feeding infants with human breast milk. Human breast milk is rich in macronutrients, micronutrients, hormones and growth factors, healthy microbial communities, and microRNAs. There are several long-term benefits of breastfeeding on cholesterol levels, blood pressure, development of obesity and T2DM. Long-term breastfeeding is also associated with improved performance in intelligence tests, which

persists even after adjustment for maternal IQ. Long-term follow-up studies suggest that breastfeeding impacts schooling and adult income. Data collected by IIPS and NFHS show there are variations in breastfeeding practices among children below 2 years in India. Pre-term born young adults fed exclusively human milk (EHM) had better left and right ventricular end-diastolic volume index and stroke volume index as compare with pre-term born young adults who were exclusively formula fed (EFF).

Pre-term birth status, feeding practices in infancy and childhood can affect weight gain and obesity in adulthood. For example, high protein intake in early childhood, more than metabolic requirements, may trigger weight gain and result in later development of obesity and associated non-communicable diseases. Thus, the risk of obesity in childhood is altered by early nutrition and environmental factors. Environmental factors include maternal and paternal obesity at conception, as well as gestational weight gain. Nutritional factors include the absence of breastfeeding during the first year of life, and high infant protein intake in infancy.

Disclosure: Author declares no competing interests.

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- Deputy Editor of Journal of AAPI

Portrait of Hippocrates (1787), by the Majorat of Setúbal.
Image in Public Domain

Science is the father of knowledge, but opinion breeds ignorance.
- Hippocrates