Review

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Association of human gut microbiota with rare diseases: A close peep through

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SUMMARY The human body harbors approximately 10^{14} cells belonging to a diverse group of microorganisms. Bacteria outnumbers protozoa, fungi and viruses inhabiting our gastrointestinal tract (GIT), commonly referred to as the "human gut microbiome". Dysbiosis occurs when the balanced relationship between the host and the gut microbiota is disrupted, altering the usual microbial population there. This increases the susceptibility of the host to pathogens, and chances of its morbidity. It is due to the fact that the gut microbiome plays an important role in human health; it influences the progression of conditions varying from colorectal cancer to GIT disorders linked with the nervous system, autoimmunity, metabolism and inheritance. A rare disease is a lethal and persistent condition affecting 2-3 people per 5,000 populaces. This review article intends to discuss such rare neurological, autoimmune, cardio-metabolic and genetic disorders of man, focusing on the fundamental mechanism that links them with their gut microbiome. Ten rare diseases, including Pediatric Crohn's disease (PCD), Lichen planus (LP), Hypophosphatasia (HPP), Discitis, Cogan's syndrome, Chancroid disease, Sennetsu fever, Acute cholecystitis (AC), Grave's disease (GD) and Tropical sprue (TS) stands to highlight as key examples, along with personalized therapeutics meant for them. This medicinal approach addresses the individual's genetic and genomic pathography, and tackles the illness with specific and effective treatments.

Keywords disorders, human gut microbiome, personalized therapeutics, rare diseases

1. Introduction

Microorganisms are ubiquitous, living in and on us. The human body is made up of distinct populations of billions of microorganisms that inhabit certain areas of the same, and execute various metabolic and immunological functions. Exclusively 25% of the human body is made up of human cells; the rest is of hundreds of species of bacteria, fungi, protozoa and viruses. The genome of all microbes is collectively known as the "microbiome". Microbes contribute an additional 2 million genes to the 20,000 genes already encoded by the human genome (*1*).

The balanced connection between the host and the microbiome maintains a healthy human body. The diversity of the microbiome has an overall influence on human health in various categories, and its malfunctioning or dysbiosis directs to ailment, the diversity of which is distinguished by the abundance and diversity of distinctive species of bacteria correlated with such diseases (*2*).

A microbial community constitutes from the time when a human being is first exposed to the environment. The human body has an extensive spectrum of areas for bacteria to infiltrate, and one of the most prominent is the mucous membrane, which is found throughout the body. The microbiome aids in the extraction of energy and nutrients from the food we eat, as well as impeding the colonization by pathogens (*1*).

This microbial community emerges from the birth process, and has a significant influence on health. The infant microbiome and its assembly are determined by maternal-offspring exchanges of microbiota. The human body attains the microflora that is present along the birth canal during parturition, whereas individuals born by Caesarian section have a distinct skin microbiome as compared to individuals who are born vaginally (*3*). It is considered better to be born through the normal routes that acquire a more beneficial microbiome. The origin of microbes in the intrauterine environment, complex genetic dynamics of transmission and their site-

specific colonization, and immune system development in the infant remain to be determined yet. The maternal microbiota and its metabolites transferred to the fetus play a key role in influencing infant immune responses. Immunoglobulin G (IgG) from breast milk in many mammalian species is delivered into the neonatal circulation through intestinal epithelium. It contains about 88% water, and 124 g/L macronutrients, including about 7% (60-70 g/L) carbohydrates, 1% (8-10 g/L) protein, and 3.8% (35-40 g/L) fat. Breast-fed infants have higher levels of fatty acid oxidation products (preference for fat metabolism) in comparison to formula-fed ones (*4*). Therefore, the best source of cellular energy and nutrients for the rapid growth of the brain in an infant is breast milk in the early growing months. Breast milk is a fundamental contribution to the gut microbiota. The most researched organisms of gut microbiome that are transferred *via* breast feeding include *Lactobacillus* spp., *Bifidobacterium* spp. and *Bacillus subtilis*. There are very few genetic variations in the *Lactobacillus* spp., while there are comparative phenotypic and genetic variants seen in *Bifidobacterium* spp.; both in infants and mothers (*5*). Breast feeding is also an excellent indicator of promising health, as it protects against infections through specific and non-specific immune factors, and demonstrates beneficial effects on the intestinal flora of an infant. Breast milk strengthens the immature immune system of the neonates, and amplifies their defences against foreign entities. Immunoglobulins (Ig) excreted in milk are IgG that protect mainly against enteric infections. Breast milk also contains anti-idiotypic antibodies capable of increasing infant antibody response. Newborns that have a defect in fetching maternal immunoglobulins from breast milk are therefore at high risk of systemic infectious diseases (*6*).

Ailments or infections can be amassed in two ways: exogenously acquired infections from an external source such as bacterium in the environment, and endogenously acquired infections produced by agents inside the body as a result of antibiotic therapy altering the microbiome. Diseases become rare or ultra-rare when there is a consequence on a relatively low number of individuals worldwide and are often caused by errors in DNA (genetic cause). Drugs, cognitive and emotional stress, diets high in protein, simplified sugars/refined carbohydrates, fat or fructose, chemotherapy, radiotherapy and intestinal infections are all probable factors of dysbiosis. To reduce the cause of dysbiosis, probiotics and fecal biotherapy play a crucial role. Fecal biotherapy or fecal transplantation and Probiotics are important in reducing the etiology of dysbiosis (*7,8*). The presence of viruses, fungus, and bacteria is used to interpret the microbial community, and if there is a low abundance and density of these communities, it is referred to as the dark matter of the human microbiome. These values can also be misinterpreted by the dysbiosis of the microbes (*9*).

There are so many different rare diseases that do not necessarily mean it is very rare to have a rare disease. Studying these rare diseases is given utmost importance, with research investigations revealing deeper insights into human body working mechanisms. This is because many rare diseases are caused by relatively simple and known mechanisms, and these can even reveal about the bases of relatively common diseases that occur. There are interconnections between microbiota imbalances or alterations, and certain disease manifestations. Changes in microbial compositions can cause diseases such as neurological and autoimmune disorders, besides cardio-metabolic and genetic diseases, as well as impacting an individual's behavior to even trigger behavioral disorders in some cases (*10*).

2. Human gut microbiome and its association with rare diseases

2.1. Pediatric Crohn's disease (PCD)

PCD is a rare, inflammatory disease of the intestinal wall or portions of the gastrointestinal system, primarily symptomized by severe, chronic inflammation. This ailment is thus categorized as a subtype of inflammatory bowel disease (IBD) induced by altered microbial populations and disruptive intestinal immune responses. PCD mainly prevails in children of age below 2-3 years, and impacts 2 in 1,00,000 children aged younger than 10 years. A peak preponderance of PCD is seen in children aged 10-14 years, and it is very common in major nations like Australia, Scotland, and UK (*11*). Epidemiological studies indicate that there is an incremental increase in the number of affected individuals in Europe and the USA (*11*). PCD is an autoimmune ailment in which the immune system targets its tissues, inducing metabolic alterations (*12*). It is accelerated by the inactivation of the mucosal immune response correlated to host genetics, microbial community alterations and environmental factors. *Faecalibacterium prausnitzii* is an anti-inflammatory commensal bacterium (*13*). Reduced microbial multiplicity illustrates dysbiosis in the gut microbiota, and those with PCD have lower levels of *F. prausnitzii* and higher levels of *Escherichia coli* (*14*). Butyrate, the end product of intestinal bacterial fermentation of primarily non-digestible carbohydrates such as resistant starch, is absorbed by the colon cells through transport pathways. There, the butyrate is metabolized to generate energy that sustains the integrity and health of the colon cells. Butyrate, being a substrate of fatty acid metabolism generates ATP in our body, furthermore maintaining the lining of the colon. Decreasing levels of *F. prausnitzii* can reduce ATP intake in these cells, resulting in a loss of anti-inflammatory function and a weakening of the ability to fight infections (*15*). The affected individuals may forfeit digestion and absorption functionalities. Treatment of PCD involves restoration of

the mucosal lining, wherein "exclusive enteral nutrition (EEN)", formulated with polymeric nutrition, is fed to the affected individuals. EEN aids in the diagnosis of intestinal microbiota and faecal microbiota alterations. It incites the alterations in gut microbiota, which leads to a reduction in inflammation (*16*).

2.2. Lichen planus (LP)

Lesions on the skin, urogenital tissue and nails, and eyes are observed in LP-affected individuals. Oral bacteria not only maintain oral hygiene, but also influence the development of many oral diseases. *Capnocytophaga sputigena*, *Eikenella corrodens*, *Lactobacillus crispatus*, *Mobiluncus curtisii*, *Neisseria mucosa*, *Prevotella bivia*, *Prevotella intermedia*, and *Streptococcus agalactiae* are the microbes that tend to infect the oral mucosa and are found in oral lesions. The metabolic disturbance or the imbalance in the metabolic process is the main cause in the colonization and proliferation of fungal species that affect the epithelial cells in lesions and the nutrient uptake and release of cytokines are hindered causing the disease condition (*17*).

Oral lichen planus (OLP) could either accompany cutaneous lesions in the oral cavity, or precede them. These lesions are designated as lichenoid mucositis or lichenoid lesions. Stress and anxiety are known to be substantial factors in inciting this condition. A combination of drugs and other foreign bodies may also elicit a host response to induce these lesions (*18*).

OLP lesions manifest themselves in a variety of clinical forms namely, reticular, atrophic or erythematous type, erosive or ulcerative, plaque or hypertrophic form, and bullous form. Reticular OLP is a common type of condition where it manifests in buccal mucosa and other sites such as the tongue, gingiva, and lips. It is characterized by numerous interlacing white keratolytic lines striae, called Wickham's striae. This occurs with mild symptoms or may be asymptomatic. Atrophic or erythematous form occurs as a red patch in conjunction with reticular striae (white straie) and with an erosive variant. Symptoms like burning sensation, discomfort and lesions are manifested on gingival, producing a pattern called desquamative gingivitis, also known as pemphigus vulgaris, cicatricial pemphigoid or epidermolysis bullosa. The erosive or ulcerative form manifests with an ulcer covered with pseudomembranous exudates associated with reticular striae and also erythematous patches. White raised or flat plaques may occur as a variant of lesion usually on the tongue and buccal mucosa. This may occur in conjunction with white striae and irregular smooth plaques, often involving one or more than one affected area. OLP also manifests as patchy areas of reactive melanosis due to stimulation of melanocytes by inflammatory cells (*19*).

Another variant of this disease is the "lichen planus pigmentosus-inversus" which is characterized by spots on cervical, axillary and popliteal regions. This disease-inducing immune system generates an autoinflammatory response in the oral cavity, hair, and nails (*20,21*).

Lichen sclerosus is another form of autoimmune condition and is triggered by *Borrelia burgdorferi* which is the evidential cause of Lyme disease. Salivary mycobiome (*Candida* spp., *Torulopsis glabrata*, *S. cerevisiae*, *Aspergillu*s spp., *Erysiphe* spp.) dysbiosis leads to a shift in oral bacteriome associated with the disease (*21*). Some of the other species of fungi involved are *Epidermophyton inguinale*, *Trichophyton gypseum*, *T. interdigitale*, *T. purpureum*, *Cryptococcus hominis*, and *Oidium pulmoneum* (*22*).

Some of the viruses also involved in this disease are herpes simplex virus 1 (HSV-1), Epstein Barr virus (EBV), human papillomavirus (HPV), hepatitis virus and cytomegalovirus (CMV) (*23,24*).

2.3. Hypophosphatasia (HPP)

HPP is a disease of bone mineralization. Patients with severe instances, with a rare presentation of one in every 100,000 individuals, have fragile bones that are frequently fractured and deformed. The occurrence of persistent pain, as well as the early loss of teeth and fractures, is common (*25*).

This condition is caused by a gene mutation that inhibits the body from producing the enzyme alkaline phosphatase. This enzyme regulates the formation of a chemical called pyrophosphate, which is present in blood and urine, and it stops the key mineral in our bones from growing. Mineralization does not occur in the body due to pyrophosphate build up, resulting in the disease condition of HPP. Intestinal alkaline phosphatase is also helpful in improving and maintaining appropriate gut barrier function, and serves as a gut mucosal defense mechanism. It is influenced significantly by bacterial exposure (*26*).

Individuals who have HPP also have periodontitis, which is a polymicrobial infectious disorder that affects the teeth enamel. Periodontitis is caused by a shift in the microbial ecology of the teeth. *Porphyromonas* species are found in the subgingival cavity, resulting in the deterioration in the arrangement of teeth in people suffering from this disease (*27*). *Porphyromonas gingivalis*, *Treponema denticola* and *Tannerella forsythia* are periodontopathic bacteria that play a significant role in the pathogenesis of the disease. Among these three pathogens, *P. gingivalis* is most commonly seen in patients with periodontitis. The bacterial flora differs at both subgingival and supragingival levels, and so do the metabolites produced by the pathogens. Plaques occur at the supragingival level as a result of the bacterium *Streptococcus mutans* producing lactic acid, which directly causes dental caries by decreasing the pH of enamel. In the progression of periodontal disease, the periodontal pathogen *Fusobacterium nucleatum* and

P. gingivalis produce short-chain fatty acids (SCFA), including butyric acid, as metabolites. Butyric acid, also known as butyrate, is known to function intrusively on periodontal tissues. Increased butyrate concentrations have been associated with inflammatory disease in the brain, and cause apoptosis in human gingival fibroblasts following long-term exposure to butyrate (*28,29*).

2.4. Discitis (diskitis)

Discitis (diskitis) is an inflammation or infection in the spine. These are unique to the intervertebral discs of the spine. Pressure on the disc causes inflammation or swelling, which finally leads to discomfort or agony. There are two forms of discitis, namely intervening discitis and spontaneous discitis. In the intervening discitis, diagnostic or therapeutic procedures can induce infection at the location and cause inflammation, whereas spontaneous discitis is caused by microbial invasion through the blood circulation (*30*).

If the intervertebral discs are not furnished with blood, microorganisms may intrude and cause infection. These microorganisms can enter the bloodstream by any route, including the urinary tract, the respiratory tract, the pelvic region, and the gums. Younger adults are more susceptible to this infection, with rare occurrence in the older people. It is common only in people with diabetes (*31*).

Spondylodiscitis (SD) is a form of spontaneous discitis in which the inflammation in the intervertebral discs or nearby vertebral bodies is caused by bacterial interventions. There are several forms of SD, including pyogenic (bacterial), granulomatous (fungi) and parasitic (*Echinococcus* spp.) (*32*).

Staphylococcus aureus, *Streptococcus* spp. and *Enterococcus* spp. induce pyogenic SD by releasing proteolytic enzymes that disintegrate the discs. These bacteria penetrate the metaphyseal arcades and deposit on the cartilaginous plates, which allow them to live and release the enzyme. The infection can also cause pus to accumulate around the spinal cord (paravertebral abscess), and fractures can happen, eventually leading to meningitis, spinal epidural abscess, and neurological impairment (*33,34*).

Some of the other infection forms are vertebral osteomyelitis, spondylitis, epidural empyema, epidural phlegmon and diabetic foot ulcerations (DFU) (*35*). The opportunistic pathogen *S. aureus* causes DFU by colonizing the wound in multi-layers and forming biofilm. This pathogen is also commonly responsible for spinal osteomyelitis/vertebral osteomyelitis. The wound will aggravate as glycemic control deteriorates, causing the immune system to fail to react (*36,37*).

Septic arthritis is rare, with morbidity rates of 40-50 percent and death rates of 10-20%. It is caused by microbial entry through the circulation, which creates joint pain (*38)*.

2.5. Cogan's syndrome

DG Cogan reported the classic form of the Cogan's syndrome disease in 1945. It is a conglomeration triad of non-syphilitic interstitial keratitis, vestibuloauditory illness, and respiratory tract symptoms (*39*). It is also a cause of vasculitis (autoimmune vasculitis) (*40*).

Cogan's syndrome is a very rare autoimmune disorder in which autoantibodies cause tissue damage in portions of the ear, including endothelial cells and inner sensory epithelial cells. Cogan's syndrome symptoms are comparable to Meniere's syndrome, with the abrupt onset of nausea, vertigo, vomiting and hearing loss. It is characterized by continual inflammation of the frontal portion of the eye, particularly referring to cornea (*41*). The pathogenesis of ocular infections in Cogan's syndrome includes *Chlamydia psittaci* (Psittacosis), *C. pneumoniae* (pneumonia), and *Chlamydia trachomatis* (trachoma) (*42,43*). *Chlamydia psittaci* causes myocarditis and valvular lesions (*44,45*).

The ocular condition is characterized by interstitial keratitis which causes vision impairment, conjunctivitis and inflammation around the eye, as well as an increase in light sensitivity. Interstitial keratitis can coexist with syphilitic disease, which is often caused by a combination of bacteria and viruses associated with systemic vasculitides (*46,47*). Viruses such as Herpes simplex virus (HSV), Epstein Barr virus (EBV) and Rubulavirus cause viral infections presented in corneal disease. Corneal inflammation has been linked to a number of diseases, including Polyarteritis nodosa, Wegener granulomatosis and Rheumatoid arthritis. Rubulavirus causes lacrimal gland inflammation that involves the cornea, resulting in "blue eye disease". Rubulavirus also causes another sickness known as Waardenburg syndrome, which is a rare, genetically inherited illness characterized by hearing loss and a pigmentation defect that causes blue and brown eye pigmentations in the eye. This blue pigmentation is induced by a member of the *Orthorubulavirus* viral species. The virus enters the body *via* exposures, and is hypothesized to replicate in the nasal mucosa and tonsils before spreading to the brain and lungs (*48*).

2.6. Chancroid disease

Chancroid disease is a rare infection caused by the Gram negative, facultatively anaerobic bacterium *Haemophilus ducreyi,* and is acquired through sexual contact. It is a genital ulcer condition, which has been linked to human immunodeficiency virus (HIV) transmission (*49*). *H. ducreyi* penetrates the skin through a breach in the mucosa, where it produces a toxin (cytocidal distending toxin) that destroys individual cells in the infected region, while also triggering a local inflammatory reaction that causes necrosis and leads to ulcer aggravation. Within the first week of onset, infected individuals will develop

papules, which will subsequently develop into pustules, which are more prevalent in males than females, and inevitably ulcers, which can be excruciating (*50*). Lymph node inflammation (lymphadenitis) also occurs, resulting in a tiny lump that causes severe pain. These nodes rupture in some cases, resulting in abscesses (*51*).

This disease also includes the forms of syphilis, genital herpes and donovanosis (granuloma inguinale) (*52*). These diseases are solely caused in humans, with no intermediate hosts, and it is extremely infectious and contagious. Donovanosis is caused by the bacterium *Klebsiella granulomatis*, which causes scarring and necrosis in the afflicted region. Ulcers most commonly develop on the labia and internal to the vaginal or on cervix in women, and on the penile foreskin in men (*53,54*). Chanchroidal ulcers are greyish in appearance, which differentiate it from ulcers caused by donovanosis and syphilis (*55*).

2.7. Sennetsu fever

Sennetsu fever is a fever-like disease caused by *Ehrlichia sennetsu*, a member of the *Ehrlichia* bacteria family. It is a rare disease condition that belongs to the Human Ehrilichioses category of diseases. Human monocytic ehrlichiosis (HME) caused by *Ehrlichia chaffensis* and Human Granulocytic ehrlichiosis (HGE) caused by Anaplasma phagocytophilium are two related types of the ehrlichial infections. Individuals who are infected or who have contact with infected people can develop symptoms such as high fever, headaches, myalgia, nausea, vomiting, anorexia and insomnia (*56*).

The consumption of raw fish is thought to be the primary source of this fever, which will eventually progress to the disease state. The encystment of larval nematode can be found in raw or undercooked fish, and it is passed to humans *via* outer membrane proteins of the bacteria attached to the host cell, where it activates an inflammatory response by associating with capillaries and arteries (*57*). Transglutaminase activity initiates endocytosis by allowing phagocytes to enter the host. Endocytosis is activated in response to pathogen entry, and creates a vacuole for pathogen survival in the host cell. It will inhibit macrophage entry and cause the macrophage to dissolve and thus cause enlargement of liver, spleen and lymph nodes (*58*).

2.8. Acute cholecystitis (AC)

Gall bladder plays an imperative role in storage and concentration of bile juice secreted by the liver, but development of gallstones near the cystic duct leading to severe gallbladder inflammation is commonly referred to as AC (*59*). Predominantly the incidents of AC occur due to impediment of the cystic duct by gallstones, or in few cases, it can be due to aggregation of gallbladder sludge. Protracted obstruction of the cystic duct leads to severe inflammatory responses in gallbladder, which in turn, triggers gut-wrenching infections and formation of biliary sludge or gallbladder sludge, *i.e*. aggregation of sedimented particulate matter consisting of remains of bile juice, calcium salts, crystals of cholesterol and pigmented calcium bilirubinate (*60,61*).

This gastrointestinal disorder closely interacts and houses the secondary bacterial infections from the enteric microbes, as well as contributes towards the proliferation of opportunistic microbes (*62*). According to clinical researches conducted worldwide, enteric Gram-negative anaerobic gut microbiome interactions present in the biliary system points to an imperative association, which help us in understanding the patho-physiological conditions of the patients affected with AC, comprising of the growth of *Clostridium perfringens*, *Citrobacter freundii*, *Klebsiella* spp., *Escherichia coli* and *Enterobacter cloacae* (*63*).

Consistently higher populations of enteric gut microflora near the biliary region of the patients affected by AC play a significant role in the production of bile juice and to the development of gallstones (*60*). Traces of elevated similarity have been found between the microflora present in the duodenum with the biliary microbiome, which actively participates in the polymerization and oxidation of bile juice, leading to the development of gallstones (*64*).

The secretion of the enzyme cholecystokinin (CCK), which plays a considerably significant role in the storage and concentration of bile juice in the gallbladder, is produced by the immunological stimulation of buccal microbial population. Development and progression of oxidative stress conditions, inducing free-radical reactions in the bladder mucosal cells, stimulate the process of gallstone formation, and impedes the physiological functioning of the gallbladder (*65*).

Other pathogenic microbes like the spiral-shaped *Helicobacter pylori* perpetrates in elevation of clinical complexities like up-regulation of urease which stimulates the precipitation of calcium ions during the development of gallstones, leading to the progression of chronic and AC. Furthermore, *H. pylori* elevates the inflammatory responses produced in the patients suffering from AC, with traces of interleukins (ILs) also detected in them, namely classes I and VI, along with tumor necrosis factor (TNF)-α, eliciting such immunological responses (*66*). Immunocompromised patients with several co-morbidities and other complexities tend to develop enriching bacteriological infections which can be lethal (*63*).

Nowadays, advanced diagnostic techniques involve ultrasonography (USG), computerised tomographic (CT) scan or by hepatobiliary iminodiacetic acid (HIDA) test, which can easily diagnose and detect any abnormalities in the biliary duct. Primarily the treatment stratagem involves surgical procedures like cholecystectomy *i.e*. an invasive surgical protocol

to remove the malfunctioning gallbladder with the gallstone (*63*). In certain minor cases, endoscopic retrograde cholangiopancreatography (ERCP) can be used to eliminate the gall stones obstructing the cystic duct. Administration of antibiotics and painkillers are subject to variability, depending on the degree of microbial infection or inflammatory pain (*67*).

2.9. Grave's disease (GD)

The thyroid gland plays a significant role in regulating our metabolic rates *i.e*. synchronizing the rate at which our body utilizes the energy. However, during hypersecretion of thyroid hormone (thyroxine), it can cause an autoimmune disorder termed as GD or hyperthyroidism (*68*).

As an autoimmune disorder, the immune system tries to attack thyroid gland for the over or hypo-secretion of thyroxine (*69*). The primary immunological cause for the hypersecretion of thyroid glands is the attachment of an immunoglobulin molecule produced as an autoimmune response, termed as thyroid-stimulating immunoglobulin (TSI) which basically substitutes the natural thyroid stimulating hormone (TSH) (*70*). A person with pre-compromised immunity or undergoing an existing autoimmune disease like vitiligo, rheumatoid arthritis, lupus or celiac disease have a greater chance of developing this condition (*71*).

According to scientific reports and research conducted worldwide, the gut microflora population elicits promising insights on diagnosis, patho-physiology and treatment of Grave's disease. Following next generation sequencing (NGS) and characterization, varied gastrointestinal microflora populations were reported from the faecal samples of patients and healthy controls. A peculiar microfloral trend was observed during pathological diagnosis and research, where species of *Prevotella, Bacilli*, Lactobacillales, *Veillonella* and *Megamonas* outnumbered in samples of an infected individual, whereas species of *Alistipes*, *Ruminococcus* and Rikenellaceae were found to decline in the infected sample when contrasted to a healthy control sample (*72*). This particular scientific finding furnished a preliminary insight that the noticeable alterations in the gut microflora population between healthy controls and infected patients had certain promising links with the occurrence and progression of the disease (*72*).

Antibiotics play an imperative role in decreasing a bacteriological infection but instances of using it can affect the gut microflora and remarkably which can alter the levels of blood pressure, progressing towards the development of hypertension, an essential characteristic of GD. It was studied and observed that bacteria belonging to *Bacteroidetes* and *Firmicutes* have an interrelation with elevated blood pressure levels in the body, which directly relates to hypertension (*73*).

As reported by dry and wet lab research, *Lactobacillus* and *Bifidobacterium* stimulate the production of high levels of cross-reactive immunogenic responses which escalates the autoimmune condition elicited by patients (*74*).

The levels of TSH in the blood, preferably higher, are an indicative clinical marker for an efficiently-functioning thyroid gland. These healthy levels can be easily measured in the bloodstream by performing simple blood tests as a diagnostic measure for adequate prior treatment. Alternatively, USG or CT scans can be used to visualise the abnormalities in the thyroid gland, such as certain protrusions or enlargement. Treatment approaches encompasses clinical methods to reduce the hypersecretion of the thyroid gland, which can be achieved by employing anti-thyroid drugs or radioactive iodine. In certain grave conditions, the thyroid gland might have to be surgically removed or destroyed by using radioactive iodine to reduce the ill-effects of hypersecretion of the gland (*75*).

2.10. Tropical sprue (TS)

TS, a rare digestive disease of unknown etiology, mainly affects the small intestine of tribes living in tropical or temperate regions such as the Caribbean Islands, India, South Africa, and Southeast Asia. TS are characterized by the intestinal malabsorption of nutrients and minerals, besides persistent diarrheal conditions in the body (*76*).

Clinical findings and pathophysiological studies confirm the correlation between gastrointestinal microflora and TS infections (*77*). Pathogenesis of TS is peculiar, postulating that the mucosal injury of the jejunum and ileum leads to bacterial overgrowth in the small intestine (*78*). Subsequently, folate and vitamin B12 deficiencies cause the mucosal lining to become more susceptible to damage. Increased secretions of enterotoxins by the gastrointestinal bacterial population (*Klebsiella*, *E coli* and *Enterobacter*) mediate the infection (*79,80*). Bacterial colonization elicits unregulated production of a gut hormone (enteroglucagon) and motilin peptide by endocrinocytes of the proximal small bowel (*81*).

The clinical findings of TS show dyspepsia, anorexia, weight loss and multiple nutritional deficiencies that arise from dysfunctional fat digestion at the intestinal level. Insufficient pancreatic lipase, defective mucosal membrane and impaired intestinal transport system causes disruptions in the bacterial flora, and influences the development of gastrointestinal infections in TS (*82*).

Absorption and digestion of long chains of fatty acids is a principal function of the small intestine by bile and pancreatic juice. Digestive juice breaks the fats into simpler compounds and absorbs nutrients in the duodenum. Triacylglycerides (TAGs) upon emulsification and hydrolysis forms L-glycerol and free fatty acids (FFAs). Later, enterocytes utilize these FFAs for the biosynthesis of fats (*83*). Thus, it is apparent

that the gut microbiota is affected by a diverse range of dietary TAGs, and could play a role in the pathogenesis of TS (*84*).

The combined therapy of antibiotics (tetracycline or ampicillin) along with folic acid and vitamin B12 supplementation improves the symptoms of the infection, and reduces the bacterial population. Anti-diarrheal drugs may control the severity of diarrhea, but D-xylose malabsorption and water and electrolyte secretory defects persist, despite prolonged therapy owing to the damaged mucosal membrane (*80*).

3. Personalized medicine (PM) in rare diseases

Human genome is very unique; it varies from person to person, and people show differential responses to different treatments. Personalized medicine (PM) streamlines medication based on a patient's genetic make-up, by focusing on molecular profiling, medical imaging, clinical statistics and data (*85*). The Father of the PM is Archibald E. Garrod (1857-1936), who described the ubiquity of the individual variations (*86*). PM is also termed ‘precision medicine' as it customizes the diagnostics, drug/or products based on the patient's response to disease and its severity, in order to offer the optimal therapeutics. With the advent of technology, the dawn of precision medicine has revolutionized the medical sector. Scientific advancement has paved the way to new recognition of the treatment and management of complications in diseases at personal levels. PM is thus a welcome deviation from "one-size-fits-for-all" medical approach with different applications such as in oncology, cardiology, autoimmune disorders, nutrition and rare diseases (*87,88*).

According to a recent report by the World Health Organization (WHO), there are about 7,000 rare diseases that affect 7% of the total population with no appropriate treatments for approximately 95% of such rare diseases. Patients with undiagnosed and unknown etiology of the diseases often are overlooked by an uncertain and unpredictable journey, referred to as a "diagnostic odyssey" (*89*). PM is a medical tool to end this diagnostic odyssey by giving way to new therapeutics.

Mutations in genotypic or phenotypic traits influence the severity and reactivity of the diseases to a particular potential therapy. The cellular response and the behavior of particular mutations to various therapeutic options vary in great lengths among different individuals when contributing to certain drug responses, as well as on the patho-physiology of the disease they are struggling with. The concepts and definitions of PM are based on the patient's genomics, epigenomics, proteomics, metabolomics, lipidomics and other data relevant to lifestyle. Rarity of the diseases creates ultimatums when citing fundings, affordability of treatments and diagnostics, computational analysis and clinical trials. Therefore, the approach of precision medicine is an evolution gateway in healthcare and disease management. Perspective of precision medicine is to intercept disease prevention and treatment as per the variability of genes, environment and lifestyle of an affected individual (*90*).

Precision therapeutics aims to escalate the efficacy and diminish the toxicity of the drug in healthcare. PM is not only an individualized drug, but a medicine that incorporates both standardization and individualization (*91*). Thus, harnessing PM in the treatment of rare disease could prove effective, and employ alternative budding therapies and diagnostics for rare diseases in the coming few years. However, there are many challenges in the future that we might have to deal with, such as lack of therapeutic efficacy for various ailments, high cost of pharmacological diagnosis and its clinical trials, wide comprehension of genetic diversity, broadening the medical research projects and better implementation of computational analysis. Despite the use of complex technologies and large-scale whole-genome sequencing (WGS), it is still difficult to understand the adaptive nature of the biological system regarding changes or responses to drugs (*92*). Thus, personalized therapeutics need implementation at a holistic level to overcome many of these barriers in the development of a new medical era.

4. Conclusion

The development and progression of a disease depends upon multiple facets of phenotypic, genetic and epigenetic factors which are designated and demarcated by distinct geographical regions. Deriving a concrete precision and clarity about a particular ailment can be ambiguous, and can depend upon manifold surveys conducted on interconnected flora, fauna, humans, microbes and their subpopulations associated with it. The dearth of concurrent facts and scientific research in a particular domain of disease biology might affect its diagnosis, therapeutic approaches and future research.

Rare diseases torment millions of lives belonging to all age groups globally, which could prove life-threatening. Specific rare diseases differ in multi-facets with distressing shifts. Most of these diseases arise due to genetic mutations and are inherited, which goes on undiagnosed for several years or maybe generations. A number of rare diseases reported till date varies by a margin and newly identified illnesses are reported weekly. In 2017, National Policy for Treatment of Rare Diseases, India, estimated that there were around 5,000 to 8,000 rare diseases, with 450 of these recorded in India, affecting 72 million - 96 million Indians, with the majority being children.

Rare diseases belong to such a field in biology which has lack of concurrent evidence on common medical symptoms, disease development, genetic history, pathogenesis, and transmission routes. Rare diseases have been customarily interpreted as the set of ailments

which only affects a fewer section of the population, and if the clinical manifestations are not dealt with adequate medical attention, then it can be lethal. The prime complication and setbacks faced by the medical and clinical research fraternity is the ardousity in identifying and comprehending the odd patho-physiological manifestations for the rare pathologies. To some extent, recent advancements in the sectors of clinical research, biosciences and medicine have paved a path in smooth diagnosis, prognosis and treatment for the patients, but still we require full-proof solutions to the unsolved clinical challenges raised since time immemorial for the treatment of rare diseases.

Standing today, the predominant challenge lies in adequate identification of the rare diseases and fabricating a specific diagnostic and therapeutic approach to mitigate the shortcomings, but this identification is shrouded with an array of coinciding definitions, theories, concepts and metadata which influence the disease identification. Corroborating such a plethora of juxtaposed concepts with computational aids to segregate the subtypes of rare diseases based on genetic, pathogenic and epigenetic factors is something that has been done and is still under process. Worldwide researches have been conducted to clinically computerise and conglomerate such meta-information to aid in developing a holistic and in-depth knowledge about the rare diseases.

The human body is a compatible host for the microbiota that it inhabits; the human microbiome plays an imperative role in interconnecting the missing links between progression of an ailment and our body. It is scientifically proven that human microbiota is of prime importance when it impacts our metabolism, physiological behaviour, disease responses, immunological manifestations and other physio-chemical manifolds of human anatomy. Predominantly our body houses a substantially colossal load of microbes in the gastrointestinal and urinary tracts, whose imbalance in our body can lead to several irritable discomforts and to a certain extent, it escalates into development of a clinical ailment requiring immediate medical attention. The diversity, utility and complexity of the microbiota found in a human being is a subject of debate, the factors which can determine and characterize the nature of microbiome population remain deluded and varies from person to person, lifestyle, genetic or epigenetic conditions, and more often intervene in all life processes.

Advancements in science and technology in recent years have significantly unlocked the heap of data, yielding insights into the role of the human gut microbiome in existing models of rare diseases and clinical assortments. Understanding the nature of gut microbiota, and their dynamic interplay with host and other agents have enabled scientists and researchers to devise new diagnostic techniques and interventional strategies. Interestingly, at least 5-10% rare diseases are linked with human gut microbiota. Gut complications of secluded populace are often exacerbated by alterations in gut microbiome population, leading to occurrence of the disease. The gut microbiota is a pivotal agent of body homeostasis, barrier function, and development of immunity, nutritional responses and metabolism processes in humans. The impact of commensal microorganisms is not limited to the gastrointestinal tract, but rather encompasses all organs of the human body. With the abundance of metagenomic data and increasing research on gut microbes, one can precisely claim the association between commensal bacterium and pathogenesis of the diseases. For example, a myriad of investigations have reported changes in the gut microbiota not only during obesity, diabetes, kidney and liver problems but also cancer, and even some rare neurodegenerative diseases. In addition to regulation of infection and commensal spread, microbiome-mediated-immunity are implicated in a variety of ‘non-communicable' gastrointestinal diseases, as well as extra-intestinal disorders. Emerging evidence establishes that the microbiomes of extra-intestinal mucosal surfaces provide niche-specific functions that aid in the pathogenesis of certain underlying disorders.

The aim of this review is to summarize the clinical findings and research analysis by introducing the reader to emerging challenges, potential trends and current directions in microbiome research. It is challenging to state a correlation between a local microbe and disease before showing the implication of bacterium on the onset of the particular disease. For numerous rare diseases, basic knowledge such as the etiology of the disease, patho-physiology and epidemiological data hinders the prevention and treatment of the disease. Furthermore, the association between the human microbiota with the host is far more complex than observed with tremendous data till date. Hence, emendation of experimental designs and regular diagnosis to study the disease from its progression to latent stages is the call of the hour.

The idea behind this discussion is to delineate the effective therapeutics to overcome the limitations of existing treatments and identify the budding interventional approaches. Human microbiome research is a rapidly accelerating field with the preliminary studies increasing exponentially, and more discoveries continue to be made in the frontiers on the role of gut microbiome in human wellness. With the dawn of this new era, human microbiome research is becoming a more transdisciplinary field with a colossal range of applications and strategies for understanding it. Anticipation of mathematical and computational tools to understand the microbiome has reformed the status of diagnosis, prognosis, prophylaxis and prevention of human diseases in ongoing research. In-order to fill the current vents, translation and transplantation of experimental evidence through consistent use of pre/or probiotic matrix to protect our gut from pathogens and versatile methods can be done to assess changes in

health outcomes. As researchers learn more about the human microbiome and develop more-robust techniques for probing to leverage our insights, a plethora of new diagnostic tools and interventional methods that could revolutionize medicine and treatment of rare diseases would come to the limelight.

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