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Advanced Medical Personalized Treatment for Autoimmune Disorders: A review Article for in-depth Insight into Personalized Autoimmune Medicine

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Abstract:

Autoimmune disorders are complex conditions that result from a combination of genetic and environmental causes and currently have no recognized therapy. Various therapeutic strategies may be used in various illnesses to promote remission or, at the very least, alleviate the symptoms. For customized therapy to be implemented, it is necessary to identify groups of individuals who are generally similar and share pathogenic signaling pathways. Therefore, research about autoimmune disorders mainly focuses on identifying new biomarkers, uncovering novel targets for therapy and agents, and understanding the processes involved in developing various disorders. We are just at the nascent phase of implementing tailored therapy for autoimmune illnesses. Hence, this research delved into the examination of several autoimmune illnesses and the impact of personalized therapy on their progression.

Keywords: Genomic analysis, Autoimmune disorders, Personalized medicine

Introduction

Millions of individuals use prescription drugs every day that do not benefit them, even if they seem to (1). Additionally, it is conceivable that such medications cause dangerous new illnesses to arise, complicating the original illness (2). Patients suffering from autoimmune illnesses experience these catastrophes to a greater extent (1, 2). Indeed, there is no general agreement about the course of therapy due to the variability of these disorders (3). More than 80 autoimmune diseases have no known cure, yet with an effective treatment plan, the symptoms may be effectively controlled (4). The majority of people with autoimmune illnesses are treated with the same restricted immunosuppressants, even though one medication does not work for everyone. Since the development of many biological medications, such as monoclonal antibodies, which target specific signaling pathways, most patients take these medications without awareness (4). Very few trustworthy indicators of treatment response that may be considered prior to therapy for autoimmune illnesses have been found (3, 4). This has produced inconsistent outcomes on the effectiveness of medications. Among the examples are tumor necrosis factor-α (TNF-α) inhibitors, which have

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been linked to insufficient response or intolerance in some autoimmune disease patients (5).

Furthermore, it has been shown that anti-TNF medications may cause psoriatic lesions in some inflammatory bowel disorder individuals (6). Rituximab, an anti-CD20 monoclonal antibody, is another frequently prescribed biological medication. It treats several autoimmune diseases, including pemphigus, RA, and systemic lupus erythematosus (SLE) (7). While almost all individuals see a decrease in B cells after using rituximab, not all benefit from the medication (8). Furthermore, after receiving rituximab, individuals with pemphigus have experienced a worsening of their condition (9). These inconsistent outcomes in individuals with the same illness classification might support the variety of autoimmune disorders, which most likely have distinct regulating signaling pathways (10). Serum autoantibodies, pathology findings, and specific clinical symptoms are employed to classify autoimmune disorders into several forms. However, that is only part of the story (8-10). Individuals who fit the exact parameters according to the methods above may not necessarily belong to the same variation. Distinct signaling pathways with the same effect may cause the illness (9, 10). Understandably, different individuals react differently to therapy in this situation. As a result, we should update our criteria to make autoimmune disorder variations more precise.

Personalized treatment for distinct autoimmune disorders

Autoimmune disorders occur when the body's immune system reacts to self-antigens due to tissue injury, malfunction, or imbalance (11). It is influenced by several variables, with host genes and the environment playing a crucial role. The immune system may target the whole body, specific systems, or specific organs based on a combination of hereditary variables, environmental influences, and self-antigens presented for identification (12).

The following autoimmune disorders' precision medications are covered in detail below (Figure 1):

1. Sjogren Syndrome
2. Myasthenia Gravis
3. Type 1 Diabetes
4. Rheumatoid Arthritis
5. Multiple Sclerosis
6. Lupus Erythematosus
7. Pernicious Anemia

Genomic analysis of multiple sclerosis

Multiple sclerosis is an inflammation and autoimmune condition that targets the myelin in the brain and spinal cord (13). It may impact individuals of all ages and lead to neurological impairment if not adequately treated. Over 200 loci have been recognized as a separate factor in the development of multiple sclerosis (14). Multiple sclerosis often presents in individuals aged 30 to 50 and is more prevalent in females than men (15). To comprehend the development of multiple sclerosis, it is necessary to analyze it using a multifactorial approach that considers the interplay of genetic, epigenetic, infectious, nutritional, climatic, and other environmental factors, along with sunlight exposure and smoking. The interaction of these elements results in self-intolerance and a decrease in immunological balance in the brain and spinal cord (15, 16). Peripheral mononuclear cells enter the brain and spinal cord organs, resulting in myelin breakdown and gliosis, which may cause neurological impairment. The individual diagnosed with multiple sclerosis has been treated using two main approaches based on the autoimmune hypothesis of the disease's development (17). The previous approach involves the administration of potent global immunosuppressive drugs. Simultaneously, the latter refers to using more specialized agents to pinpoint particular components of the body's immune response (18).

Researchers have investigated the impact of common genetic variations on multiple sclerosis, specifically focusing on various HLA alleles (19). These variants were discovered to be equally prevalent in both the control and the sample groups. Additionally, the statistical evaluation revealed that the odds ratio approaches one as the sample size increases (19). Biomarkers play a crucial role in the genetic evaluation of Multiple Sclerosis by demonstrating various features of the disease's diversity. They assist in diagnosing, categorizing, and predicting the progression of diseases, as well as in identifying effective treatments and creating tailored treatment plans based on anticipated responses (20). Since 2016, MRI has been the most suitable tool for diagnosing MS (21). The recommended field strength for brain MRI is 1.5 T. However, 3.0 T is considered superior (21). Recent research suggests that a 7 T field strength may identify central veins in brain lesions of MS patients (21, 22). However, this can also be achieved with T2-weighted sequences at 3 T, aiding in separating from microangiopathic lesions. While MRI is often used to diagnose MS, its true challenge lies in distinguishing MS from other illnesses such as neuromyelitis optical spectrum diseases (NMOSD), which similarly present with brief spinal cord lesions in the beginning (21, 22). It is advised to use T2-weighted and contrast-enhanced T1-weighted brain MRI for monitoring illness development, but an MRI of the spinal cord is not indicated. Aside from MRI biomarkers, bodily fluid biomarkers may indicate various stages of MS and

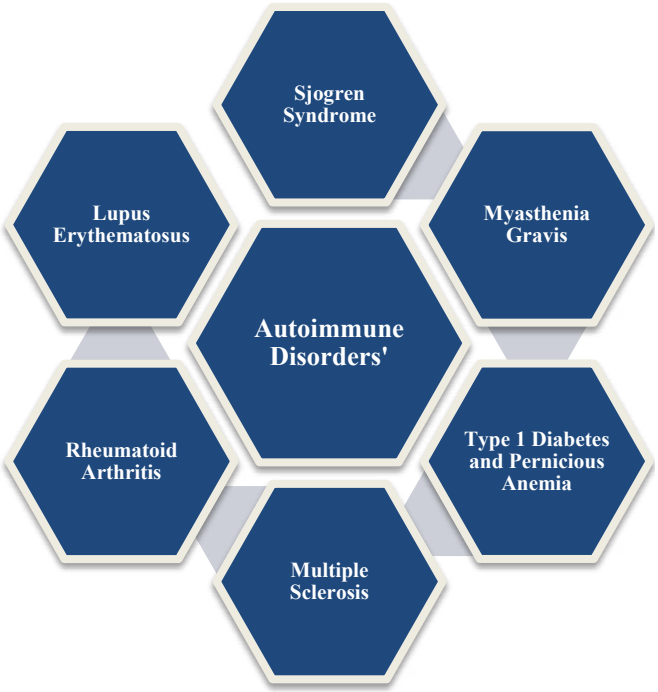

Fig1. Autoimmune disorders investigated in this study.

distinguish each stage from related diseases (23).

Body fluid indicators may be categorized into three primary groups: those indicating the initial stage of MS, those linked to the progression of the illness, and those related to the reaction to therapy (24). A low vitamin D concentration in the cerebrospinal fluid indicates the early stage of multiple sclerosis (25). A high level of Astrocyte-derived chitinase 3-like 1 (CHI3L1) in the cerebrospinal fluid (CSF) is a significant independent risk factor associated with the advancement of disability, as shown by multivariate Cox regression models (26). A proteomic method was used to establish that CHI3L1 is the strongest predictor of a transition to multiple sclerosis in individuals with clinically isolated syndrome (CIS). A multivariable analysis identified the CSF CHI3L1 level, MRI results, and age as the most significant predictors of multiple sclerosis risk. Neurofilaments (NF-L) have been suggested as a biomarker in the first stage of MS (27).

High-mobility group box protein 1, a transcriptional regulator, aids in distinguishing individuals with relapse-onset multiple sclerosis from those with primary progressive multiple sclerosis (28). Proteomic research indicates that distinguishing between multiple sclerosis patients with aggressive and benign disease courses may be achieved by analyzing two isoforms of vitamin D-binding protein and apolipoprotein E (29). Secretogranin-1, a calcium-binding protein, is reduced in the cerebrospinal fluid with the progression of the illness compared to the initial stages of multiple sclerosis (30). Stable multiple sclerosis patients have elevated B cell activating factor levels in their plasma samples compared to relapsing individuals (31). SLC9A9 is a biomarker linked to the lack of response to IFN beta (32). NLRP3 inflammasome upregulation is a biomarker for lack of response to IFN beta therapy (32). The biomarkers for predicting the response to glatiramer acetate include RGC-32, FasL, and IL-21 (33). Increased mRNA levels of RGC-32 and FasL and decreased expression of IL-21 in peripheral blood cells of responders compared to non-responders serve as the foundation for using these biomarkers (29-33).

Genetic analysis of myasthenia gravis

Myasthenia gravis (MG) is a form of autoimmune disease managed with long-term immunosuppressive therapy because of the effects of autoantibodies targeting the complex structure underlying the neuromuscular junction (34). The variability in patients' reactions to therapy and adverse effects justifies the need to identify biological indicators for predicting treatment success for every individual (35). Anti-AChR antibodies are a valuable biomarker for diagnosing MG. However, it cannot assess illness severity since no direct association was shown between MG severity and levels of anti-AChR antibodies (36). MiR-323b-3p, MiR−409-3p, MiR−485-3p, MiR−181d-5p, and MiR−340-3p have been identified as potential biomarkers for predicting and indicating immunosuppressive medication sensitivity in individuals with myasthenia gravis (37).

miRNAs may be analyzed in the blood as a robust

Table 1. Genetic factors involved in myasthenia gravis from the perspective of personalized medicine

Row	Genetic factor of myasthenia gravis	Role
1	miR-323b-3p	Decreased in non-responsive individuals
2	miR−409-3p	Decreased in non-responsive individuals
3	miR−485-3p	Decreased in non-responsive individuals
4	miRNA-181d-5p	Increased in non-responsive individuals
5	miR−340-3p	Increased in non-responsive individuals
6	*SPP1 gene*	Increased/ decreased non-responsive group

biomarker for therapy response (38). Patients who do not react as anticipated can be directed to other therapies, enhancing cost-effectiveness. MiR-323b-3p, MiR−409-3p, and MiR−485-3p were decreased in non-responsive individuals, but miRNA-181d-5p and MiR−340-3p were increased in non-responsive individuals (38, 39). An important link has been found between a patient's reaction to azathioprine and two specific genetic variations: the TPMT3E haplotype in the thiopurine S-methyltransferase and a haplotype in the ATP-binding cassette sub-family C member six transporter (40). MG individuals who did not respond to glucocorticoid medication were discovered to have a genetic variation in the *SPP1* gene expressing osteopontin, linking them to the non-responsive group (Table 1) (38-40).

Evaluating the genome in cases of pernicious anemia

Pernicious anemia (PA) is an inflammatory illness caused by a chronic Helicobacter pylori disease and atrophic body gastritis (ABG) (41). The ongoing disease is being progressively eliminated by an autoimmune response that permanently depletes the stomach mucosa (42). Vitamin B12 insufficiency has also been linked to the cause. Hence, the clinician's objective in treating severe anemia is to prevent anemic symptoms, address consequences, including nerve and heart muscle damage, and pinpoint the exact cause using precision medicine (43). The National Heart, Lung, and Blood Institute (NHLBI) is doing fundamental and clinical research to integrate personalized medicine and enhance the medical management of the illness (44).

Genetic analysis of rheumatoid arthritis

Rheumatoid arthritis (RA) is a varied condition that may manifest as either mild, self-limiting arthritis or rapid progressive joint deterioration (45 ,46). An intricate interplay between human genetic composition and environmental factors initiates the phenomenon (47). Environmental factors and genetics are insufficient to explain the diverse clinical characteristics of the illness fully. The condition is also defined by synovial hyperplasia and joint damage, potentially resulting in joint deformity (48).

The treatment of RA focuses on controlling inflammation. Early and effective medication significantly reduces the risk of joint damage, death, and disability (49). In 2017, significant research has concentrated on identifying biomarkers that might predict a patient's response specifically to Methotrexate (MTX), the first non-biologic treatment drug given (50). Approximately 30% of patients do not respond to TNF inhibitors (TNFi), but they are still often used as the first option among biological treatment medicines (51). The gene *SLC19A1* from the solute carrier family 19 member 1 shows the most reliable and significant evidence. It is a transport carrier that facilitates the entry of MTX into the cell (52).

Anti-CCP antibodies are a genetic marker linked to an unfavorable prognosis regarding disease severity and joint destruction. HLA-DRB1 alleles encoding common epitopes are also a signal for disease severity in RA (53).

Genomic evaluation of Sjogren's syndrome

Sjögren's syndrome (SS) is a kind of B cell hypersensitivity characterized by the production of too many autoantibodies and a high likelihood of developing B cell non-Hodgkin lymphoma (NHL) (54). Approximately 5% of primary Sjögren's syndrome individuals are susceptible to developing lymphoma (55). It is crucial to have a particular biomarker to identify patients early to monitor and detect them early and choose the proper treatment (54, 55). Diagnostic biomarkers aid in diagnosis, whereas predictive biomarkers provide further insights for clinical decision-making. Cytopenias are a recognized predictive indicator for the onset of lymphoma (56). Many suggested biomarkers for evaluating SS still need validation via more

comprehensive investigations before being used in clinical practice (57).

Genomic analysis of systemic lupus erythematosus

SLE presents many signs and symptoms that differ across individuals and affect several organs, including the joints, skin, kidneys, lung capacity, and CNS (58). It is a persistent inflammatory, immunological condition. A link has been identified between Systemic Lupus Erythematosus (SLE) and particular human leukocyte antigen (HLA) haplotypes, including HLA-DR3, DR9, DR15, and DQA1*0101 (59). A considerable correlation has been discovered between vitamin D levels in the blood and the genomic binding domains of vitamin D receptors of systemic lupus erythematosus (60).

Genomic analysis of type 1 diabetes

Type 1 diabetes (T1D) occurs due to the death of beta cells by the immune system, causing a decrease in insulin production and leading to high blood sugar levels (hyperglycemia) (61). The impact of precision medicine on type 1 diabetes is not well established (62). Patients with type 1 diabetes exhibit varying severity based on differences in their pancreatic autoantibody profile and the pace of beta cell destruction (62, 63).

Genetic research in precision medicine has identified over 50 genetic markers, particularly in the HLA area, that impact the propensity to T1D (64). Diagnostic indicators for T1D include a mix of glucose, C-peptide, glycated compounds, and autoantibodies. However, these molecules often indicate the advanced phase of the illness (65).

Recent advancements in genomic research include administering islet autoantigens or peptides to individuals at risk of Type 1 Diabetes, showing potential effects on immune modulation of islet autoimmunity (66). The issues persist in terms of dosing frequency, dose, method of administration, and the use of adjuvants (Figure 2).

Future outlook

Researchers should thoroughly study the systemic monitoring of variant genes such as *TNFRSF1A*, which is associated with the risk of multiple sclerosis. This gene might provide crucial insights into the cause of multiple sclerosis and novel approaches to therapy (67).

Myasthenia gravis-related genetic regions may contribute to the development of immune diseases by enhancing immune response, inhibiting immune suppression mechanisms, and modifying the process that distinguishes between self and non-self-molecular structures via immune tolerance. Therefore, studying single nucleotide polymorphisms (SNPs) linked to myasthenia gravis in the broader population can enhance the accuracy of diagnosis, treatment, and prognosis (68).

Genome editing techniques have successfully treated sickle cell disease and β-thalassemia. This approach might cure pernicious anemia by studying the gene responsible for the mitochondrial transportation of vitamin B12 (69).

Studies on rheumatoid arthritis should prioritize discovering additional genes linked to the condition

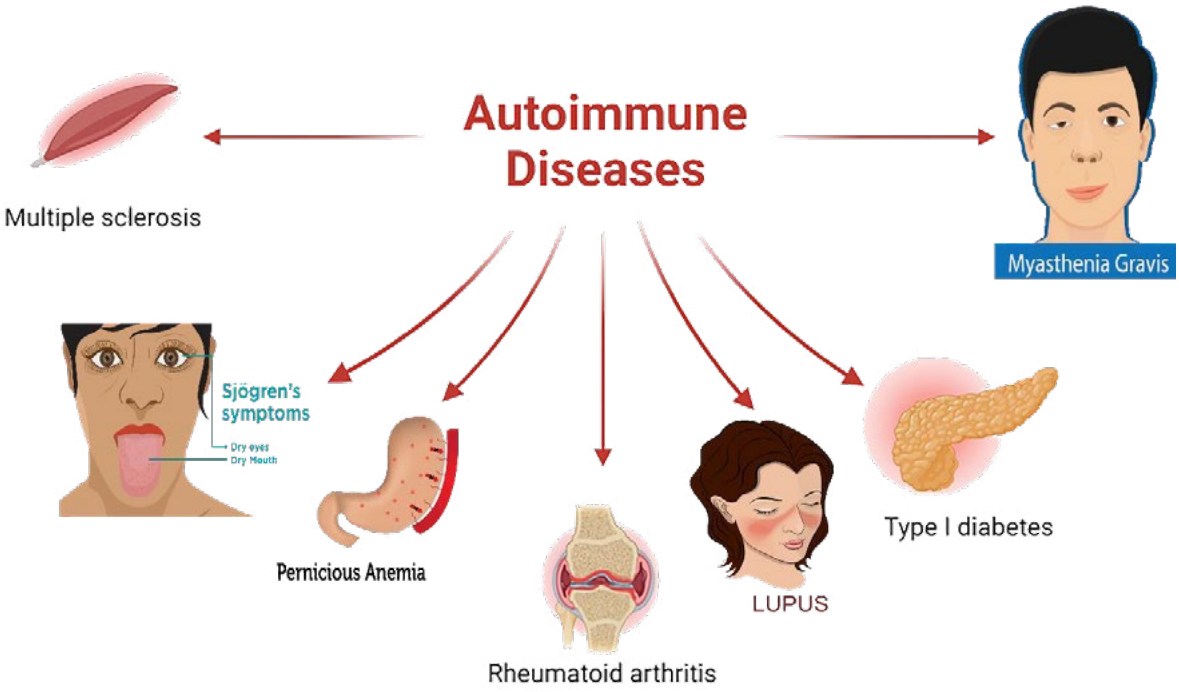

Fig2. Autoimmune diseases and their symptoms

and their corresponding impacts. Transcriptomic and epigenomic approaches should be utilized to identify indicators for reaction to treatment and pathways associated with therapy. Integrating genetic, clinical, and environmental information is essential for developing personalized medicine in treating rheumatoid arthritis (70).

Novel therapeutics for Sjogren syndrome might be discovered by identifying genetic risk factors, such as the significant interferon signaling pathway, including *IRF5* and *STAT4* genes (71).

The future therapy of systemic lupus erythematosus involves preventing the disorder by analyzing genetic profiles and creating novel biomarkers for immunological activation and modification (72).

Studying genes and pathways related to type 1 diabetes may uncover the timely involvement of the death of β-cells and the development of clinical illness by the innate and adaptive immune system. The Type 1 Diabetes Genetics Collaboration (T1DGC) globally provides materials that may assist in diagnosing, intervening, and monitoring the effects of treating type 1 diabetes (73).

In the age of 'Big Health Data,' using various algorithms for machine learning and deep learning is crucial for improving the diagnosis, prognosis, and therapy monitoring of autoimmune disorders by identifying patterns and clusters among distinct disease groups. This will facilitate the discovery of more relevant indicators and streamline the translation of biomarker research to clinical practice. The advancement of personalized healthcare in autoimmune illnesses relies on developing next-generation sequencing technology, which aims to provide a comprehensive, cost-effective analysis of the exome or transcriptome (74,75).

Conclusions

Genomics information is crucial for precision healthcare since it helps explain individual variability and development. However, the practical use of chromosomal information in clinical settings must be enhanced to address issues identified by researchers, such as the disparity between the molecular and medical data forms poses a challenge due to the vast amount of genomic information, making it difficult to handle clinical data in practice without further manipulation. Genomic and observational information utilized in clinical contexts varies due to the vast amount of data in genomic operations, making it distinct from data in clinical systems. Challenges arise when aligning genomic and clinical information for medical interpretation, particularly in specific sequencing, where information is often processed before medical analysis. There needs to be more global validation for the biomarkers being used, highlighting the need for international cooperation to evaluate the existing biomarkers. Conquering these obstacles will provide further possibilities for using genetic data in therapeutic settings.

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Authors' Contribution

Zahra Azami and Mahnaz Piri-Gharaghie were involved in the conceptualization, design, and support of the study. All authors read and confirmed the final manuscript.

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Competing interests

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The Bright Future of Cancer Immunotherapy: DNA Vaccines on the Front Lines Of Lung Cancer

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Abstract:

The advancements in immuno-oncology have created a new and unparalleled opportunity for the advancement of vaccination methods. Therapeutic DNA cancer vaccines are now regarded as an excellent way to stimulate the immune system in its fight against cancer. Lung cancer is well recognized as one of the primary factors leading to patient mortality worldwide. Despite significant advancements in innovative tumor immunotherapy, including the use of immune checkpoint inhibitors or oncolytic viruses, the overall 5-year survival rate of individuals with lung malignancies remains very low. Therefore, there is an urgent need to find efficacious vaccinations for the treatment of lung cancer. DNA vaccines are now regarded as a viable immunotherapy approach to stimulate the host immune system against lung cancer. First, we discuss antigen repertoire selection and delivery strategies to improve cancer vaccines. We summarize the recent advances in DNA vaccines that target lung cancer antigens and highlight their implications for disease treatment.

Keywords: Immunotherapy, DNA vaccine, Cancer vaccine, Vaccine development

Introduction

It is essential to conquer aggressive tumors, which are the most common reason for death, to raise worldwide longevity. In 2020, there were an estimated 19.3 million new cases of cancer and nearly 10 million deaths attributable to malignancy. This emphasizes the urgent nature of this crisis (1). Traditional cancer treatments, such as as surgery, radiation therapy, and chemotherapy, can be highly hazardous and have limited effectiveness (2). This highlights the need for the development of more effective methods for treating cancer. Recent research seems to indicate a strong correlation between cancer progression and a phenomenon known as "cancer immunoediting" (3). The changing interaction suggests that the immune system may eliminate newly formed cancer cells by identifying altered oncogenic genes or promoting an immunosuppressive condition that supports tumor growth. Thus, the destiny of cancerous cells is dictated by an imbalance inside the immune system (4).

Tumor vaccination, sometimes referred to as cancer immunization or cancer immunotherapy, is a therapeutic approach aimed at activating the immune system to recognize and combat cancerous cells. The primary objective is to impede the growth, recurrence, or dissemination of tumors while enhancing the immune system's capacity to identify and eliminate malignant cells (5). Cancer vaccines work by eliciting an immune response that selectively addresses tumor-associated antigens (TAAs), which are molecules generated by cancerous cells. The

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activation of several immune cells, including T cells and B cells, triggers this immunological response, which ultimately destroys cancerous cells (6). Cancer vaccines have two main uses: preventative (to protect at-risk populations) and therapeutic (to treat patients who have already received a cancer diagnosis). Cancer vaccines have great potential as a means of preventing and treating the disease by using the immune system (7). Cancer vaccines may be categorized into four primary types: tumor-cell-based vaccinations, peptide or protein vaccines, viral-vector-based vaccines, and nucleic-acid-based vaccines (DNA or RNA vaccines) (7). Between these powerful vaccinations, DNA vaccines show great promise as immune-therapeutics for treating many types of malignancies due to their numerous benefits. DNA vaccines may stimulate both innate immune responses and effectively generate both the humoral and cell-based immunological responses of the host. Furthermore, a potent DNA vaccine may include many genes that encode tumor-specific antigens, hence enhancing immune responses against tumor antigens that play a role in tumor genesis, development, and migration (8). For instance, DNA vaccines have undergone thorough examination to create innovative approaches to combat melanoma, prostate cancer, breast cancer, and lung cancer. In addition, DNA vaccines are more convenient to produce and provide superior durability and safety in comparison to conventional vaccinations (9). Despite numerous attempts to create cancer vaccines, the therapeutic treatments including these vaccines remain relatively ineffective due to the considerable variability of tumor antigens and the limited immune system reactions they elicit. This study offers a thorough and detailed examination of the existing cancer vaccines. Initially, we outline techniques for choosing antigen repertoires and delivery technologies to enhance the creation of cancer vaccines. We provide a concise overview of the latest significant developments in the development of DNA vaccines that specifically target antigens associated with lung cancer, and discuss their importance for the management of this disease.

Cancer vaccine strategies

Cancer vaccines use many strategies to activate the body's immunity and elicit a potent anti-tumor reaction. A popular strategy includes using dendritic cells (DCs), which are very effective antigen-presenting cells (APCs). DCs may be obtained either from the blood of a person or produced in a laboratory, using one approach. Subsequently, they undergo maturation and activation by the use of immune-stimulating substances or tumor antigens (10). Following the introduction of tumor-specific antigens (TSAs) produced from tumor cells or genetic material, the loaded dendritic cells (DCs) are then delivered back to a person. The DCs move to lymphoid organs, where they engage in interactions with several types of immune cells, including T cells, B cells, and natural killer (NK) cells. The DCs display the tumor antigens to CD4+ helper T cells and CD8+ cytotoxic T lymphocytes (CTLs), resulting in their stimulation (11). Excited T cells provide stimulatory signals to other immune system cells, augmenting the body's defense against cancerous cells. CTLs particularly identify and attack cancer cells that display the tumor antigens, leading to their eradication. Furthermore, this vaccination seeks to elicit a memory answer, enabling a more efficient immune response when encountering cancer cells again in the future (11).

Peptide-based subunit vaccines, which consist of chemical and biosynthetic formulations of anticipated or confirmed individual tumor antigens, elicit a strong immune reaction targeting the specific tumor antigen location (12). A combination of peptide-based subunit vaccination and adjuvants may effectively stimulate the production of antibodies by the immune system, making it useful for both preventing and treating viral infectious illnesses. The vaccinations for liver and cervical malignancies, HBV and HPV respectively, were predominantly composed of peptide-based subunit vaccines. In the past few years, virus-like particles (VLP)-based subunit vaccines, which can stimulate cellular immunity, demonstrated significant anti-tumor efficacy (13).

Another option is using whole-cell preparations obtained from cancerous cells. Tumor cells are obtained either from the individual's tumor or from existing cell lines associated with cancer (14). These cells are rendered inactive or genetically altered to diminish their capacity to proliferate and induce illness. Upon reintroduction into the patient's body, the entire cells are identified by different immune cell types, such as DCs, macrophages, and NK cells, which initiate an immediate non-specific inflammatory reaction. Initiation of an immune response occurs when stimulated immune cells digest cancer antigens and deliver them to T cells. While CD8+ CTLs identify and destroy tumor cells expressing the given antigens, CD4+ helper T cells communicate with other immune cells to assist. Another goal of whole-cell cancer vaccines is to trigger a memory answer so that the immune system can better prevent tumor recurrence (14).

In situ, cancer vaccines are directly delivered at the tumor site or a neighboring lymph node. This strategy consists of the stimulation of antigen-presenting cells such as DCs, macrophages, neutrophils, and natural killer (NK) cells, inside the tumor microenvironment (TME) (15). The vaccination triggers an inflammatory reaction, stimulates the creation of cytokines, and attracts immune cells. Antigen-presenting cells

capture tumor antigens that are produced when the vaccination is administered, undergo the processing of these antigens, and then present them to T cells (16). CD8+ and CD4+ helper T cells are activated by this, and they collaborate to effectively eradicate tumor cells. Excited immune cells generate activator chemicals and facilitate the eradication of tumor cells inside the TME. In situ, cancer vaccines additionally strive to induce a memory reaction to enhance defenses against the reappearance of tumors (16).

The nucleic acid vaccine elicits robust CD8+ T cell responses mediated by MHC I, making it a popular choice for cancer vaccination. Nucleic acid vaccines can deliver numerous antigens at the same time, which may activate both humoral and cellular immunity. Furthermore, nucleic acid vaccines can encode whole tumor antigens, enabling antigen-presenting cells (APCs) to cross-present multiple epitopes or show multiple antigens at the same time. Ultimately, the process of creating the nucleic acid vaccine is uncomplicated and rapid, making it well-suited for the creation of individualized neoantigen cancer vaccines (17).

Several variables must be taken into account while choosing a vaccination technology. The duration necessary to create personalized vaccines is crucial in choosing vaccination platforms (18). Nucleic acid vaccines are the optimal option for some metastatic illnesses due to their ability to save time. While preparing vaccines, it is possible to utilize mixed therapies to reduce the severity of illness exacerbations and create an advantageous immunological milieu that improves immunity (19). Furthermore, while choosing a vaccine production platform, it is

important to take into account the method of use and the frequency of immunizations. Aside from selecting the appropriate platform, the optimization and design of antigens are also crucial factors. Linking tumor antigens to binding vectors (such as tetanus endotoxin or diphtheria toxoid) might enhance the ability of the antigen to stimulate an immune response (20). Utilizing protein structure, antigen-optimized design, such as virus-like particle vaccinations, has the potential to augment the immune response. Furthermore, it is essential to use bioinformatics and deep sequencing methods to facilitate vaccine design. In this study, our objective was to provide a concise overview of the most recent optimization techniques used in the development of four distinct kinds of cancer vaccines, with a particular focus on nucleic acid vaccines (20).

DNA vaccine

The fundamental idea behind cancer immunotherapy is to present different tumor antigens into the host to enhance the immune system's ability to eliminate cancer cells. Hence, the capacity of a certain medication to elicit strong immune reactions directly and significantly affects its efficacy (21). Experimental and pre-clinical trials of many immunotherapies, such as cancer vaccines, adoptive T-cell treatments, cytokine therapies, and antibody therapies, have been conducted. Among the several cancer vaccine options, DNA vaccines show the most promise for eliciting immune reactions of this magnitude. To facilitate in vivo creation and expression by the host's protein expression machinery, plasmid DNA encoding antigen and other relevant genes is introduced into the host's tissues and then transfected into the cells (22). DNA vaccines can stimulate natural immune reactions, and based on their composition and administration locations, they may also elicit humoral and cellular immune responses that are associated with particular antigens (23).

It has been demonstrated that DNA vaccines using plasmids originating from bacteria may elicit innate immune responses. It seems that the DNA of the bacterium acts as a ligand that activates Toll-like receptors (TLRs), a family of dendritic cell membrane-spanning proteins that identify molecular features related to pathogens and serve a crucial role in the innate immune system (24). The hypomethylated CpG dinucleotides pattern, which is abundant in bacterial DNA but uncommon in human DNA, reacts with TLR9 in particular. TLR9 is present in several immune cells, including dendritic cells, B cells, and natural killer cells. These cells get activated when they encounter foreign DNA, through direct transfection or phagocytosis (25). TLR9 stimulation triggers a series of inflammatory reactions, leading to the synthesis of several mediators. The localized inflammation and heightened production of cytokines resulting from the natural immune system reactions might attract and stimulate more immune cells, like lymphocytes, hence augmenting future specialized immune system reactions. Specifically, the activation of TLR9, mediated by MyD88 signaling, triggers the activation of interferon regulatory factor (IRF) 7, which in turn leads to the production of Type I interferons (IFNs) (26).

DNA vaccines serve as uncomplicated carriers for in vivo transfection and the generation of antigens. A DNA vaccine consists of a plasmid DNA that contains the genetic code for the desired antigen. This genetic code is regulated by a mammalian promoter, such as CMV-intA or CMV immediate/early promoter, together with its neighboring intron A sequence (27). The modified DNA sequence to be studied is administered to the skin (intradermally), subcutaneously, or to the muscle using several delivery mechanisms. The plasmid utilizes the cellular machinery of the host to reach

the nucleus of transfected local cells, like myocytes or keratinocytes, which also include resident APCs. In this process, the plasmid initiates the expression of genes, resulting in the production of foreign antigens. Two comprehensive models have been suggested. The plasmid encodes an antigen that is synthesized in host cells. This may occur in professional APCs, which directly stimulate immunological responses, or in nonprofessional cells. In the latter case, the antigen can be transmitted to APCs, resulting in cross-priming (28).

DNA-based vaccine administration systems

Getting DNA plasmids into the right cells and tissues is a huge hurdle for DNA vaccine researchers. To activate the host immune system and lessen certain adverse consequences, it is believed that selecting an appropriate delivery mechanism is crucial. We provide a brief overview of the current state of cancer DNA vaccine delivery systems, such as topics such as electroporation, gene-gun delivery, nanoparticle delivery, and self-assembling peptides (29). Electroporation is a well-researched method used to enhance the transfer of DNA plasmids into antigen-presenting cells (APCs). Electroporation administration enhances cell porousness by creating temporary holes, facilitating the entry of more DNA plasmids into the cells (30). Furthermore, electroporation serves as an adjuvant by attracting certain immune cells, like as dendritic cells, to the locations where DNA is injected. This, in turn, stimulates the production of proinflammatory cytokines and enhances the strength of the immune system's reaction specific to cancer proteins. Several clinical studies have examined the effectiveness of delivering the DNA vaccine by electroporation to treat diseases (31). Another frequently used method involves the use of a gene cannon to deliver a DNA vaccination, which is coated with a gold particle. This delivery technique enhances cytotoxic T-cell reactions and requires fewer DNA strands in various tests. Multiple compelling pieces of data have shown that the efficacy of cancer vaccines in combating different types of cancer, like lung cancer, may be augmented by gene gun administration. Despite their importance, electroporation and gene-gun-based delivery methods have many limitations, including the induction of significant pain upon injection and their unsuitability for widespread population immunization (31).

A novel delivery strategy has been developed to improve the absorption of certain DNA vaccines by using nanoparticle-based drug delivery systems. This innovative delivery technology can overcome the restrictions related to the movement of medications inside the body and enhance the effectiveness of pharmaceuticals that have low levels of absorption or solubility. So far, a range of nanoparticles has been used to transport DNA-based vaccines and enhance the body's immune response against tumors (32). These nanoparticles include polymeric nanoparticles, liposomes, silica nanoparticles, bisphosphonate-modified calcium phosphate nanoparticles, gold nanoparticles, virus nanoparticles, and carbon nanotubes. Self-assembling peptides (SAPs) are compact biomaterials that may serve as a very efficient drug delivery mechanism for transporting antigens to cancer cells. SAPs may be fabricated into many structures including nanomicelles, nanotubes, nanovesicles, nanotapes, and hydrogels (33). The novel delivery method has various benefits in comparison to liposomes or nanoparticles, including superior drug-loading efficiency, little drug leakage, enhanced absorption, and exceptional biodegradability. In addition, it may stimulate a long-lasting immunological response without the need for an adjuvant, as stated in reference (33). Recent research demonstrated the efficacy of a novel delivery platform, known as Glycosaminoglycan (GAG)-binding enhanced transduction (GET), in facilitating the transfer of nucleic acids for gene therapy in lung organs. The tripeptide binds to the DNA plasmids, forming complexes with them. These complexes are then encapsulated in nanoparticles. The nanoparticles may be transported to different organs, with a particular focus on the lungs. This method shows promising promise for delivering DNA vaccines. However, the primary disadvantage linked to low pH in superabsorbent polymers (SAPs) is the necessity for enhancement (34).

Cancer DNA vaccines advantages and limitations

The utilization of DNA as a means of vaccination was initiated during the 1990s. This involved the introduction of a plasmid DNA that contained the genetic code for the influenza A nucleoprotein. As a result, a targeted and effective immune response was triggered, namely involving CTLs (35). Subsequently, DNA vaccines have been created to address a range of conditions, such as allergies, infectious disorders, autoimmune diseases, and cancer. DNA vaccines utilize bacterial plasmids to carry genetic information for antigens and immunostimulatory substances such as IL-2 and GM-CSF (36). They can be administered through several methods, such as intramuscular (IM), intradermal (ID), subcutaneous (SC), and mucosal. Physical approaches, including electroporation, sonoporation, DNA tattooing, or gene guns, are frequently employed for delivering DNA to the nucleus (37). These techniques effectively bypass obstacles within and outside the cell to transport DNA. Upon entering the nucleus, the antigen coded by the DNA vaccine must be produced and displayed on major histocompatibility molecules (MHC) to

activate T cells. A significant benefit of DNA vaccines is their ability to convey the encoded antigen through MHC class I and class II, thereby stimulating both CD4 and CD8 T cells and, informally, humoral immunity (38). Moreover, the inherent components of plasmid DNA might potentially trigger the natural immune reaction as a result of the identification of the double-stranded DNA structure by cytosolic sensors. Mouse models have shown the successful activation of a targeted and effective immune response against many antigens and tumor-associated antigens in various cancer types (39). Cancer DNA vaccines provide benefits over nonspecific and nontargeted medicines in terms of antigen sensitivity and security. Unlike these treatments, which may have numerous adverse effects and cause significant harm to healthy tissues, DNA vaccines are more targeted and pose less risk. Cancer DNA vaccines elicit a systemic immune response, making them efficient against metastatic tumors, which are resistant to surgical removal. Furthermore, DNA vaccines differ from antibodies and small molecule inhibitors in that they stimulate the development of immune system memory (40).

Nevertheless, regardless of advancements in delivery methods, DNA vaccines exhibited suboptimal immunogenicity throughout human studies. Various molecular techniques, including codon optimization, have been experimented with to enhance their effectiveness (41). This gene engineering strategy allows for the substitution of synonymous codons to enhance protein synthesis and plasmid immunity. Cancer optimization DNA vaccines have shown high effectiveness in several preclinical models, particularly in preventive settings, and have established a strong safety profile in people. Regrettably, the efficacy of medicinal vaccination remains restricted, even in preclinical studies (42). The drawback primarily arises from the different kinds of resistance that occur throughout tumor growth. These processes include the loss or alteration of epitopes that immune cells understand, T cell exhaustion, antigen tolerance, and the infiltration of immunosuppressive cells including regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), and tumor-associated macrophages (TAMs). These cells generate suppressive cytokines like TGF-β and IL-10 and also contribute to a deprivation of nutrients and oxygen (41). Therefore, it is essential to develop novel techniques to fully eliminate malignancies. Upon analyzing the most recent 5-10 years of experimental and clinical studies, two primary patterns emerged. Choosing the appropriate encoded antigen(s) for a DNA vaccine might enhance its potency and stimulate a wide-ranging immune system reaction, therefore addressing issues related to epitope loss, alterations, and resistance. Furthermore, the implementation of techniques that integrate several treatments has been carried out to hinder the penetration of immunosuppressive cells and the generation of suppressive cytokines, to diminish suppression inside the tumor microenvironment (43).

The mechanisms by which lung cancer DNA vaccines engage the immune system

Lung cancer is now the primary cause of cancer mortality globally. Despite several recent advancements, the annual incidence of lung cancer exceeds 2 million cases, with a rising prevalence among those who do not smoke and women. Non-small cell lung cancer (NSCLC) accounts for around 85% of newly detected instances of lung cancer, with almost all patients being identified with advanced-stage illness (44). Significant advancements have been made in the last ten years regarding the management of NSCLC, mostly due to the emergence of specific medicines and immunotherapy. Immune checkpoint inhibitors (ICIs) are currently the primary therapy for severe non-small cell lung cancer (NSCLC), with some patients experiencing unprecedented responses and extended life, which was not previously seen in the context of metastatic NSCLC (45). Nevertheless, it is important to note that not all patients have a sustained positive outcome when treated with immune checkpoint inhibitors (ICIs). The crucial factor for a successful response appears to be the penetration of T-cells that can identify and eliminate cancer cells. Data indicates that immune checkpoint inhibitors (ICIs) are less effective in "cold tumors," which are characterized by a deficiency of T-cell infiltration. Additional measures are required to enhance the clinical results, expanding the advantages to a larger number of individuals while minimizing needless exposure for those who are unlikely to get any sort of advantage (46).

The fundamental idea behind a DNA vaccine for lung cancer is to deliver promising and efficient tumor antigens into the host, therefore stimulating the host's immune system to eliminate tumor cells. To develop a potent DNA vaccination for lung cancer, the genes that encode particular tumor antigens or immunostimulatory elements are inserted into a plasmid that can be expressed in eukaryotic cells. The vaccinations may be administered to the host by many immunization methods, such as intramuscular, intradermal, transcutaneous, and mucosal injections (47). Furthermore, the DNA plasmids may be introduced into the cells by mechanical processes such as electroporation, sonoporation, or gene gun. Upon uptake of the plasmid, the target cell proceeds to produce the desired antigen and then offers it to lymphocytes via the signaling pathways of the major histocompatibility complex (48). Subsequently, the foreign antigens are shown to MHC class II molecules and instruct CD4+ T cells to stimulate the production

of tumor-antigen-specific antibodies. Similarly, the acquired foreign substances can be transmitted to MHC class I molecules and trigger targeted cellular immune reactions by engaging with CD8+ cytotoxic T cells, which is crucial for eliminating cancerous cells. The ability to combat cancer greatly relies on the effectiveness of the particular CD8+ T cell-induced immunity (49). DNA vaccines are very efficient in stimulating CD8+ T cell responses. Currently, there are just two cancer vaccines that have been authorized for use in humans, namely Sipuleucel T and T-VEC. Sipuleucel-T (Provenge) was the first dendritic-cell-based cancer vaccine sanctioned by the U.S. Food and Drug Administration (FDA) to manage prostate carcinoma. T-VEC (talimogene laherparepvec) was the pioneering oncolytic viral vaccine for treating those suffering from melanoma (50). Noteworthy preclinical research showed that a genetically modified DNA vaccination effectively reduced tumor nodules and had strong anticancer effects in a mouse model of lung cancer. Despite the shown ability of DNA vaccines to generate beneficial immune responses against tumors, the development of DNA vaccines specifically for lung cancer is now limited to clinical trials. Advancements in the delivery and optimization of DNA plasmids will enhance the effectiveness of DNA vaccines in clinical trials, hence facilitating their implementation in patients for translational purposes (51).

Lookahead Possibilities

Based on an examination of current experimental and clinical studies, it appears improbable that the existing curative cancer vaccines, when used in isolation, would have a substantial influence on cancer results. Extensive testing of combinations with different approaches has revealed that the combined approach exhibits a more substantial capacity for enhancing clinical results in comparison to the individual treatment. Personalized methods will be critical for clinical achievement, encompassing both the creation of vaccines and the selection of combination therapies. In addition, given the safety and tolerability of DNA vaccines, their integration with other therapeutic approaches may eventually become the norm for the treatment of numerous cancers. DNA vaccines represent a paradigm shift in immunotherapy, integrating the principles of precision medicine and immunoenhancement. They can provide an approach to therapy for a large number of malignancies, such as lung cancer, in the context of DNA vaccines. DNA vaccines, notwithstanding the noteworthy advancements observed in cancer studies, encounter certain constraints and difficulties during clinical studies. These include inadequate immunogenicity in human subjects, restricted applicability to protein immunogens, and the induction of passable antibody production against DNA. Moreover, immunologic tolerance and early designs of DNA vaccines are the primary reasons for their lack of success in human clinical studies. Efforts have been made in recent times to augment the host's immune response against lung cancer through the incorporation of innovative immunological adjuvants, including cytokines and chemokines, as well as TAAs or TSAs. While intramuscular injections are a prevalent method for administering DNA vaccines, device-mediated vaccinations, particularly electroporation and gene guns, remain a prevalent approach. Molecular adjuvant-based DNA vaccines and nanoparticle-based delivery systems have also demonstrated enhanced potential for effectiveness in a multitude of ongoing research studies. The latest clinical studies suggest that the present cancer vaccines are inadequate in producing optimal results alone via a single component. Hence, the integration of additional tactics, such as incorporating innovative adjuvants and delivery platforms, will enhance the clinical results in comparison to using a single treatment. Moreover, the use of a customized approach in the creation of DNA vaccines would be crucial for achieving success in clinical applications. To effectively treat patients with lung cancer with DNA vaccine vaccination, more comprehensive research is required in the future.

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Genomic Data Is Used In Person-Centered Medicine to Enhance Diagnosis By Focusing On The Immune System

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Abstract:

Genomic data is crucial for precise treatment, known as customized medicine. Its use in treating autoimmune diseases will lead to a significant advancement in medicine. Autoimmune illnesses occur when the body's immune response identifies and reacts to self-antigens. Various methods may incorporate precision medical data into the clinical care of autoimmune disorders, such as identification, prognosis, classification, and prediction of therapy reactions. Various indicators are available to assist in clinical decision-making, with other indicators currently being discovered and suggested. This article focuses on information and databases in personalized medicine for autoimmune medical conditions and exchanging information. The discussion focused on personalized medicine for specific autoimmune disorders, examining different indicators for identification, prognosis, classification, and treatment response tracking.

Keywords: Genomic data, Immunological systems, Personalized Healthcare

Introduction

The immunological system's role is to defend the body against illness by eliminating infectious organisms that assault the body or are transmitted via vaccination (1). The body's defense system operates via tightly controlled biological mechanisms that help identify and distinguish between bodily and foreign cells (2). The body's immune system cells often cohabit alongside other cells that possess a self-marker protein (3). Immune responses are initiated when a substance, such as a bacterium, part of an organism, or a chemical, is detected on the outermost layer of a cell and recognized by the body's defensive mechanisms (4).

The human defense mechanism consists of two divisions: innate and developed immunity. Innate immunity acts as the first protection against infectious diseases upon recognition by the body, whereas acquired immunity eliminates infections in the later stages of illness. When the body's immune system is activated, it identifies and eliminates alien entities (5). However, under some aberrant circumstances, the immune system may exhibit insensitivity to antigens, hypersensitivity to substances or mistake cells with self-markers as alien cells (6).

Various medical problems may impact the immune

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system's function, resulting in various symptoms collectively known as immunological disorders. Immune-mediated illnesses contain congenital and acquired immune deficiency immune-proliferative diseases such as cancers (multiple myeloma, lymphoma, leukemia), autoimmune conditions like rheumatoid arthritis, and immunological hypersensitivities like allergies (7, 8). Primary immune deficiency, frequently referred to as inherited immune deficiency, encompasses many immunological illnesses that affect the growth and operation of the immune system and its functions (9). Primary immunodeficiency refers to disorders caused by monogenic germline mutations that lead to loss of function, gain of function, or loss of expression. Externally and environmental variables may negatively impact the immune system, leading to acquired immunodeficiency. This is a regular occurrence in clinical settings and can result from several illnesses (10).

Personalized healthcare refers to the shift in medical procedures, particularly in medical care and diagnosis, from a generalized approach to a more individualized and genetic-based classification of patients to gather more specific information regarding the illness and the individual receiving treatment (1, 10, 11). The intricate nature of the immune system in the body and the cells' capacity to transition between several activation stages in both standard and abnormal settings contribute to the variety of treatment strategies (12). Immune disorders may be different, leading to variances in reaction to treatment. The variation in the illness progression underscores the need for identifying individualized markers for diagnosing immunological diseases. Genetic evaluation is crucial for selecting the most effective therapy method among several possibilities with varied mechanisms, dangers, and effectiveness (13, 14).

This article covers medical precision kinds of data, genomic information in precision medicine, genome-wide and customized medicine database servers, and data sharing, access, and usage. This article also discusses the application of genomic techniques and information in disease comprehension, evaluation employing specific indicators, forecasting monitoring employing prognosis indicators, personalized therapy for immune-related conditions, and monitoring response to therapy employing reaction biomarkers.

Personalized medicine for distinct autoimmune conditions

What's referred to as the immune system?

Immunization is the body's capacity to avoid illness through fighting against the growth of dangerous microorganisms known as pathogenic organisms (15). Immunity may be roughly divided into two types:

1. Innate or Natural Immunity 2. Acquired Protection

Innate or natural immunity

Humans encounter several possible infections every day via touch, ingestion, and inhalation. The immune system's adaptive function plays a crucial role in our capacity to prevent infection by recognizing and eliminating specific pathogens upon subsequent contact (16). Upon first exposure to a novel pathogen, adaptive immune reactions are delayed due to the activation and expansion of particular clones of B and T cells, resulting in a successful response taking about a week to develop (17). On the other hand, a single microorganism with a doubling period of one hour may generate about 20 million offspring within one day, causing a complete infection (18). Thus, in the first crucial hours and days of encountering a novel pathogen, our natural immune system is essential for shielding us against infection (19).

Unlike adaptive immune system reactions, innate immune system reactions lack specificity towards a particular disease (20). They rely on a set of molecules and phagocytic cells that identify common characteristics of infections and rapidly become active to assist in eliminating intruders. The adaptive immune system, or immune system, emerged in evolution fewer than 500 million years ago and is exclusive to vertebrates (21). In contrast, innate immune reactions are present in both invertebrates and vertebrates, as well as in plants, with conserved regulatory mechanisms (20, 21). Natural immunity, controlled by phagocytes, is the first line of defense versus disease-causing substances (22). The human body's innate defense detects intruding germs via germline-encoded pattern-recognition receptors (PRRs). Pattern Recognition Receptors (PRRs), such as Toll-like and cytoplasmic receptors, identify specific microbial components of invading pathogens and stimulate immune cells (20-22).

The way in which innate or natural immunity functions

Upon detecting non-self-agents, Pattern Recognition Receptors (PRRs) located on the cell's outer membrane, intracellular components, or in body fluids carry out opsonization, stimulate complement and coagulation processes, facilitate phagocytosis, initiate pro-inflammatory signaling processes, trigger apoptosis (23). The intracellular signaling pathways produce overlapping and distinct genes that play a role in inflammatory immune reactions and are crucial in personalized medicine. Innate immune reactions include phagocytes (neutrophils, monocytes, and macrophages), inflammatory mediator-releasing cells (basophils, mast cells, and eosinophils), and natural killer (NK) cells (24).

Acquired immunity

Adaptive immunity is not established at birth. It has been acquired (25). The learning process begins when an individual's immune system comes into contact with external intruders and identifies non-self-substances known as antigens (26). The different elements of acquired immunity develop to effectively target each antigen and create a memory specific to that antigen. Acquired immune systems, also known as particular immunity, target a specific antigen met earlier. Its distinguishing features are its capacity to acquire knowledge, adjust, and retain information (25, 26).

Adaptive immunity requires a period to establish after initial exposure to a novel antigen. Following the first exposure, the immune system retains memory of the antigen, resulting in faster and more efficient responses upon repeated encounters (27).

The white blood cells contributing to acquired immunity include Lymphocytes consisting of T cells and B cells. Other components of acquired immunity include Dendritic cells and cytokines (28). The immune system's complement system boosts the efficacy of antibodies. Acquired immunity is the body's defense system that develops after exposure to a pathogen, either through previous infection or through the transfer of chemicals that protect from mother to child. Adaptive immunity is mediated by T and B lymphocytes that are clonally dispersed and exhibit specificity and memory. Stimulation of the innate body's immune system often stimulates acquired immunity. Helper T cell subset formation and cytokine production impact adaptive immunity (25-28).

Mechanism of Acquired Immunity

Naïve T-helper cells develop into two subsets that are TH1 and TH2 when triggered by Antigen-presenting Cells (APCs). Interferon-γ (IFN-γ) is secreted by TH1 cells and enhances explicitly cellular immunity. TH2 cells generate interleukin 4, 5, 10, and 13 (IL-4, IL-5, IL-10, and IL-13). IL-12 drives TH1 differentiation, whereas IL-4 promotes TH2 differentiation. TH2 has a significant role in enhancing humoral immunity (27-29).

Development of immunological disorders

Immunological illness arises from the dysfunction of many components of the mammalian immune system's function. The immune system reaction identifies and removes antigens while also tolerating its tissues (30). The classification of immune-mediated illnesses depends on the significant immune pathology lesion. Immune-mediated illnesses may be categorized into acute hypersensitivity, autoimmune diseases, immune-complex illness, and delayed-type hypersensitivity. Autoimmunity may be categorized into adaptive immunity-mediated and innate immunity-mediated. Most illnesses are characterized by positive pathogenic feedback among adaptive and innate immune systems. Figure 1 below illustrates the development of immunological disorders (31).

Personalized Healthcare

Personalized healthcare involves customizing diagnostic methods, therapy, and preventative measures based on specific patient features to achieve the best possible result for every individual, focusing on availability and cost-effectiveness (32). Personalized healthcare utilizes an individual's unique genetic composition to inform clinical treatment decisions (33). Researchers constantly seek prognostic, diagnostic, and predictive biomarkers to assist in clinical decision-making and guarantee that the most appropriate medicine is provided to the correct patient at the optimal moment (34). Figure 2

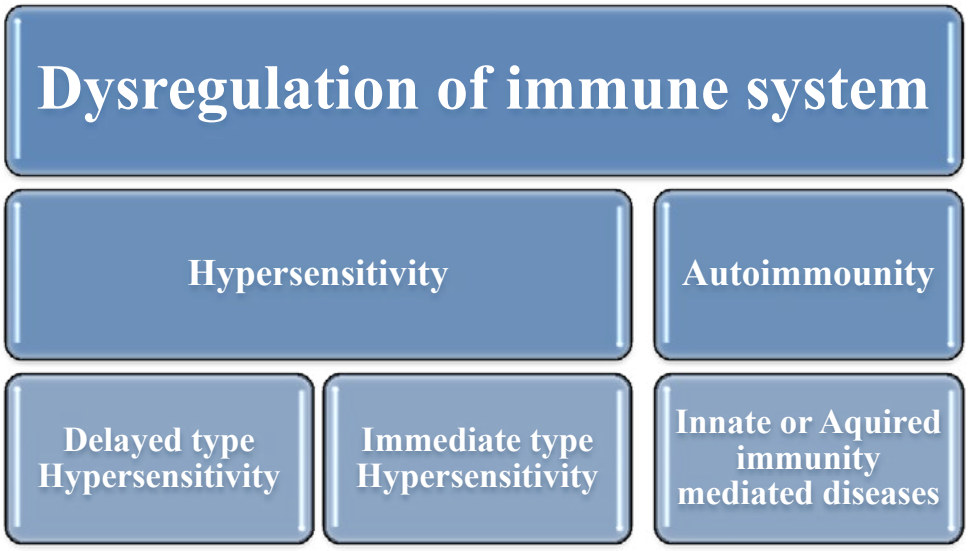

Fig 1. Diagram illustrating the development of immunological disorders.

illustrates the subdivision of customized medicine. The method of application of precision medicine is given in Figure 3.

Individualized medicine and genetic information

Personalized healthcare often consists of a large amount of genetic data. Advancements in power systems have enhanced the application of massive amounts of information in customized or precise healthcare. The advancement of genomics data provides several opportunities for developing clinical procedures, diagnostics, and preventative strategies and predicting the most effective therapies for various illnesses associated with distinct locations and lineages (35).

Types of data used in precision healthcare

Information about patients is being systematically collected and becoming more complicated, especially in neuroimaging, where over 10 petabytes of data are generated annually. Precision healthcare research utilizes various types of data including imaging information (CT, PET, ultrasound, and MRI), bio-sample information (serum, plasma, and urine amount), molecular information, genomics information (nucleotide sequences), proteomic identifying information (mass spectrometry), digital pathology information, biomedical instrument information (blood pressure, heart rate, and insulin level), and clinical information (death/survival data, demographics, and medical-based questionnaire) among others (35, 36).

Advancements in personalized medicine have resulted in the development of tailored brain models for patients with intractable epilepsy and breakthroughs in understanding the epigenetic mechanisms of hematopoiesis. A comprehensive grasp of several informatics domains, such as data science, data management, data curation, and bioinformatics, is essential for combining and

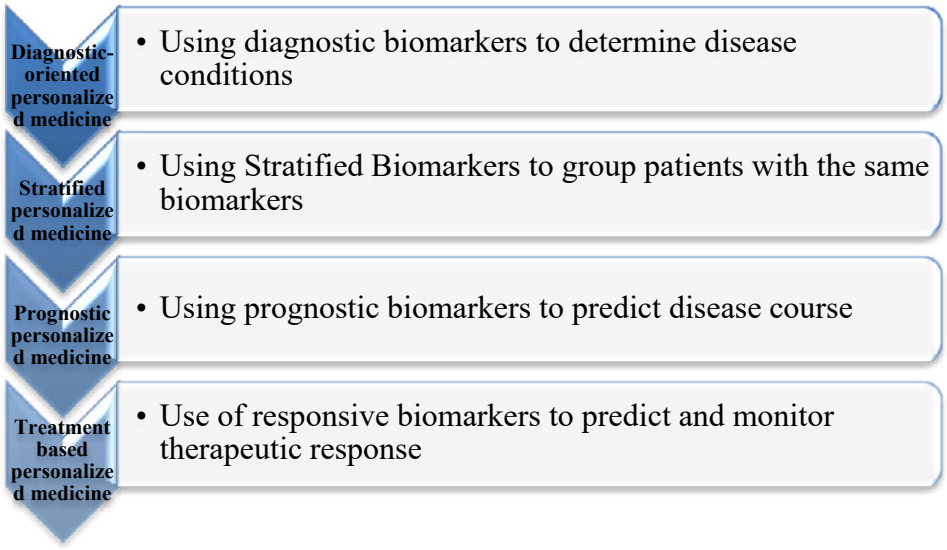

Fig 2. A diagram illustrating the many divisions of precision healthcare.

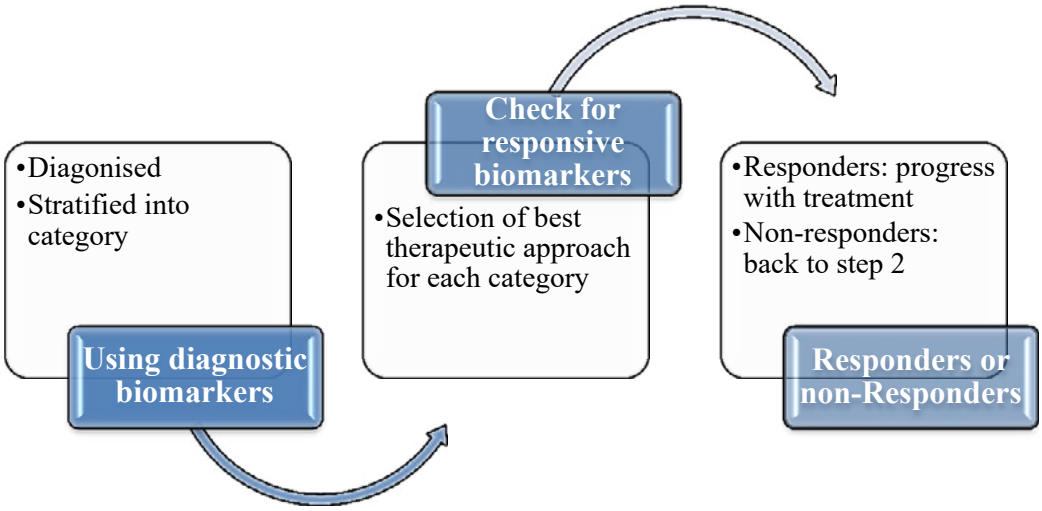

Fig3. The implementation of the precision healthcare approach is shown in Figure 3.

integrating numerous data kinds (37).

Platform for genomic and customized healthcare

A database of information is an organized collection of information managed by the database management system (DBMS) on a computing device. A relational database management system consisting of data, DBMS, and related applications is often called a database. Each database includes certain forms of data. Here, we shall introduce databases related to customized or precision healthcare (38).

Immune Epitope Database (IEDB)

The IEDB is an open-access database valuable for vaccine and pharmaceutical research. It contains experimental information on immunoglobulins Major Histocompatibility Complex (MHC), attaching information gathered from various antigenic resources, as well as Helper T Lymphocyte (HTL) and Cytotoxic T Lymphocyte (CTL) epitopes for human and other animal species. The collected information also assists in forecasting and analyzing different types of epitopes (39). The database is accessible at https://www.iedb.org/.

Prostate cancer-related lifestyle database (PCaLiStDB)

Lifestyle therapy focuses on the relationship between lifestyle choices and chronic or immune-related illnesses. PCaLiStDB is a lifestyle collection focused on accuracy in preventing prostate cancer and other lifestyle-related disorders. The database contains lifestyle-related genes, biomarkers linked with lifestyle types, and individualized predictors of lifestyle-related diseases (40). The database URL is http://www.sysbio.org.cn/pcalistdb/.

Clinical Genome Resources (ClinGen)

The ClinGen database structure, supported by the National Institute of Health (NIH), collects clinically significant data for personalized research and medicine. This data collection extracts clinically significant genes and variations for accurate diagnosis and therapy (41, 42). The database may be accessible via the website https://clinicalgenome.org/.

Personal Genome Project (PGP)

The personal genomics research collection is considered a significant advancement in healthcare technology. This information collection is accessible to anyone focused on creating a tool for individualized treatment and furthering research. The database contains diverse data sets for several locations, such as PGP-UK, PGP-AUSTRIA, PGP-CHINA, PGP-CANADA, and PGP-UNITED STATES. The information system provides Genome, Methylome, transcriptome, and phenotypic data for the application of precision medicine (43). The genome database may be accessed at https://www.personalgenomes.org/.

Online mendelian inheritance in man (OMIM)

The information system was established at the beginning of the 1960s, with an online version developed in 1985. OMIM is an open-access library for specialists specializing in genetic diseases, genetics researchers, and advanced medical students. Information about human genes, genetic diseases, clinical characteristics, phenotypes, and genes (44). The URL for this database is https://www.omim.org/.

Human gene mutation database (HGMD)

This collection of files compiles known gene mutations responsible for human hereditary disorders. Data collection contains precise healthcare information, including gene symbols, genomics coordinates, splicing, various diseases, phenotypes, and alterations in the human chromosome (45). The database may be accessed at http://www.hgmd.cf.ac.uk/ac/index.php.

Clinical Genome Database (CGD)

The Clinical Genomic Library is a crucial resource at the intersection of clinical and genomic healthcare, providing medically relevant genetic information and possible therapies. The CGD provides information regarding allelic circumstances, gene symbols, clinical categories (manifestation and therapies), affected populations, mode of inheritance, and pathogenic mutations for all captured illnesses in the database (46). The database is accessible at the following link: https://research.nhgri.nih.gov/CGD/.

Other database related to precision/personalized medicine

Other collection initiatives are also under progress to enhance the current ones, such as The Human Variome Project (47). Additionally, several websites and information related to precision healthcare are beyond the scope of this article to cover in detail. Table 1 below contains more database information on precision healthcare in general and their corresponding connections (40-47).

Application of Genomic and Personalized Healthcare Information

The exchange of information involves the transmission of a single data source across several applications or users, allowing for the exchange, access, and reuse of copies of information. Data may be categorized as open access (publicly accessible) or controlled (limited). Distributing data includes both original information (such as nucleotide sequences) and additional information (previously used or processed information) (63). Access to precision healthcare data, such as clinical information, may be open or limited. Authorization from an authorized individual is required to utilize the data for therapeutic, diagnostic, and research purposes (64).

Table 1. The database is associated with precision healthcare in general and its connections**.**

Database	Link	Ref
NetPath (signal transduction)	http://www.netpath.org/	48
Entrez – (encompasses sub-Databases)	http://www.ncbi.nlm.nih.gov/sites/gquery	49
GeneCards	http://www.genecards.org/	50
Human Genome Resources	http://www.ncbi.nlm.nih.gov/projects/genome/guide/human/	51
Ensembl Human Genome Browser	http://www.ensembl.org/IIomo_sapiens/Info/	52
Online Mendelian Inheritance in Man (OMIM)	http://www.ncbi.nlm.nih.gov/omim/	53
Gene Expression Omnibus	http://www.ncbi.nlm.nih.gov/geo/	54
ENCODE Project: ENCyclopedia of DNA Elements, NHGRI	http://www.genome.gov/ENCODE/	55
PubChem	http://pubchem.ncbi.nlm.nih.gov/	56
PhenX Toolkit	https://www.plienxtoolkit.org/	57
Human Genome Project, NHGRI	http://www.genome.gov/10001772	58
NCBI BioSystems	http://www.ncbi.nlm.nih.gov/biosystems/	59
National Human Genome Research Institute (NHGRI)	http://genome.gov	60
ExPASy Proteomics Server	http://expasy.org/	61
HUPO: Human Proteome Organization	http://www.hupo.org/	62

Conclusions

Genomics information is crucial for precision healthcare since it helps explain individual variability and development. However, the practical use of chromosomal information in clinical settings must be enhanced to address issues identified by researchers, such as the disparity between the molecular and medical data forms poses a challenge due to the vast amount of genomic information, making it difficult to handle clinical data in practice without further manipulation. Genomic and observational information utilized in clinical contexts varies due to the vast amount of data in genomic operations, making it distinct from data in clinical systems. Challenges arise when aligning genomic and clinical information for medical interpretation, particularly in specific sequencing, where information is often processed before medical analysis. There needs to be more global validation for the biomarkers being used, highlighting the need for international cooperation to evaluate the existing biomarkers. Conquering these obstacles will provide further possibilities for using genetic data in therapeutic settings.

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Authors' Contribution

Hossein Amin-Anaraki and Hamidreza Ashrafi were involved in the conceptualization, design, and support of the study. All authors read and confirmed the final manuscript.

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All data are obtainable after an appeal from the corresponding author.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

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Advancements and Potential Future Applications of Medication Delivery Systems Using Nanotechnology

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Abstract:

The development in molecular pharmacotherapy and enhanced comprehension of disease mechanisms have necessitated the precise targeting of cells responsible for initiating and advancing illnesses. This is particularly true for the majority of life-threatening illnesses that need treatment medicines with many adverse effects. Therefore, precise tissue targeting is crucial to avoid systemic exposure. Modern drug delivery systems (DDS) are created utilizing cutting-edge technology to expedite the administration of drugs across the body to a particular target area, optimizing the effectiveness of treatment and reducing the build-up of drugs in unintended areas. Consequently, they significantly impact the management and therapy of diseases. Recent drug delivery systems (DDS) have significant benefits over older methods in improved performance, automation, accuracy, and effectiveness. Nanotechnology and nano-delivery techniques are emerging fields of study that focus on using materials at the nanoscale to function as diagnostic instruments or transport therapeutic drugs to particular targeted areas in a controlled way. This review provides an up-to-date overview of recent progress in nanotechnology and drug delivery methods based on nanotechnology. It thoroughly examines the use of nanomaterials to enhance the effectiveness of new and existing drugs, including natural products, and their role in targeted diagnosis using disease indicator molecules.

Keywords: Drug delivery system, Nanotechnology, Pharmacokinetics, Drug targeting

Introduction

Drug delivery mechanisms are technical systems that use advanced methods to prepare and preserve molecules of medications in appropriate formats, such as tablets or solutions, for administration (1). They expedite the delivery of medications to the precise intended location in the body, optimizing the effectiveness of treatment and reducing the buildup of pharmaceuticals in unintended body areas (1, 2). Drugs can be introduced into the body through different routes (3). The drug's physiochemical qualities are determined by its components, which also affect the changes it induces in the body when consumed (4).

Drug delivery systems (DDS) have successfully managed illnesses and enhanced health in recent decades (5). This is primarily attributed to their ability to enhance systemic circulation and regulate the pharmacological impact of the medication. The progress in pharmacological and pharmacokinetics has shown the significance of drug release in influencing the success of treatment, leading to the emergence of the idea of controlled administration (6). The approval of the controlled-release formulation

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for medicine dates back to the 1950s, and it has since garnered substantial interest owing to its notable benefits compared to traditional pharmaceuticals. It dispenses medications at a pre-established pace and for a particular duration (7).

Furthermore, regulated drug delivery methods are unaffected by physiological circumstances, allowing them to maintain their effectiveness for extended periods ranging from days to years. Furthermore, they offer spatial drug release regulation, allowing for consistent or adjustable release rates (8). Moreover, they enhance the solubility of drugs, facilitate their accumulation at the intended location, increase their effectiveness, enhance their pharmacological activity, enhance their pharmacokinetic characteristics, promote patient acceptability and compliance, and decrease medication toxicity (9).

Although organic product-based discovery of drugs and medication delivery systems have several benefits, pharmaceutical corporations are reluctant to increase their investment in this area (10). Instead, they prefer to focus on exploring the existing libraries of chemical compounds in order to identify new medications (11). There is ongoing research to evaluate the potential of natural substances in treating several significant illnesses such as cancer, diabetes, cardiovascular diseases, inflammatory diseases, and microbiological diseases (10, 11). The primary reason is that natural medications provide distinct benefits, including reduced toxicity and side effects, affordability, and significant therapeutic potential. Nevertheless, the biocompatibility and toxicity problems related to natural chemicals provide a significant obstacle to their use as medication. As a result, several natural substances are not progressing through the clinical trial stages due to these issues (10-12). Using bulky materials in drug administration presents significant obstacles, such as in vivo instability, low bioavailability, limited solubility, inadequate absorption in the human body, challenges in achieving target-specific distribution, suboptimal efficacy, and potential side effects of pharmaceuticals. Thus, using novel drug delivery technologies to target medications to particular anatomical regions might address these crucial challenges (13). Therefore, nanotechnology is crucial in developing sophisticated medicine and medication formulations and precisely targeting drugs and their controlled release and administration, achieving remarkable results (1, 13).

Nanotechnology effectively overcomes the division between biological and physical research by using nanostructures and nanophases across several scientific disciplines, particularly in nanomedicine and nano-based medicine delivery systems, where these particles are essential (14). *Nanomaterials* are defined as substances with diameters ranging from 1 to 100 nm. These materials significantly impact several aspects of nanomedicine, including biosensors, microfluidics, drug transport, microarray assays, and tissue engineering (14-16). Nanotechnology utilizes therapeutic substances at the nanoscale to create nanomedicines. Nanoparticles have played a crucial role in advancing the science of biomedicine in areas such as nanobiotechnology, delivery of medications, biological sensors, and tissue engineering (17). Nanoparticles are often nanospheres that consist of materials manufactured at the atomic or molecular scale (18). Therefore, smaller materials have more mobility inside the human body than more extensive materials. Nanoparticles have distinct characteristics in structure, chemistry, mechanics, magnetism, electricity, and biology due to their tiny size. In recent years, nanomedicines have gained recognition for their ability to serve as delivery agents by encapsulating medications or attaching therapeutic substances. They can transport these therapies to target tissues with greater precision and controlled release (14-18).

Nanostructures remain in the bloodstream for an extended duration and provide the controlled release of combined medications at a predetermined dosage. As a result, they induce fewer variations in plasma with fewer negative consequences. Due to their nanoscale size, these structures can enter the tissue system, allowing for simple medication absorption by cells, enabling effective drug distribution, and ensuring focused action at the desired site. The cellular uptake of nanostructures is much greater than larger particles measuring between 1 and 10 µm (14-18). Consequently, they interact directly to effectively treat the affected cells with enhanced efficacy and few or insignificant adverse effects.

Nanotechnology has several advantages in treating chronic human illnesses through the precise and targeted delivery of medications to specified sites. Insufficient understanding of the toxicity of nanomaterials is a significant concern that requires more study to enhance the effectiveness and safety of these medications for safer practical use (1, 13, 18). Hence, meticulously formulating these nanoparticles might be beneficial in addressing the issues linked to their use. This review aims to provide an overview of various nano-based systems for drug delivery, the critical applications of nanomedicines derived from natural compounds, and the topics of bioavailability, targeting locations, and controlled diffusion of nano-drugs. Additionally, it will address the challenges associated with using nanomaterials in healthcare.

The first phase of medication delivery systems

In antiquity, individuals relied on botanical remedies for their medical needs. Despite their advantages, these drug delivery methods were inconsistent and

lacked uniformity and specificity (19). Before the implementation of controlled medication delivery, all medicines were manufactured and preserved in tablet or capsule compositions. Upon coming into contact with gastrointestinal liquids, the substance dissolves, penetrates the wall of the intestine, and then absorbs into the circulation via blood capillaries (20). The medication's release dynamics could not be controlled due to a lack of capacity. Rhazes and Avicenna invented covered technology to mask medications' unpleasant taste. This coating technique modified the pace at which the medication was released. Gold, silver, and pearl-coated tablets were introduced in the 10th century (21).

Advanced coating technology, including enteric, pearl, glucose, keratin, and shellac, was also developed in the 20th century. However, collagen and shellac were ineffectual because of their high pH and unstable storage, making it difficult for the small intestine to dissolve properly (21, 22). Scientists developed an enteric-coating substance using polymer-based cellulose acetate phthalate that dissolves at a low alkaline pH, similar to the small intestine. This characteristic makes it ideal for use in controlled-release formulations for the intestines (21, 22).

Current advancements in medication delivery systems and their practical uses

Significant progress has been made in recent decades in the development of delivery methods for drugs employing inorganic, biological, and combination nanomaterials as transporters for targeted drug administration, particularly in the field of chemotherapy (21, 22). Modern drug delivery systems (DDS) are designed with enhanced characteristics, including reduced particle size, enhanced permeability, better solubility, effectiveness, targeted administration to particular sites, stability, reduced toxicity, and prolonged release. They have the potential to significantly enhance the effectiveness of medicinal agents compared to traditional dose forms (21, 22).

Recently, there have been significant advancements in delivery systems for administering therapeutic agents or naturally derived active chemicals to specific target locations for treating different ailments (23). Several drug delivery methods have been effectively used in recent times. However, there are still specific issues that must be addressed, and sophisticated technology must be created to ensure successful drug delivery to target areas (20-23). Currently, researchers are studying nano-based drug delivery devices to enhance the efficiency of medication delivery.

A)Principles of nanotechnology-based methodologies in developing drugs

Significant advancements have recently been made in delivery systems for administering therapeutic agents or naturally derived active chemicals to specific target locations to treat different ailments (24). Several drug delivery methods have been effectively used recently. However, specific issues must be addressed, and sophisticated technology must be created to ensure successful drug delivery to target areas. Currently, researchers are studying nano-based drug delivery devices to enhance the efficiency of medication delivery. Extensive research has been conducted on developing drugs at the nanoscale, which is currently the most advanced method in nanoparticle applications. This technology offers significant benefits, including the ability to change properties such as dissolution, drug release characteristics, diffusivity, bioavailability, and immunogenicity. As a result, this may lead to the enhancement and advancement of easy methods of administering medication, reduced toxicity, fewer adverse effects, better dispersion throughout the body, and a longer lifespan of the drug (Table 1) (23, 24). Personalized drug delivery systems may be designed to target a particular place specifically or to release therapeutic substances in a regulated

Table 1. Different stages of nanotechnology expansion and development.

Stage	Research focus	History
First nanoparticle therapeutic	Devoted to facilitating the creation of various oral and cutaneous controlled-release compositions.	1950-1980
Second generation (2G)	The researchers aimed to create drug delivery systems that maintain a consistent rate of drug release, include self-regulating capabilities, have long-term depot formulations, and are based on nanotechnology, specifically nanoparticle formulations. During this time period, researchers created formulations of peptide/protein medications that released the medication slowly over an extended period of time.	1980-2000
Third generation	The contemporary age of controlled dispensing technique. The physiochemical challenges occur because to insufficient water dissolution, the significant molecular mass of therapeutic substances such as peptides and proteins, and the difficulty in achieving precise and controlled drug release. On the other hand, the biological barrier challenges pertain to problems related to the distribution of drugs throughout the body.	2000-2024

manner at a specific spot. Their development entails self-assembly, whereby well-defined shapes or patterns are spontaneously generated from building components (24). In addition, they must overcome obstacles such as opsonization and sequestration via the mononuclear phagocyte system (24).

Nanotechnology structures may provide drugs via two mechanisms: inactive or active delivery. In the first case, medications are predominantly delivered into the internal chamber of the material via the property known as hydrophobic. While nano-structured substances are directed towards specific locations, they release the desired quantity of the medicine due to the low concentration of the pharmaceuticals enclosed in a hydrophobic microenvironment (25). In contrast, the medications meant to be released in the latter scenario are directly linked to the carrier nanostructure substance to facilitate their distribution. The timing of drug release is critical in this strategy since the drug will rapidly detach from the carrier and fail to reach the intended region. Conversely, if the drug disappears from its nano-carrier network at the appropriate moment, its bioactivity and effectiveness will be diminished. (24, 25) Drug targeting is a crucial use of nanomaterials or Nano formulations as systems for delivering drugs. It may be categorized into two types: active targeting and passive targeting. Active targeted delivery refers to the process of connecting elements, like as immunoglobulin and amino acids, to a system for delivering drugs in order to bind them to specific target complexes at the intended site. A passive targeting approach refers to the process of circulating a mix of a medication and carrier through the circulatory system, with subsequent delivery to the desired place dependent on parameters such as affinity, binding, pH, heat, molecular position, and shape. The main goals inside the human system involve the receptors situated on the outer layers of cells, the lipid components of the cell, and antigenic substances or proteins found on the outside of cells (1, 25). Most nanotechnology-based medication delivery systems are specifically designed to target and treat cancer.

B)Application of biopolymeric nanoparticles in the fields of diagnostics, detection, and imaging.

Theragnostic, a combination of therapy and diagnosis, is widely used in cancer treatment (25, 26). Theragnostic nanoparticles can aid in illness diagnosis, accurately pinpoint the disease's site, determine the disease's stage, and offer insights into the effectiveness of the therapy. Furthermore, these nanoparticles can transport a therapeutic substance to the tumor, allowing for the precise delivery of therapeutic doses by molecular and external triggers (26). *Chitosan* is a biopolymer with unique characteristics such as biocompatibility and the inclusion of functional groups (25, 26). It is used in encapsulating or coating different kinds of nanoparticles, creating particles with diverse functionalities. These particles can potentially be utilized to identify and diagnose various illnesses (25 -27).

Researchers (28) used oleic acid-coated FeO nanoparticles encapsulated in oleic acid-conjugated chitosan (oleyl-chi-tosan) to investigate the accumulation of these nanoparticles in tumor cells. This was done by studying their ability to penetrate and be retained in the cells through the enhanced permeability and retention (EPR) effect in an in vivo setting. This study aimed to explore the potential analytical applications of these nanoparticles using near-infrared and magnetic resonance imaging (MRI) techniques. Through in vivo assessments, both approaches demonstrated significant signal intensity and enhancement in tumor tissues due to a more substantial EPR effect after intramuscular administration of cyanine-5-attached oleyl-chitosan nanoparticles (Cyanine 5) (28).

Furthermore, dextran, a polymeric substance, is considered a neutral polymer and the first significant instance of microbial exopolysaccharides utilized for medicinal applications (29). An outstanding benefit of using dextran is its excellent tolerance, lack of toxicity, and biodegradability in humans without any adverse effects on the body (30). Photodynamic radiation therapy is a targeted treatment for cancer that causes little harm to healthy cells. Researchers (31) created a composite system of nano-sized particles by enclosing Fe3O4 nanoparticles inside dextran nanoparticles linked to redox-responsive chlorine 6 (C6). This system was designed for near-infrared (NIR) and magnetic resonance (MR) scanning. The nanoparticles demonstrated a redox cell reaction to the fluorescent signal that alternated between "off" and "on" states, leading to precise monitoring of the tumor (31).

Furthermore, we discovered exceptional magnetic targeting capacity both in vitro and in vivo, significantly enhancing the photodynamic treatment's effectiveness. The researchers (31, 32) synthesized theranostic nanoparticles for glioma cells in C6 mice. The particles comprise gadolinium oxide nanoparticles coated with folic acid-conjugated dextran (FA) or paclitaxel (PTX). The MTT test was used to investigate the bioprotective properties of the dextran coating and the chemotherapy impact of PTX on the C6 glioma cells. The produced nanoparticles have shown their ability to penetrate C6 tumor cells by receptor-mediated endocytosis. They also exhibit improved contrast (MR) concentration-dependent operation, which is attributed to the paramagnetic nature of the gadolinium nanoparticle. Coated gadolinium nanoparticles exhibited greater

efficacy in decreasing cell viability than uncoated ones. Consequently, using FA and PTX-coupled nanoparticles as theranostic agents with both paramagnetic and chemotherapeutic characteristics is feasible (31, 32). Furthermore, dextran, a polymeric substance, is considered a neutral polymer and the first significant instance of microbial exopolysaccharides utilized for medicinal applications. An outstanding benefit of using dextran is its excellent tolerance, lack of toxicity, and biodegradability in humans without any adverse effects on the body (33). Photodynamic radiation therapy is a targeted treatment for cancer that causes little harm to healthy cells. Researchers created a composite system of nano-sized particles by enclosing Fe3 O4 nanoparticles inside dextran nanoparticles linked to redox-responsive chlorine 6 (C6). This system was designed for near-infrared (NIR) and magnetic resonance (MR) scanning. The nanoparticles demonstrated a redox cell reaction to the fluorescent signal that alternated between "off" and "on" states, leading to precise monitoring of the tumor (30-33).

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Current commercial offerings using nanotechnology

There are many products based on medical nanotechnology available today (34-36), some of which are being used in clinical settings (Table 2). Notably, these nanomedicines are mostly created for medications with high toxicity and poor water solubility. These nano formulations may often increase the drug's pharmacokinetic qualities while lowering its toxicity. A recent assessment found that even though the FDA hasn't regulated many nanomedicines, there are several clinical trial activities underway that might soon lead to the release of many novel pharmaceuticals based on nanotechnology. Of the nanomaterials under investigation, 18 are focused on chemotherapeutics; 15 are meant to be antibacterial agents; 28 are meant for various medical applications, including autoimmune illnesses, psychiatric problems, and many others; and 30 are meant to be nucleic acid-based treatments (Figure 1) (34-36). Table 2 displays the list of nanomedicines that the FDA has authorized, sorted by the kind of carrier material utilized to prepare the formulation.

The future of medication delivery systems and nanomedicine

Nanomedicine technological advances is now among the greatest captivating areas of study. Multiple investigations done in this field over the last two decades have already led to the submission of applications and the completion of several clinical investigations (37). Carcinoma is a disease that has

Table 2. FDA approves of nanomedicine categorized according to automobile type.

Drug	Ingredient active	Carrier	Application	Approved year
Plegridy® (Biogen)	interferon-beta (IFN-β1a)	PEGylated IFN-β1a protein	Multiple sclerosis	2015
Invega® Sustenna® (Janssen Pharms)	Paliperidone palmitate	Nanocrystals	Schizophrenia schizoaffective disorder	2014
Nanotherm® (MagForce)	Iron oxide	Aminosilane-coated Iron nano-particles	Brain tumor	2010
EquivaBone® (Zimmer Biomet)	Hydroxypatite	Nanocrystals	Bone substitute	2009
Mircera® (Hoffman-La Roche)	Methoxy polyethylene glycol-epoetin beta	Chemically synthesized erythro-poiesis-stimulating agent	Anemia associated with renal failure	2007

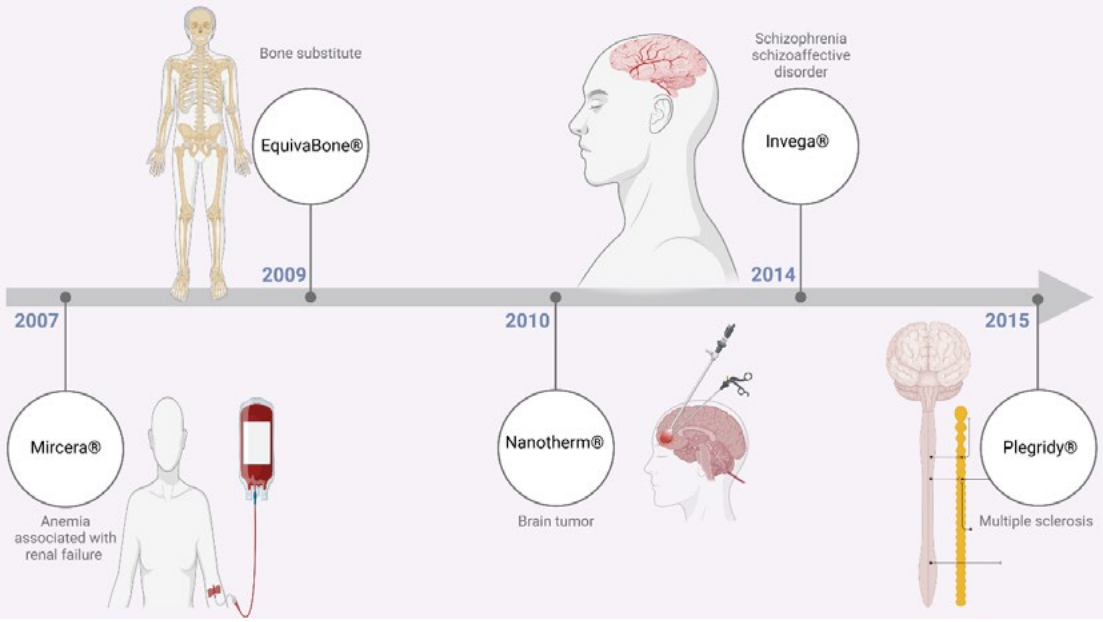

Fig 1. Schematic of some commercial drugs developed according to nanotechnology.

benefited from the use of nonmedical technology in both treatment and detection, as previously addressed in other parts. The utilization of nanotechnology and nano-drug delivery techniques is unquestionably the current state of affairs in the realm of advancement and research. These systems employ various nanoparticles to administer precise dosages of medication to specific cells, such as malignancies or tumor cells, while leaving cells that are normal unaffected. Although possible uses of nanotechnology in medicine and nanodrug methods of administration are well recognized, their impact on the medical field, particularly in the areas of cancer treatment and diagnostics, is currently limited. This is due to the fact that the discipline is still relatively young in science, having only seen two decades of serious investigation, and many important, fundamental characteristics remain unknown. Future research will primarily concentrate on studying the fundamental indications of diseased tissues, namely essential biologic indicators that allow for effective targeting without altering the normal cellular processes. Ultimately, when our understanding of diseases advances to include the molecular structure or the subcellular size of nanomaterials, with comparable biomarker identification, the area of nanotechnology will enhance, leading to the emergence of novel approaches for both detection and therapy (35-38).

Conclusion

In recent years, drug delivery and nanotechnology have drawn a lot of attention from researchers, experimenters, and clinical trials alike. It has emerged as one of the most exciting areas of study in contemporary science. The recent delivery system for drugs has a lot of potential, despite the obstacles that have prevented it from being used in clinical settings. To help achieve this efficiency, we will need to collaborate across the disciplines of academia, laboratory experimentation, medical knowledge, pharmaceutical knowledge, and excellent research. Researchers anticipate that using cell treatments will help provide an effective single dosage and address the bio-acceptability problems that drug delivery methods encounter. In actuality, cell treatments promise to dismantle intrinsic biological barriers, produce reactions that look natural inside the system, and provide a seemingly persistent stream of complicated biologics. To address some of the issues surrounding medication delivery, researchers have proposed the use of molecular imprinting polymers, micro fluids, and inorganic mesoporous nanomaterials. Researchers have found that using priming agents that can alter the biological environment in which drugs are administered—particularly those that can alter tissue structure and function to make administered drugs more advantageous without endangering patients—can increase the effectiveness of drug delivery. Additionally, since cells are a natural part of the human body, cell-based drug systems—which combine the use of cells with nanomaterials—should be taken into consideration in the field of biomaterials. This is a novel approach that is still in theory but looks to be very creative, encouraging drug delivery methods in an effort to achieve the greatest drug delivery arrangement. To support the effectiveness of these contemporary drug delivery methods and the difficulties associated with their use, a great deal of study and clinical studies are still required.

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Seyedeh Sahar Ebrahimi Hosseini and Eskandar Hoseinnzhad Lazarjani were involved in the conceptualization, design, and support of the study. All authors read and confirmed the final manuscript.

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A Personalized Medicine Perspective on the Microbiome's Role in Colorectal Cancer Progression

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Abstract:

Colorectal cancer (CRC) is a very prevalent kind of cancer that is regularly diagnosed on a global scale. The lifestyle is recognized as a significant risk factor for CRC, particularly in cases of sporadic colorectal cancer. The gut microbiota undergoes significant alterations in its natural composition over the first ten years of life. Ensuring homeostasis in the gut is crucial because the structural and metabolic activities of the commensal microbiota prevent the colonization of pathogens in the intestines. Dysbiosis, which refers to an abnormality in the function or structure of the intestinal microbiota, has been linked to several disorders, including CRC. Without a doubt, some probiotics, when correctly prescribed and given, may effectively restore balance to the gut microbiota. This might potentially have a beneficial impact on immunological regulation in the gastrointestinal tract and reduce inflammation of the intestinal lining. New research strongly supports the concept that regular use of certain probiotics might be a practical method to successfully shield patients from the potentially harmful effects of radiation treatment or chemotherapy. Conversely, emerging therapeutic methods known as personalized medicine have provided a fresh perspective in the field of medical science. The correlation between microbiome and personalized medicine has emerged as a particularly intriguing area of further study, with significant implications for the treatment of diseases like cancer. This study aims to investigate the potential relationship between dysbiosis in the intestinal microbiota and colorectal cancer, as well as the possible involvement of probiotics in the improvement of colon cancer. Also, the relationship between personal medicine and intestinal microbiome in the development of various diseases related to the intestine has been mentioned.

Keywords: Colorectal cancer, Gut microbiota, Probiotics, Precision medicine

Introduction

The gut microbiome encompasses the combined genetic material and genome of all bacteria that inhabit the gastrointestinal tract (GIT) (1). The human gastrointestinal tract (GIT) harbours a population of more than 100 trillion microorganisms, with the bulk of them being concentrated in the colon. Metagenomic investigations reveal the presence of

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around 1,952 bacterial species in the human gut that have not been successfully grown in a laboratory setting. Furthermore, a significant number of these species have not yet been categorised or classified (2). This enhances significant variety within the microbial environment. The interaction between host and microorganism may either be mutually beneficial or disease-causing. The microbial ecology is significantly impacted by several external variables, including nutrition, medicine, and lifestyle (3). The symbiotic relationships between humans and microbes have many implications for physiological functioning and general well-being. The advantageous substances serve several purposes, including supplying essential nutrients, controlling immunity, regulating enterocyte action, impacting metabolism, and inhibiting the colonization of harmful microbes (4). The composition of the intestinal microbiome is strongly influenced by a person's diet and its chemical constituents since the bacteria metabolise and flourish in response to the ingested food. Dietary fibres, carbohydrates that can be accessed by the microbiota (MAC), and certain proteins obtained from plants are metabolised to produce short-chain fatty acids (SCFAs) (5). Short-chain fatty acids (SCFAs) possess anti-inflammatory characteristics, protect the structural integrity of the mucosal lining, and preserve bacterial diversity. Fluctuations in the levels of vital components and harmful poisons are associated with several diseases, including cancer (5). The primary processes implicated in cancer development due to the microbiome include changes in microbial diversity, compromised immune response, and the production of chemicals that are carcinogenic or genotoxic (5). This study aims to provide novel insights into the role of the gut microbiota in the advancement of colorectal cancer (CRC). Furthermore, we researched the potential of nutritious dietary changes to repair and maintain a properly functioning layer of cells in the colon, hence reducing the risk of colorectal cancer.

Colorectal cancer

Lung cancer is the predominant cancer reported in both men and females, comprising 11.6% of all reported cases. Among women, breast cancer has the highest incidence rate at 11.6%, while prostate cancer is the second most common disease among males, affecting 7.1% of the male population (6). Colorectal cancer has the third highest occurrence rate at 6.1%, but it is the second most common reason for death, responsible for 9.2% of all cancer-related fatalities. By 2035, it is estimated that deaths caused by rectal cancer will increase by 60%, while fatalities resulting from colon cancer will climb by 71.5%. Therefore, sickness is often regarded as a reliable measure of the socioeconomic advancement of the country (7). Lifestyle choices, levels of body fat, and dietary trends all contribute to the rise in morbidity. There is significant proof indicating that participating in physical activity has a protective impact (8). Greater consumption of red and processed meat, as well as alcoholic beverages, elevates the likelihood of having the condition. In addition to ameliorating socioeconomic circumstances, advancements in civilization and economic growth give rise to a transformation in dietary habits known as the "Westernisation of the lifestyle." This results in an increased intake of animal lipids, processed foods, refined cereals, and desserts, while dietary fibres, fruits, and vegetables are scarcer, and physical activity is reduced (9). The prevalence of overweight or obesity frequently arises as a consequence of such a way of life. By 2035, it is projected that fatalities from rectal and colon cancer will rise by 60% and 71.5% respectively. The variation in these values among countries is contingent upon the level of economic advancement. Hence, the ailment is commonly seen as an indicator of the nation's socioeconomic progress (10).

Factors that increase the CRC

Multiple variables have been linked to the onset of colorectal cancer. Studies have shown that individuals are more prone to colorectal cancer (CRC) if they or their relatives have cancer over the course of history, prior polyps in the colon, inflammatory bowel conditions, diabetes, or have had cholecystectomy (11). Environmental factors have a crucial role in the occurrence of CRC. The research findings indicate that various factors increase the likelihood of developing colorectal cancer (CRC), such as being overweight or obese, a lack of exercise, drinking and smoking, and an unhealthy diet characterised by low levels of fibre, fruits, vegetables, calcium, and nutritional content, and high consumption of red and processed meat (12). Moreover, the susceptibility to colorectal cancer is impacted by variables like gut microbiota, age, gender, ethnicity, and economic position.

Genealogical and Individual Background

An individual's predisposition to colorectal cancer is significantly increased by a family history of the illness. This phenomenon is impacted by both hereditary susceptibility that is inherited over generations and lifestyle factors. Key determinants for forecasting the likelihood of future colorectal cancer encompass (i) the discrepancy in age between individuals at risk and their immediate family members; (ii) the age at which relatives in the first degree were diagnosed with colorectal cancer; (iii) the count of family members diagnosed with colorectal cancer; (iv) the existence of additional

cancer types (such as endometrial, ovarian, urinary tract, and pancreatic) within the family; and (v) the familial cancer tumour history of a person (13). Previous studies have shown that those with a single first-degree relative (parents, siblings, or children) affected by CRC had, on average, a two-fold higher likelihood of acquiring CRC compared to individuals without a family history. The chance of developing CRC is substantially elevated if a family member is diagnosed with the disease before to the age of Sixty (14). Furthermore, an increased number of relatives who are afflicted by the condition, including not only first-degree but also second and third-degree relatives, further amplifies the chance of developing the disease (14).

Inflammatory bowel disease (IBD) is classified as the 3rd major reason for the occurrence of colon cancer, behind HNPCC and FAP. IBD is a collection of persistent and untreatable conditions that impact the immunity of the gut, resulting in ongoing inflammation. Crohn's condition and ulcerative colitis are the main forms of IBD. The aetiology of IBD remains uncertain (15). The onset of IBD is thought to be a result of the interaction of genetic, immune-mediated, and external factors. persons with IBD have a significantly increased chance of acquiring CRC due to the promotion of tumour development and progression by chronic inflammation. This risk is estimated to be 2-6 times greater compared to healthy persons. The likelihood of developing CRC is higher as the length of IBD rises, along with the degree and severity of the condition (16).

Colon polyps, referred to as precancerous neoplastic lesions, are abnormal tissue growths that protrude from the mucous membrane of the colon. From a histological perspective, these polyps may be classified into two main groups: non-neoplastic (such as hamartomatous, hyperplastic, and inflammatory polyps) and malignant. Adenomatous polyps are very noteworthy since they have the intrinsic ability to transform into malignant tumours (17). Adenomatous polyps are thought to be the source of around 95% of colorectal cancer cases. Although the majority of cancer cases originate from adenomas, it is anticipated that only around 5% of polyps develop into colorectal cancer (18). The time frame for the development of an adenomatous polyp into invasive adenocarcinoma varies between five and fifteen years of age. The probability of polyps developing into cancer increases with bigger polyp size, higher level of dysplasia, and advanced age of individuals. Polyps exceeding a diameter of 1–2 cm, displaying a significant degree of dysplasia, and occurring in older individuals are unfavourable prognostic factors. Considering that over 40% of adults aged 50 or older possess one or more adenomatous polyps, it is essential to identify and eradicate these polyps before their progression into cancer (19).

The impact of food choices and lifestyle on CRC

Currently, it is predicted that 30%-40% of various types of cancers are attributed to dietary, nutritional, and other lifestyle variables, hence rendering cancer to some extent avoidable. Compelling epidemiological evidence indicates that dietary variables, namely those leading to excessive weight and obesity, have a significant impact on the incidence, severity, and death rates of several malignancies, including CRC (20). In response to this, the Department of Health and Human Services at the National Institutes of Health and The Agency for Healthcare Research and Quality has endeavoured to introduce lifestyle changes to the general public, to emphasise the significance of eating habits and healthy habits in preventing diseases, such as cancer. The correlation between nutrition and cancer may be disguised by confounding factors that impact health, including smoking, drinking, a lack of activity, and susceptibility to external toxins (21). All of these characteristics are widely acknowledged as risk factors for the onset of cancer. While it may be difficult to pinpoint precise nutritional risk variables in epidemiological studies, animal studies have clearly shown the influence of diet on cancer development (22).

The correlation between the incidence of CRC and an overabundance of lipids and proteins (especially from animal sources), processed meat, and high levels of alcohol intake (above 30 g per day) demonstrates the direct influence of dietary components on cancer development (23). Higher consumption of heterocyclic amines increases an individual's susceptibility to getting CRC. The main heterocyclic amines generated are 2-amino-1-methyl-6-phenyl-imidazo[4,5-b]pyridine (PhIP), 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx), and benzo[a]pyrene (Bap), which belongs to the class of polycyclic aromatic hydrocarbons. These chemical carcinogens were the first ones to be recognised as detrimental to human cells (24). On the other hand, a vegetarian diet seems to provide a defence against cardiovascular diseases, type 2 diabetes, and cancer. The presence of antioxidants in fruits and vegetables is responsible for successfully eliminating damaging free radicals and preventing DNA damage (25). A vegetarian diet encompasses a diverse range of nutrients that are linked to a decreased risk of cancer. These substances may safeguard cells by influencing the processes of bio-transformation and detoxification (phases I and II), as well as the cell signalling and endogenous antioxidant system (26). Extensive research has been conducted on certain micronutrients, namely

zinc and selenium, which appear to play significant roles in preventing cancer. On the other hand, complex compounds like carotenoids, flavonoids, curcumin, silymarin, resveratrol, folate, and total oligomeric flavonoids have demonstrated both direct anti-tumour activity and immunomodulatory effects in laboratory studies (27).

The relationship between the gut microbiome and CRC

The gut microbiota may have an impact on the development of CRC via many mechanisms. Disruptions in the gut microbiota can lead to the presence of harmful substances in the gastrointestinal tract (GIT), such as secondary bile salts, trimethylamine-N-oxide (TMAO), hydrogen sulphide (derived from amino acids containing sulphur), heme, nitrosamines, heterocyclic amines, and polyaromatic hydrocarbons (28). These substances are often found in red or processed meat and diets lacking in fibre, and they can cause inflammation and damage to genetic material. Dietary components, together with lifestyle variables such as alcohol use, smoking, and being overweight or obese, enhance the likelihood of developing abnormal growths in the cells that make up the lining of the colon. The colon houses the primary bacterial population in the human body (29). A "reference man" weighing 70 kg is predicted to have around 3.8×10^{13} germs. The human symbiotic bacteria play an additional role in enhancing the immune system to fight against harmful strains, in addition to the inherent defences of the gut. The immune system, in response, produces many inflammatory mediators, mostly including anti-microbial peptides, inflammasomes, and cytokines such as interleukin (IL)-22, IL-17, and IL-10. Crucially, continuous stimulation of the immune system has its detrimental consequences (30). Inflammation over time may initiate oxidative stress by producing reactive oxygen species (ROS), which have both toxic and damaging effects on the cells of the intestinal mucosa. In response to inflammation, the innate immune system produces inflammasomes, which may lead to colitis and increase the risk of developing CRC (31). Furthermore, the continuous release of growth factors caused by inflammation, the inhibition of apoptosis, and the enhanced formation of new blood vessels are additional factors that contribute to the development of tumours. Carcinogenic metabolites, also known as oncotoxins, are produced due to alterations in microbial metabolism resulting from changing eating habits, including the consumption of processed and refined foods. These oncotoxins are associated with the promotion of CRC (32). Yang et al. conducted a comprehensive study using metagenomic and metabolomic analysis. They discovered that a decrease in microbial diversity and a rise in the generation of harmful polyamines, including cadaverine and putrescine, are linked to a higher risk of CRC (33). Consuming diets that are rich in red and processed meats and lacking in dietary fibres elevates the risk factors for CRC. The gut microbiota metabolises indigestible food fibres in the lower GIT into short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. These SCFAs have an anti-inflammatory impact on the mucous membrane of the colon. The dysbiotic microbiome contributes to CRC via several pathways, such as enhanced microbial adhesion to colon cells, suppression of tumour suppressor genes, triggering of oncogenes, production of genotoxic impacts on colonic enterocytes, and stimulation of angiogenesis. External variables can influence the gut microbiome, which may have either a stimulating or regulating effect on the development of tumours in the intestinal microenvironment (34, 35).

There is a strong correlation between a decrease in microbial diversity and an increased probability of acquiring CRC. Wu et al. discovered a significant occurrence of Helicobacter spp. in right-sided CRCs that were moderately to weakly distinguished. In contrast, the Firmicutes phylum exhibited a higher prevalence in developed CRCs with lymph node metastasis, as compared to CRCs without lymph node metastasis (36). Colonic adenomatous polyposis (CAP), an earlier-stage lesion to CRC, is distinguished by an excessive presence of Bacteroides and Citrobacter species, whereas *Weissella* and *Lactobacillus* are conspicuously scarce. The main metabolites identified in the fecal samples of individuals with community-acquired pneumonia (CAP) were acetic acid and butyric acid (37). In contrast, healthy individuals had elevated amounts of the protective compound t10, c12-conjugated linoleic acid, which is distinct from dietary linoleic acid. Conjugated linoleic acid, namely c9, t11-CLA, may be produced by some natural gut bacteria such as probiotic Bifidobacteria species. Additionally, strains of ruminal bacteria, such as *Megasphaera elsdenii*, create t10, c12-conjugated linoleic acid (38). Although butyrate has shown pro-apoptotic and anti-proliferative effects in CRC, it has paradoxically been seen to stimulate the growth of polyps in mice with impaired mismatch repair, namely Apcmin/+Msh2−/− (adenomatous polyposis colimin/+ and mutS homolog 2−/−) animals. Eliminating the secretion system inhibits the production of proteins that are involved in bacterial adhesion to HT29 cells in a laboratory setting, and reduces the colonisation of *Streptococcus gallolyticus* subspecies gallolyticus in mouse colon cancer models. This indicates that some bacterial proteins generated by certain species can promote tumour growth (39).

The significance of probiotics in both the avoidance and treatment of colon cancer

In the past few years, probiotics, which are natural sources with anti-carcinogenic characteristics that can prevent colon cancer, have garnered considerable interest. Several investigations have shown that regular use of probiotics may improve the makeup and properties of the gut microbiota, resulting in a reduction in chronic inflammation and the production of carcinogenic chemicals during an imbalance in intestinal bacteria (40). Liu et al. conducted research where persons with CRC who were having a colectomy were given a high dose of *L. plantarum*, *L. acidophilus*, and *B. longum* for 16 days. The study found that this frequent intake enhanced the variety and microbial richness in these individuals. The gut microbiota makeup of the sick closely mirrored that of the healthy persons in our investigation (41). Certain intestinal enzymes, including β-glucosidase, β-glucuronidase, nitrate reductase, azoredutase, and 7-α-dehydroxylase, can convert aromatic hydrocarbons and amines into active carcinogens by synthesising aglycones, phenols, cresols, ammonia, and N-nitroso compounds. These enzymes can exhibit cytotoxic and genotoxic effects, thereby playing a role in the progression of colon cancer (42). Hatakka et al. performed research on a live creature which showed that consuming certain strains of probiotic bacteria may reduce the function of these enzymes and provide defence against colon cancer. Particular strains of probiotics may influence the immune response by activating phagocytes and assisting in the maintenance of immunological vigilance, which can eliminate cancer cells at their first stages of development (43). It should be emphasised that the immunomodulatory qualities vary according to the strain. The ability to survive and remain in the gastrointestinal tract, as well as the dosage, may also have a significant impact on the immune system. Hence, not all probiotics can regulate the immune system and avert the onset of CC. Galdeano et al. emphasised that a dose of around 10^9 colony-forming unit-CFU per day and an intestinal persistence time of 48 to 72 hours are the best parameters for inducing immunostimulation in the animal (44).

A potential use for treating colorectal cancer involves manipulating the human microbiome, which entails using certain probiotics. As far as I am aware, there are few early studies, particularly those that are randomised and controlled, that investigate whether altering the microbiota in patients undergoing therapy for colorectal cancer might impact outcomes, such as the objective response rate or progression-free survival (45). However, several studies have shown that regularly consuming probiotics may effectively decrease intestinal permeability by altering the arrangement of cell junction proteins and reducing the absorption of potentially cancer-causing substances that have a detrimental effect on the colon cells. The administration of a combination of probiotics (*L. plantarum*, *L. acidophilus*, and *B. longum*) to persons resulted in enhanced results and an augmentation in the levels and distribution of cell junction proteins (claudin, occludin, and JAM-1) inside the colonic epithelium (46). The proapoptotic activity triggered by the intake of probiotics, particularly via the augmentation of TNF-α production, has been extensively studied about human cancer. According to Wan et al., the probiotic *L. delbrueckii* was shown to boost the production of caspase-3, leading to the induction of death in tumour cells. The alteration of the microbiota composition during immunotherapy is a novel and intriguing topic that has the potential to pave the way for new treatment approaches in colon cancer (47). The first study findings indicate a significant interaction between the gut microbiota and the immune system, suggesting the potential to manipulate the microbiota to improve the effectiveness of cancer therapy. Undoubtedly, more comprehensive investigations will be required to assess the correlation between the microbiota and the effectiveness of colon cancer immunotherapy (48). Emerging research indicates that microbiota, particularly the microbiota of the gut, may impact the reaction to cancer therapy and the probability of encountering adverse side effects. The increasing evidence highlighting the microbiota's ability to impact chemotherapy, radiation, and immunotherapy, particularly in terms of microbial composition, is becoming more noteworthy.

Probiotics' mode of action

Inhibiting the proliferation of tumour cells

Probiotics may inhibit the growth of cancerous cells by triggering programmed cell death pathways, including both internal and external mechanisms. The pro-apoptotic impact has been validated by several in vitro investigations, often by manipulating the expression of apoptosis-related proteins, including death ligand receptors, procaspase, caspase-3, 8, and 9, as well as Bax/bak and Bcl-2/Bcl-X (49). Probiotics regulate the various phases of the cell cycle to restrict the growth and division of cancer cells, which may be identified by alterations in cyclin expression. Studies have shown that two types of probiotic bacteria, *Propionibacterium acidipropionici* and *Propionibacterium freudenreichii*, generate short-chain fatty acids (SCFAs) like propionate and acetate (50). These SCFAs can trigger cell apoptosis in the HT-29 human colon cancer cell line and colorectal adenocarcinoma. Cell apoptosis is triggered by the activation of the caspase 3 enzyme, which leads to the condensation of chromatin, the formation of apoptotic nuclei, and the generation of reactive oxygen species.

One research has found the apoptotic impact of heat-inactivated probiotic yeast strain *Saccharomyces cerevisiae* PTCC 5052 on human colorectal cancer cells (51). This research demonstrated that the apoptotic process was disrupted due to the upregulation of BAX, caspase-3, and caspase-9, as well as the downregulation of Bcl-XL, procaspase-3, procaspase-9, p-Akt1, and Rel-A (52).

Immune system regulation

The interaction and correlation between the intestinal microbiome and immunity in the intestines are crucial for creating favourable circumstances for equilibrium. The gut microbiome provides instructions to immune cells, allowing them to operate optimally by effectively eliminating harmful bacteria while also tolerating beneficial bacteria (53). When different compounds produced by microorganisms function as ligands or microorganism-associated molecular patterns (MAMPs), Toll-like receptors (TLRs) on epithelial cells often respond to them, triggering a cascade of events. They initiate certain safety protocols. Dysbiosis, an imbalance in the ecology of microorganisms in the intestines, triggers the activation of MAPK (mitogen-activated protein kinases) and NF-κB pathways (54). This activation leads to the synthesis of pro-inflammatory cytokines, such as nitric oxide and IL-8, eventually contributing to the pathogenesis of IBD and colon cancer. Probiotic therapy replenishes the population of microorganisms in the gut and activates regulatory T cells (Treg) to release cytokines that counteract inflammation, such as TGF-β2 and IL-10 (55). Both laboratory research conducted in test tubes (in vitro) and studies conducted in living organisms (in vivo) demonstrate that the chemokine IL-8 is excessively produced in CRC cells. IL-8 has features that promote the growth of blood vessels (pro-angiogenic) and the development of tumours. It also enhances the spread of cancer cells to other parts of the body (metastasis) and their resistance to chemotherapy (chemoresistance). These findings imply that IL-8 may be present. It is an appropriate candidate for the therapy of colorectal cancer. Lopez et al. conducted an experiment demonstrating that both *live Lactobacillus rhamnosus* GG (LGG) and UV-inactivated LGG decreased flagellin-induced IL-8 production in Caco-2 cells by 66% and 59% respectively [56]. In CT26 cells, the administration of a probiotic mixture consisting of B. *longum*, L. acidophilus, and *L. plantarum*, together with prebiotics such resistant dextrin, isomalto-oligosaccharides, fructose, and stachyose oligosaccharides, had an inhibitory impact on cell proliferation and decreased cell migration and metastasis. The anticancer activities of these synbiotics are attributed to the T cell-mediated immunological response, namely the augmentation of CD8+ T cells (56).

The significance of the microbiome in individualized treatment and personalized medicine

Multiple lines of confirmation indicate that the dysregulation of the relationship between microbiota and the host is associated with many disorders, including inflammatory bowel disease (IBD), diabetes, cirrhosis, and CRC (57). Recent research has examined the interplay between microorganisms and medications used in cancer therapy. The results suggest that the participation of bacteria in the immune system is essential for the efficacy of these medications (58). However, there is limited data accessible regarding the impact of different combinations of human microbiome and its impact on the results of treatment in cancer patients. Several investigations indicate that patients with certain combinations of gut microbiota can either exhibit a positive response or not react at all to immunotherapy (59). This issue must be considered while evaluating pharmaceutical interactions. Furthermore, the significance of the gut microbiome's function as a biomarker for illness phenotype, prognosis, and treatment effectiveness is well-documented, particularly in connection to the changes in microbial population structure seen in different diseases (60). Studies have shown that there is a connection between the gut microbiome and surgery in individuals with Crohn's disease, specifically a rise in mucosa-associated *F. prausnitzii* in cases of recurrent disease (61). Although extensive research on the microbiome in IBD, there is a lack of consensus on the findings. This discrepancy may be attributed to variations in geographical locations as well as the influence of antibiotics, food, and other significant variables that impact the composition of the gut microbiome (62) Hence, more study on mucosal bacteria is required in the context of inflammatory illnesses like IBD. Furthermore, microbiome profiles are linked to several additional gastrointestinal illnesses. As an example, *F. nucleatum* is employed as a diagnostic indicator via the usage of FadA adhesin in colorectal cancer. Similarly, infection with *Clostridium difficile* (*C. difficile*) is linked to decreased diversity of bacteria and diminished synthesis of secondary bile acids (62). Furthermore, two recent investigations have shown specific microbiome patterns in individuals with *C. difficile* infection that may accurately forecast the occurrence of the illness (64, 65). Research yielded significant findings, indicating that patients saw a 90% improvement in their clinical condition after the administration of fecal microbiota transplantation (FMT) using stool samples obtained from healthy subjects (58).

Treatment reactions are correlated with a multitude of microorganisms. Illustratively, patients who

exhibited a favorable response to anti-PD1 therapy exhibited a significantly elevated prevalence of *Faecalibacterium*, whereas those who weren't responsive to treatment exhibited a high prevalence of *Bacteroidale*. According to research, microbial populations may provide bacterial immune synergy necessary for anti-PD1 treatment to be effective (63). Individuals with metastatic melanoma who experienced a more favorable response to therapy demonstrated a significant frequency of *Bifidobacterium longum*. The detection of these species in the intestines of rats with tumors indicated enhanced efficacy of anti-PD-L1 therapy. In contrast, those who did not exhibit a response to therapy were found to have two specific types of bacteria, namely *Ruminococcus obeum* and *Roseburia intestinalis*. Routly noted that the use of antibiotics during cancer treatment may be associated with the response to anti-PD1 medication. Furthermore, it has been shown that the disruption of the microbial network and the elimination of certain bacteria might hinder the effectiveness of the immune system. The patients' microbiota, in response to the medication, exhibited immunoregulatory bacteria, including Akkermansia, Faecalibacterium, and Bifidobacterium, which outperformed anti-PD1 therapy. In a separate investigation, it was noted that mice that received fecal microbiota transplantation (FMT) from people who had a positive response to therapy had a more pronounced recovery response to anti-PD1 medication compared to mice who received FMT from patients who did not react to the therapy. The study revealed that the enhanced reaction was linked to the abundance of *Faecalibacterium* in the rat feces [64, 65, 66].

These results together indicate that the personalized medicine approach, which incorporates the gut microbiome, has therapeutic promise. In conclusion, these findings indicate that endeavors are underway to develop artificial microbial communities for the management of diverse ailments such as IBD and Clostridioides difficile infection (CDI) (66). The gut microbiota may influence a person's health by interacting with several kinds of immune and non-immune cells, such as RNA, DNA, and membrane chemicals. This interaction occurs via the formation of a complex network of metabolites. It is noteworthy that patients who react to treatment may exhibit improved coordination with the therapy due to the movement of intestinal bacteria to secondary lymphoid organs, resulting in a targeted immune response against the malignancy (66).

Conclusion

One of the crucial elements of personalized medicine is the creation of diagnostic assays that use biomarkers for initial detection. CRC, or colorectal cancer, has been the subject of numerous investigations in which researchers have assessed the possibility of using fecal microbiota as a screening tool for early diagnosis. These investigations have included diverse clinical groups, such as healthy individuals, as well as those with adenoma and carcinoma. The first inquiries have confirmed the importance of the microbiome in human diseases, suggesting that the makeup of the microbiome might be used as a diagnostic and medicinal indicator shortly. Although these trials are still in their first phases, more study is necessary to carry out in vitro and in vivo studies with more definitive testing for each disease, to produce a suitable microbiome signature.

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Authors' Contribution

Akram Sadat Ahmadi and Yeganeh Yousefi were involved in the conceptualization, design, and support of the study. All authors read and confirmed the final manuscript.

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Personalized Medicine Approach in the Treatment and Status of Autoimmune Diseases

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Abstract:

Precision medicine is accomplished by the process of categorising people and administering therapy that specifically targets their condition. Evidence demonstrates that the pathological circumstances of patients who are categorized or diagnosed with a singular disease exhibit significant diversity in nearly all autoimmune disorders. Hence, the use of precision medicine is crucial in the management of patients suffering from autoimmune disorders. At present, precision medicine is not available for any autoimmune disease. This article examines the use of precision medicine in the treatment of psoriasis, Alzheimer's disease and rheumatoid arthritis. Therefore, after a comprehensive understanding of these autoimmune disorders and their treatment strategies, we will use a personalized medicine approach in the management of these diseases.

Keywords: Personalized medicine, Autoimmune disease, Psoriasis, Alzheimer's disease, Rheumatoid arthritis

Introduction

Personalized medicine (PM) is a cutting-edge and captivating subject in health and medicine. The notion can revolutionize medical treatments by offering customized therapeutic methods that consider an individual's genetic, epigenomic, and proteomic profile while also considering the patient's circumstances (1). The efficacy of preventive measures is as significant as that of therapy in the realm of project management. Enhanced implementation of molecular stratification of patients, such as evaluating mutations that lead to resistance to certain medicines, would provide medical personnel with definitive data to establish treatment regimens for particular patients (2). This innovation will eliminate the need for risky, trial-and-error approaches to medication administration. At present, patients have the option to change medications if one is not working. In terms of adverse reactions, medication interactions, possible disease development, successful therapy delays, and patient discontent, the results for patients are worse when this strategy is based on trial and error (3).

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Boguski et al. introduced the term PM in 2009 and delineated its three fundamental characteristics: knowledge regarding the aetiology of diseases, capability to identify the presence of causal agents or factors, and efficacious treatment of the underlying causes (4). In 2011, the National Research Council of the US National Academies introduced a more precise definition in their paper titled 'Towards precision medicine'. The paper centred on the reclassification of diseases using genetic information and presented a blueprint for establishing new data platforms that would merge genetic information with clinical data from specific patients (5). The paper acknowledged the promise of genomics as well as other developing technologies in studying the molecular characteristics of diseases and creating a more precise classification system for disorders. Currently, there is a widespread belief that the diverse nature of numerous illness processes indicates that the approach to treating a person with a disease, as well as monitoring or preventing that disease, should be customized or 'personalized' based on the individual's distinct biochemical, physiological, environmental exposure, and behavioural features (6). Several commendable evaluations on personalized medicine have been published, such as an increasing number of textbooks specifically designed for medical learners and doctors. Moreover, it will aid in diminishing medical expenses and enhance the likelihood of achievement in the advancement of groundbreaking pharmaceuticals, rendering it a highly anticipated sector in the future (7).

Autoimmune diseases (ADs) are complicated medical issues resulting from a combination of hereditary and environmental factors. Currently, there have been over 80 distinct autoimmune illnesses identified, and this figure is constantly growing (8). While there is now no proven remedy for ADs, many therapy approaches may be used to achieve disease remission. In addition to alternative treatments for some autoimmune diseases, including autoimmune thyroid disease, the symptoms and progression of autoimmune diseases may be managed by the use of pharmaceuticals like as corticosteroids, immunosuppressive medications, and non-steroidal anti-inflammatory agents (9). Nevertheless, these alternatives are linked to significant adverse reactions and may not consistently provide desired outcomes for persons with treatment-resistant conditions. As a result, biologics have been developed to specifically target a certain signalling route. While these therapeutic alternatives are groundbreaking for ADs, individuals exhibit variability in their response to therapy and may encounter contradictory results. Given the significant role of genetic variables in the development of ADs, it is reasonable to anticipate that the effectiveness and potential harm of biological agents, as well as traditional immunosuppressant medicines, may be anticipated by examining the genetic profiles of patients (9, 10). When evaluating several therapy choices for a specific AD, identifying the optimal choice for patients may enhance efficacy and reduce toxicity. This paper aims to investigate the adoption of PM in illness areas outside cancer and uncommon illnesses, where PM is already well-established. The objective is to progress the implementation of PM in the future. The research study included the following three diseases: Rheumatoid arthritis, an inflammatory condition, is now being investigated for treatment with antibody drugs and JAK inhibitors. Psoriasis, another autoimmune disorder, has seen the discovery of *IL-17* antibodies, *PDE4* inhibitors, *TNFα* antibodies, and *IL-12/23* antibodies, broadening the range of available treatments. The focus on Alzheimer's disease is currently on understanding its mechanisms, developing diagnostic techniques, and creating medications.

Introduction of Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a persistent inflammatory autoimmune disease characterized by significant deterioration of cartilage and underlying bone, resulting in widespread pain among individuals globally. Early diagnosis may avoid joint injury and result in better long-term results (11). Extensive research suggests that significant and lasting joint damage may occur during the first two years of the illness. Therefore, it is crucial to have effective therapy for rheumatoid arthritis within the first three to six months (12). Hence, there is a want for dependable biomarkers that can provide timely detection, precise prediction of the course of a disease, and enhanced disease control. One of the most important features of RA is the crucial involvement of immune cells infiltrating the joint, which subsequently leads to bone erosions. Regarding target antigens, many categories of auto-antibodies have been identified as distinctive features of rheumatoid arthritis (RA); two notable examples are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) (13). Additionally, it is believed that genetic predisposition accounts for around 50 to 60% of the susceptibility to RA, making it the most influential factor. The *HLA* genes are the most influential genetic variations that increase the likelihood of having RA. Specifically, the *HLA-DRB1* gene, which belongs to the *HLA* class II histocompatibility antigen-*DRB1-beta* chain, has a conserved amino acid sequence that is shared by many risk alleles linked with RA. Indeed, the *HLA* locus has mostly been linked to seropositive RA and elevated levels of antibodies (Abs) against

citrullinated proteins in the blood (14).

As previously stated, the occurrence of auto-antibodies, including RF and ACPA, is a distinctive trait of RA. They occur before the onset of illness symptoms and indicate the likelihood of developing the typical seropositive form of rheumatoid arthritis (RA); this is why these antibodies are believed to have a significant impact on the development of RA (15). Given that RA is a complex illness, its onset is influenced not only by hereditary factors but also by serological changes and external factors. Considerable resources have been allocated to comprehending the possible impact of particular environmental variables, including cigarette usage, periodontitis, particular infections, insufficient sunlight, or processed meals. Moreover, air pollution is currently a significant and relevant matter. Recent case-crossover research has demonstrated a correlation between severe air pollution, an elevation in the inflammatory marker C-reactive Protein (CRP), and the likelihood of relapses in RA (16).

Diagnosis and treatment strategies

According to the criterion, if there is inflammation with swelling (synovitis) in one or more joints and no other illness is determined to be causing the inflammation, four additional items are assessed: The factors that are considered are (1) the count of joints showing symptoms, (2) the presence of RF or ACPA, (3) the levels of CRP or erythrocyte sedimentation rate (ESR), and (4) the length of time the symptoms have been present. If the cumulative score for each of these four items is equal to or more than six, a diagnosis of RA is made and therapy with anti-rheumatic medicines is initiated. Nevertheless, it is imperative to do a comprehensive examination to determine the presence of other diseases before assigning a score, as disorders other than RA can also result in a total score of six or higher (17).

After diagnosing a patient with RA, the primary goal of treatment is to achieve complete remission or substantially reduce disease progression within around 6 months. This is done to avoid joint deterioration, disability, and systemic symptoms of RA (18). The need for timely and focused treatment for RA is emphasized by the fact that 80% of patients who receive inadequate treatment will experience joint misalignment, while 40% of patients will become unable to work within a decade of the commencement of the disease. To accomplish the desired therapeutic objectives, it is crucial to promptly commence therapy and maintain a continuous approach, while regularly evaluating both the progression of the disease and the efficacy of the treatment plan being implemented (19). Before the early 1990s, the standard approach for treating RA involved a treatment pyramid that included bed rest, the use of non-steroidal anti-inflammatory medicines (NSAIDs), and if these methods were ineffective, disease-modifying anti-rheumatic drug (DMARD) therapy. Nevertheless, the effectiveness of this therapeutic approach was restricted, and over time, RA often led to the deterioration of joints, disability, the inability to work, and higher mortality rates [20].

The primary objective of treating rheumatoid arthritis (RA) is to achieve clinical remission, a state commonly referred to as “treatment to target (T2T).” This approach aims to halt the advancement of joint damage and optimise long-term physical function (20). Methotrexate is recommended as the initial treatment for RA following a diagnosis of RA. For over two decades, methotrexate has been the primary treatment for RA in the United States. It is recommended to first use low dosages of glucocorticoids in conjunction with it to effectively and promptly decrease joint inflammation degrees. Using this initial treatment schedule, around 30% to 50% of patients with early RA can achieve either remission or a state of low disease activity. Methotrexate is not only highly effective, but its safety and toxicity profile is also well-established (21). Additionally, the expenses of treatment with methotrexate are quite inexpensive when in comparison with targeted synthetic or biological DMARD treatment. Sulfasalazine, initially developed in Sweden during the 1930s, was incorporated into RA treatment due to its antibacterial properties and the perceived role of bacterial or viral infection in the development of RA (21). Sulfasalazine, a pro-drug, is metabolized by gut bacteria in vivo into its two active components: sulfapyridine and 5-aminosalicylic acid. It is effective in treating moderate RA. Although the precise way in which they work is not understood, both sulfapyridine and 5-aminosalicylic acid have been demonstrated to possess anti-inflammatory, immune-modulatory, and antibacterial characteristics. Nevertheless, sulfapyridine has been proposed as the primary medicinal ingredient of sulfasalazine (22, 23). Chloroquine and hydroxychloroquine, primarily utilised as antimalarial medications, also have anti-inflammatory properties and immunomodulatory agent characteristics that make them appropriate for treating moderate cases of inflammatory arthritic conditions. It is important to mention that hydroxychloroquine, when employed in the management of RA, has been found to have only a modest impact on the structural damage to the joints (24).

Nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, diclofenac, and ibuprofen, are useful in reducing pain and swelling and improving joint function. However, it is important to note

that they cannot modify the underlying condition and prevent further damage to the joints. The anti-inflammatory effects of NSAIDs can be primarily due to their inhibition of prostanoid production through a mechanistic process. Prostanoids, including prostaglandin (PG) E2, PGD2, PGF2α, thromboxane A2, and prostacyclin, are molecules that serve as second messengers. They bind to and activate G-protein coupled receptors on the cell surface, which in turn regulate many cellular processes. Although NSAIDs efficiently alleviate symptoms of RA, their use often leads to adverse effects on the kidneys, liver, gastrointestinal system, and cardiovascular system (25, 26).

Obstacles in the field of PM

Although biologics have superior efficacy in treating rheumatoid arthritis (RA) compared to conventional drugs, the response to treatment varies across individuals. Not all patients attain a cure after the initiation of treatment. Although remission induction may be attainable, maintaining relapse proves to be a formidable task for all individuals (27). Furthermore, only a restricted minority of patients can sustain remission even after undergoing remission and subsequently discontinuing the medication. Immunity and inflammation are influenced by multiple factors, including a variety of immunocompetent cells and chemicals, like cytokines. Currently, there is no established approach for personalized therapy in this area. Regarding biologics, numerous studies have examined the genetic correlation between therapeutic impacts of drugs, although no genetic mutations or polymorphisms have been identified as definitive indicators (28). No indication indicators have been detected in research evaluating genetic biomarkers for TNFα inhibitors. RA includes a hereditary component, and it is classified as a multifactorial disease. This means that the disease is caused by the combined effects of several environmental and genetic variables. Among the genes linked to disease susceptibility that have been discovered so far, HLA is the most consistently connected across different populations. While the relationship between the shared epitope of HLA-DRB1 and the susceptibility, severity, and clinical manifestation of RA has been established, the specific molecular mechanisms behind this connection are still unknown. Moreover, numerous studies indicate a correlation between HLA-DRB1 and ACPA-positive individuals, making it a highly sought-after clinical biomarker.

Introduction of psoriasis

Psoriasis is a persistent skin condition that results from an over-activated immune system, characterized by inflammation. It is linked to several health conditions like psoriatic arthritis, mental health issues, heart disease, and liver problems. In 2014, the World Health Organisation officially acknowledged psoriasis as a significant non-communicable disease (29). They emphasised the emotional suffering caused by misdiagnosis, insufficient treatment, and the social stigma associated with this condition. In 2016, the Global Burden of Disease Study found that psoriasis caused 5.6 million disability-adjusted life-

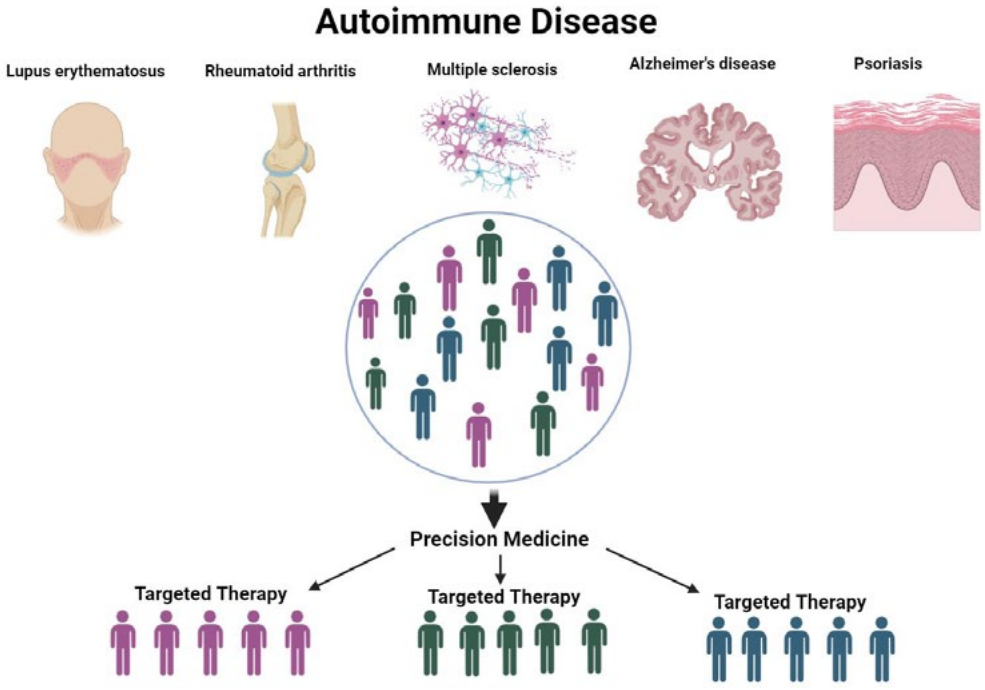

Fig1. Using a personalized medicine approach in the targeted treatment of autoimmune diseases

years (DALYs) across all age groups. This is at least three times more than the number of DALYs caused by inflammatory bowel disease. Psoriasis impacts individuals of both genders, with females and those with a familial background experiencing an earlier development of the condition. The age at which it often begins has a bimodal distribution, with the highest number of cases occurring between the ages of 30 and 39, and between the ages of 60 and 69 in men. In women, the onset tends to occur around 10 years earlier (30).

The development of psoriasis involves multiple factors, with genetics playing a significant role, particularly in individuals who develop plaque psoriasis before the age of 40. This was evidenced by twin, family-based, and large-scale population-level studies, where heritability has been calculated to vary from sixty per cent to ninety per cent (31). The probable causative genes implicated in this study are associated with several biological processes, including antigen presentation (*HLA-C* and *ERAP1*), NF-kappa B signalling (*TNIP1*), type 1 interferon pathway (*RNF113* and *IFIH1*), interleukin (*IL)-23/Th17* axis (*IL23R, IL12B,* and *TYK2*), and skin barrier function (*LCE3*) (31). The pathogenesis of psoriasis involves an intricate interaction between T cells, dendritic cells, and keratinocytes. The *IL-23/Th17* axis plays a major role in activating the immune system, causing persistent inflammation, and promoting the development of keratinocytes. Psoriasis can be worsened by various environmental factors, including being overweight, anxiety, beta-blockers, cigarette smoking, and lithium (32).

Psoriasis is characterised by persistent inflammation that causes uncontrolled growth of keratinocytes and impaired differentiation. The histology of the psoriatic plaque reveals acanthosis, which is an excessive growth of the outer layer of the skin (epidermis) (33). This excessive growth is accompanied by an accumulation of inflammatory cells in the deeper layer of the skin (dermis), including dendritic cells, macrophages, T cells, and neutrophils. Neovascularization is a major characteristic as well. The inflammatory pathways present in plaque psoriasis and other clinical variations have similarities but also exhibit distinct variances that contribute to the varying characteristics and treatment responses (33).

Diagnosis and treatment strategies

The identification of psoriasis is mostly based on clinical observations. Psoriasis has various clinical forms, with the most prevalent being chronic plaque psoriasis, which affects 80% to 90% of individuals with psoriasis. Classic plaque psoriasis is characterized by distinct, balanced, and red plaques with a layer of silvery scale on top. Plaques are commonly found on the scalp, trunk, buttocks, and extremities, however, they can appear on any part of the body. Patients may exhibit nail involvement, which may happen without accompanying plaques (34). Active lesions may cause pruritus or discomfort. Psoriasis can sometimes manifest as an isomorphic reaction, characterized by the development of new lesions in previously unaffected skin that has experienced stress or injury. The disease's severity is a useful factor in determining how to manage it, and it is categorised as mild, moderate, or severe (35).

The primary remedies for psoriasis are topical therapy with ointments, phototherapy with ultraviolet irradiation, and systemic therapy with small molecules and biologics. Granulocyte and monocyte adsorption depletion therapy may be employed as a treatment for pustular psoriasis (35). The management of psoriasis follows a systematic approach, starting with the use of topical medications such as corticosteroids and vitamin D analogues for mild to moderate signs. For moderate to severe signs, treatment options include phototherapy, oral medications containing small molecules, and biologics. Oral therapy for this condition involves the administration of immunosuppressants like cyclosporine and methotrexate, as well as *PDE4* inhibitors like apremilast. Biologics, on the other hand, utilise antibodies including *TNFα*, *IL-12/23, IL-17,* and *IL-23* inhibitors for therapy. These biologics are administered based on the patient's observations. Data suggest that *TNFα* and *IL-17* antibodies have a stronger efficacy against psoriatic arthritis compared to *IL-12/23* antibodies. Additionally, *IL-17* antibodies may worsen the efficacy of inflammatory illnesses (IBDs). The biologics were found to exhibit a significant therapeutic efficacy, however, approximately 20-30% of patients did not experience any discernible impact (36).

Personalized therapeutic approach for psoriasis based on individual biological factors

The effectiveness of anti-*TNF* treatment was assessed by examining the expression of various genes, including *HLA*: Cw6, the *TNF* cytokine, and its receptor. The *HLA*: C:06:02 gene was historically linked to positive results, however, subsequent investigations have raised doubts about this association. These disparities may be explained by the wide variety of genetic investigations and the variations in allele frequencies among different ethnic communities (37). The study examined various polymorphisms (specifically single nucleotide polymorphisms [SNPs]) in the *TNF* gene, including *rs1800629*, *rs1799964, rs1799724*, and rs361520. The results of the investigation yielded conflicting outcomes. Various research has examined the involvement of *TNF* receptor superfamily member

1B (*TNFRSF1B*) in connection to different anti-TNF drugs. The *TNFRSF1B rs1061622-TT* variant was found to be linked to a more favourable response to all anti-*TNF* treatments, and particularly to etanercept, with statistical significance. In contrast, the *rs1061622-G* polymorphism was linked to a more unfavourable outcome (38).

Ustekinumab has been extensively researched in terms of pharmacogenetics, perhaps because it has been on the market for a long time and is widely prescribed globally. The impact of *HLA*: *C:06:02* status on the response to ustekinumab has been extensively studied. Multiple studies have conclusively demonstrated that this specific allele is strongly linked to a favourable clinical outcome and a rapid response to treatment, regardless of a person's ethnicity. Consistent findings were derived from many investigations conducted on Caucasian, American, and Chinese participants. However, a subsequent meta-analysis raised doubts about the significance of the findings, as both patient groups, namely those who tested positive (*HLA: C:06POS*) and negative (*HLA: C:06NEG*), showed high response rates, albeit with modest variations. Therefore, it is advisable not to just rely on this allele when making treatment decisions. Instead, a combination of biomarkers could provide a more dependable assessment. The study evaluated polymorphisms on the *IL17* isoforms, *IL12*, and *IL23R* genes, but did not find any statistically significant results (38, 39).

Introduction of Alzheimer's Disease

Alzheimer's disease (AD) is a degenerative neurological disorder that primarily affects older individuals. The majority of patients exhibit initial memory impairment, and as the condition progresses, they will also experience language impairments, disorientation, and anxiety-related behaviours. Late-stage patients exhibit anomalous mental activity, including cognition, emotion, and behaviour, as well as a gradual loss of body functioning (40). Due to societal development and shifts in the human environment, the prevalence of AD has been steadily increasing throughout the years. The Alzheimer's Association conducted an epidemiological survey in the United States in 2017, revealing that the number of AD patients surpassed 5.5 million. Additionally, individuals aged 65 and above were shown to have double the likelihood of experiencing AD. Nevertheless, the underlying cause of AD is still not fully understood, and there are now no medications available that may effectively eradicate AD or alleviate its symptoms (40).

AD is caused by both physical and functional harm to the central nervous system (CNS), which involves the abnormal accumulation of proteins in the nervous system and the deterioration of nerve cells. Two distinct types of abnormalities have been observed in AD: amyloid plaques consisting of beta-amyloid peptides (Aβ), which gather abnormally exterior nerve cells, and neurofibrillary tangles (NFT) caused by the excessive phosphorylation of tau protein, which aggregates within neurons. AD can be viewed as a gradual series of biochemical, neurophysiological, neuroanatomical, and cognitive dysfunctions. The early aggregation of soluble Aβ in the brain leads to specific impairments in dendrites, axonal processes, and synapses (41).

In the past few decades, scientists have demonstrated an increasing fascination with neurological signs and behavioural disorders, including psychotic symptoms, sadness, apathy, aggressiveness, and sleep abnormalities. In 1996, the International Psychogeriatric Association introduced the concept of behavioural and psychological symptoms of dementia (BPSD) to describe the common symptoms of perception, thinking content, mood, and behaviour disturbances that often occur in individuals with neurocognitive disorders (ND). AD can be understood as a series of chemical, physiological, and structural alterations in the brain that can be detected several years before the appearance of clinically observable cognitive-behavioural symptoms (CBS) (42).

Current treatments strategies

Existing pharmacological interventions for AD mostly focus on managing the symptoms rather than providing a cure. The aim is to slow down the advancement of cognitive symptoms and address the behavioural and psychosocial symptoms of dementia (BPSD). There are four medications (donepezil, memantine, galantamine, rivastigmine) that have been approved for use and they can be classified into two categories: anticholinesterase blockers and anti-glutaminergics. These therapies are administered orally or through the skin (43). Anticholinesterase inhibitors are specifically engineered compounds that enhance the concentration of acetylcholine in the brain. Acetylcholine is a crucial chemical involved in transmitting data between specific neurons and is also involved in memory processes. These therapies aim to rectify the shortage of acetylcholine exhibited in the central nervous system of individuals with Alzheimer's disease. Anti-glutaminergics are employed to modulate glutamate levels by exerting a noncompetitive antagonist impact on N-methyl-D-aspartate (NMDA) receptors. Glutamate is a neurotransmitter that plays a crucial role in cognitive processes such as learning and memory (44). Non-pharmacological therapies, alongside medication, offer an additional approach to treating

neurodegenerative illnesses. Numerous research and worldwide experiments have been conducted or are currently underway to study the multidomain intervention in AD. This strategy involves the use of many activities. Studies have demonstrated a clear link between higher levels of physical exercise, cognitive training, better nutrition, and a reduction in cognitive and functional decline, as well as the severity of BPSD (45).

A personalized medicine approach in the management of AD

Aside from traditional clinical indicators, which aid in distinguishing between distinct conditions and evaluating the likelihood of concurrent illnesses, the most valuable biomarkers for predicting or confirming a diagnosis of Alzheimer's disease before death include genomic markers, epigenetic biomarkers, neurotransmitters, and levels of Aβ/tau in the brain in bodily fluids. Innovative biomarker studies aim to uncover distinct diagnostic, prognostic, and predictive biomarker traits, similar to the strategy used in oncology (46). This will be done in combination with SB (system biology), with the goal of customising therapy for each patient. Furthermore, biomarker-guided precision medicine eliminates the conventional method of trial and error in pharmacological therapies. This has significant medical implications for patients and healthcare institutions. The concept of PM aims to tailor medical treatment to the individual patient's distinct genetic, physiological, and clinical characteristics of the condition. It aims to tailor sickness prevention and therapy to the specific biological composition of each individual (customised treatment), which stands in stark contrast to the present "one size fits all" strategy (47). Due to the highly intricate nature of AD, it is highly improbable to discover a solitary medicine that can effectively treat every patient. Additionally, other disciplines including oncology and cardiology are also impacted. An effective PM strategy for AD therapy necessitates the comprehensive utilisation of genetics to provide personalised guidance. AD is related to about 600 human genes. Amyloid precursor protein (APP) mutations, with over 50 distinct variations, as well as presenilin 1 (*PSEN1*) mutations, with over 300 variations, and presenilin-2 (*PSEN2*) mutations, with over 40 variations, are found in a percentage of AD patients (5-10%) (48, 49). These mutations cause the development of brain amyloidopathy. The presence of over 100 mutations in the microtubule-associated protein tau (*MAPT*) gene, which are also found in certain patients with AD, can lead to brain tauopathies such as frontotemporal dementia and Pick's disease. Amyloidopathy and tauopathy are the two main pathogenesis hypotheses in Alzheimer's disease. Genetic factors significantly contribute to the development of AD, accounting for around 60 to 80% of cases (50). It is believed that multiple genetic factors, known as polygenic factors, are associated with the onset and progression of AD. The E4 allele of the Apolipoprotein E gene (*APOE*) on chromosome 19 is recognised as the most significant genetic risk factor for sporadic Alzheimer's disease (AD). Apolipoprotein E is one of the molecules responsible for the formation and aggregation of amyloid beta peptides. The APOE genes consist of three primary variants, namely ε (epsilon) 2, ε3, and ε4, which are present in pairs. When studying the correlation between the presence or absence of ε4 and the start of AD, individuals with one or two ε4 genotypes have a risk of getting AD that is around 3 to 12 times higher than those with no ε4 genotype (51). Nevertheless, numerous more genetic risk factors remain unidentified. Overall, genotype-specific techniques can benefit patients by utilising specific methodologies and focused methods that have been proven to be very beneficial for individuals with comparable genotypes. Further inquiry is necessary to uncover the impact of APOE on different physical activities, nutritional preferences, and lifestyle modifications as the personalised medicine approach to Alzheimer's disease prevention progresses (51).

Conclusion and Future Perspectives

Advancements in personalised medicine using genomic panel diagnosis are anticipated to be increasingly utilised in the field of oncology. Despite these diagnoses, there remains a subset of patients, approximately 10-20%, who are eligible for targeted medication selection and ongoing participation in clinical trials. Among these individuals, about half are expected to experience clinical benefits. This approach aims to promptly administer drugs that are predicted to be more efficacious. Nevertheless, there is a scarcity of evidence that unequivocally demonstrates the enhancement of patient's quality of life in real-world clinical settings. We are eagerly anticipating additional research and development of novel treatment medicines that align with the advancements in genetic analysis and diagnosis. This review examines the advancements in precision medicine and emphasises the significance of personalised medicine in diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Alzheimer's disease (AD). Precision medicine is achieved by categorising patients according to specified attributes and providing treatment that is precisely customised to meet their requirements. When both of these characteristics are effectively executed, patients are more inclined to experience favourable outcomes. The prospect of precision medicine in Alzheimer's disease is

highly promising, as ongoing research consistently uncovers novel biomarkers and focused therapeutic approaches. Utilising PM can enhance the precision of diagnoses, resulting in prompt intervention and potentially superior results. An area of research that shows promise is the utilisation of genetic biomarkers to categorise different subtypes of AD, enabling more customized treatment strategies. The aetiology of RA and psoriasis remains elusive, and the primary approach to treatment involves disease-modifying medicines that seek to ameliorate symptoms and impede disease progression. We are eagerly awaiting a more detailed understanding of how genetic backgrounds, environmental variables, and the immune system contribute to the development of these illnesses. To further our understanding of diseases, improve classification systems, and with proceed the study and creation of new medications, we hope for future progress in the fields of genetic analysis, complete analysis of gene and protein expression, analysis of epigenetic factors, genomic analysis of the gut microbiome, and the research and development of new biomarkers including miRNA.

Treating autoimmune disease with personalized medicine is more complicated than treating cancer using this method for at least three reasons. Historically, progress in the development of targeted therapies for autoimmune disorders has been slower than that of drugs for malignant tumors. Nevertheless, the authors are optimistic about the potential for change, noting the continued progress of several specific treatments. In addition, obtaining tissue samples from people with autoimmune diseases poses more logistical challenges compared to taking samples from people with cancer. Biopsies are commonly conducted in the management of malignant tumours to definitively diagnose the pathology and provide accessible samples for laboratory testing. Unlike joint biopsies, numerous autoimmune disorders, like rheumatoid arthritis, can be managed without the need for a joint biopsy. This complicates the task of identifying the genetic and metabolic variations that contribute to the disease in specific patients. Furthermore, it is worth noting that certain genetic mutations have been identified in many types of cancer. These mutations have been confirmed through the analysis of patient DNA and/or RNA expression. Consequently, they serve as highly advantageous targets for precision medicine strategies.

In contrast, the process is more intricate in autoimmune disorders since, in many instances, there is no singular dominant mutation. Consequently, it is challenging to select a viable target for therapy.

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Authors' Contribution

Yasaman Vojgani and Niusha Zeynalniya Toosi were involved in the conceptualization, design, and support of the study. All authors read and confirmed the final manuscript.

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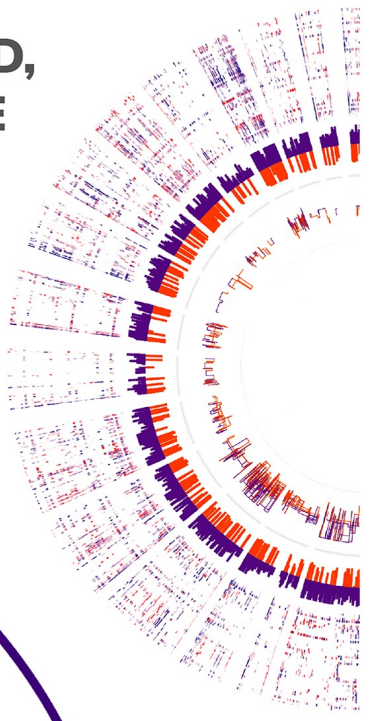
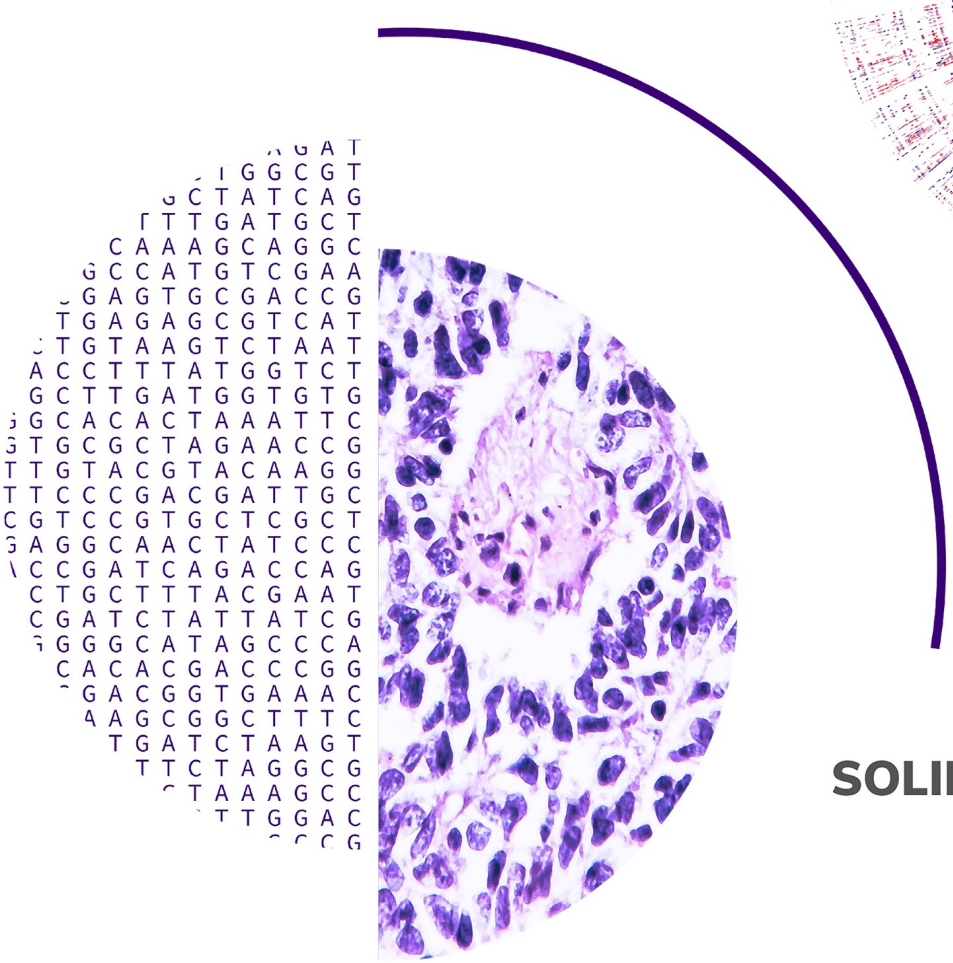
CANCER: A WORD, NOT A SENTENCE





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ABOUT SOLID TUMORS

Cancer is a disease where cells grow out of control, and these cancer cells can spread to other parts of the body without proper treatment. Solid tumors are a type of cancer that can appear anywhere (e.g. lung cancer, breast cancer, liver cancer, etc.)

Generally, this problem is caused by various gene mutations in the cells. People with the same type of cancer may have different mutations. However, scientists have been able to design specialized treatments for some of these mutations, and they are known as clinically actionable mutations. Specifically targeting clinically actionable mutations is called precision cancer treatment.

What are the available precision cancer treatments?

Precision cancer treatments are designed to be more effective at killing cancer cells and less harmful to healthy cells.

Targeted Therapies: Able to specifically target cancer cells that have certain actionable mutations or abnormalities.

Immunotherapy: Helps immune cells to recognize and destroy cancer cells.

Why do I need genetic testing?

Genetic testing can help your doctor understand what's happening in your tumor. Some genetic mutations may make certain treatments more effective, while others may indicate resistance to certain therapies. Therefore, genetic testing can help your doctor create the optimal treatment plan designed for you.

WHAT WILL YOU KNOW FROM SmarTest'S REPORT?

What gene mutations are in your tumor?
Receive a full description of the mutations occurring in your tumor, including whether these mutations may also affect your children.

What treatment may work best for you?
Help your doctor to find the best treatments for you based on what mutations were found in your tumor to work alongside the latest professional guidelines and expert consensus.

Why does my current treatment not work well?
Understand why therapy resistance occurs and receive other personalized treatment options for your doctor to consider.

We are able to deliver the report within 2-3 weeks upon receiving the sample

Please be aware that our report should not replace professional advice from a doctor. Always consult your doctor about your condition and treatment options. Additionally, not all mutations have corresponding precision cancer treatments. Even in such cases, having a better understanding of your condition can be helpful for your current and future treatment plan.

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WHAT WE OFFER

Comprehensive solid tumor panels

Our all-in-one panels are designed for all solid tumors and characterize the tumor to better guide healthcare professionals in prescribing a precision treatment.

SmarTestPRIME™ CE

A 437-gene panel covering all solid tumors and additional key biomarkers. (TMB, MMR, MSI, HRR)

SmarTestPRIME™ HRD CE

A 437-gene panel + genome-wide homologous recombination deficiency (HRD) evaluation across all solid tumors. (TMB, MMR, MSI, HRR)

SmartTestRADIOTRON™

A 474-gene panel designed for personalized radiotherapy.

SmarTestLITE™

A 196-gene panel covering major actionable solid tumor genes and some key biomarkers (MMR and MSI).

SmarTestBRCASCAN™

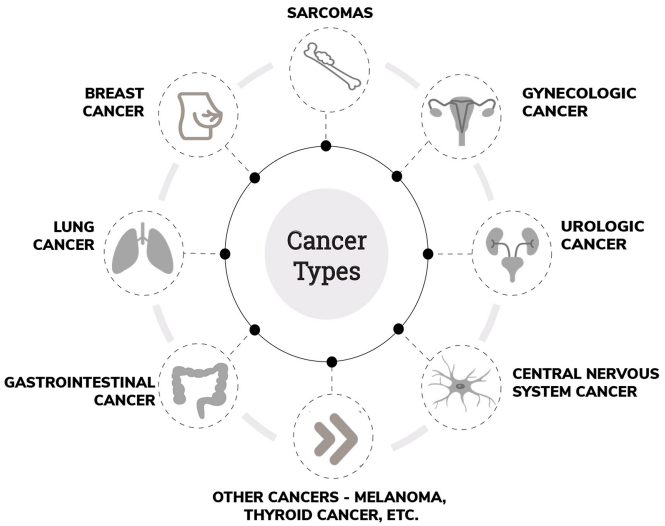
A 27-gene panel designed for cancers related to the HRR pathway (breast, ovarian, prostate, etc.) or for individuals with a family history of BRCA1 or BRCA2 mutations.

SmarTestPANCARNA™

A 117-gene panel designed for fusion genes, which are major drivers of tumorigenesis and tumor progression.

Cancer type-specific gene panels

If you prefer to test only a single cancer type, we also offer a cost-effective option that allows you to target specific types of cancer.



نشریه درمان های پیشرفته

فصلنامه پزشکی/سال ششم /شماره ۱۸ /قیمت: ۵۰۰۰۰۰ ریال /زمستان ۱۴۰۲/شماره شاپا ۶۱۵۲ ـ ۳۰۶۰

درمان های پیشرفته؛ ارائه دهنده راهکارهای چند رشته ای منحصر به فرد