Journal of Current Pharma Research
(An Official Publication of Human Journals)
An International Peer Reviewed Journal For Pharmacy, Medical & Biological Science
DOI: 10.25166 CODEN: JCPRD6 NLM ID: 101744065
ISSN: Print: 2230-7834 Online: 2230-7842
SJIF Impact Factor: 6.913

Human Journals
**Review Article**
September 2023 Vol.:18, Issue:4


# Precision Medicine - An Overview

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**Harita Toravi, Manasa Devasari, P.K. Lakshmi***

*Department of Pharmaceutics, G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad-500028, Telangana, India.*

*Department of Pharmacy Practice, G. Pulla Reddy College of Pharmacy, Mehdipatnam, Hyderabad-500028, Telangana, India.*

**Submitted:** 15 August 2023

**Accepted:** 19 September 2023

**Published:** 25 September 2023

**Keywords:** Precision medicine, Cancer, Dentistry, Cystic fibrosis, Parkinsonism disease, Alzheimer's disease, omnics, electronic health records (EHR).

## ABSTRACT

Precision medicine (PM), which utilizes genetic and molecular profiling, offers a personalized approach to medical care that is optimized for the prevention, diagnosis, and treatment of specific diseases in targeted patient populations. The purpose of this paper is to review various methods for identifying the underlying causes of diseases and treatment options for specific patients. This review will discuss the PM strategy in several medical fields, including cancer, dentistry, cystic fibrosis, and neurological diseases such as Parkinsonism and Alzheimer's disease. Additionally, this paper will provide insight into the role of omics and electronic health records in advancing precision medicine.

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## INTRODUCTION

Precision medicine is an approach to patient treatment and disease prevention that takes into account individual genetic, environmental, and lifestyle factors. This approach enables doctors and researchers to provide precise treatments for patients based on their unique needs. Traditional practices treat all patients with the same disease using the same drug and dosage form, but precision medicine is different in that it is enabled by molecular diagnostics.

Precision medicine can be defined in a variety of ways, with some definitions focusing on the result and others on the process and utilization of data. Some definitions describe precision medicine as a model that integrates other data to stratify patients into novel subgroups, which helps to attain a more precise view of patient treatment.[1,2]

In 2003, the Human Genome Project was conducted, which found that humans have up to 20,500 genes, with 99.5% of them being similar among individuals. The remaining 0.5% consists of variations that differentiate humans from each other in terms of blood type, eye color, and other factors. Single nucleotide polymorphism (SNP) is the most common type of DNA sequence variation found in the human genome, constituting 11 million SNPs that act as biological markers and determine individual responses to certain drugs. Structural variations, including deletions, insertions, inversions, tandem repeats, and copy number variations, are another type of DNA sequence variation.[1]

The Precision Medicine Initiative (PMI), also known as "All of Us," was announced by President Obama in 2015, with the aim of enrolling over 1 million people. Participants share their data generated over 20 years through sequencing, electronic media records, and digital health technologies, which are then used for analysis to obtain an understanding of disease and pathology and precision-driven health care for individual patients. The PMI also contributes to healthcare and enhances precision medicine being used from reproductive counseling and prenatal testing at conception to healthy aging and a molecular autopsy at death.[3,4]

The PMI has helped upcoming scientists and researchers find innovative ways to detect, measure, and analyze large biomedical information, including molecular, genomic, cellular, clinical, behavioral, physiological, and environmental parameters. The launch of the PMI also caused a change in the cost of medicine and increased DNA sequencing. Other technology platforms that are genome-based are used for disease state classification and predicting

clinical outcomes. This formed the basis for a new molecular taxonomy of disease, providing more accurate ways to screen and predict disease preclinically, and utilizing the genetic variations of the patient, selection of the drug has to be guided. Digital and molecular profiling tends to shift healthcare strategies to focus on patient health and the prevention of disease. [5]

Two approaches used for understanding and analyzing precision medicine are omnics and electronic health records (EHRs). Omnics is the comprehensive study of the roles, relationships, and actions of various types of molecules in cells of an organism. It is classified into transcriptomics, proteomics, metabolomics, epigenomics, lipidomics, metagenomics, glycomics, connectomics, cell omics, and even foodomics, which are used along with pharmacogenetics to predict drug response in individual patients. EHRs serve as a clinician's key to all patient information, including genetic data, and provide clinicians and researchers with electronic clinical decision support (CDS) that provides information about genetic information through an e-resource or info-button. The CDS system guides clinicians through complex situations that take multiple patients' genetic information and helps to form a proper learning healthcare system.[6,7]

Clinical decision support (CDS) alerts clinicians about important information based on the medical history of a patient. The NCI-MATCH (Molecular Analysis for Therapy Choice) trial aims to improve patient outcomes by evaluating treatments for molecular abnormalities in cancer, and the Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial (ALCHEMIST) uses the concept to treat patients suffering from early-stage non-squamous NSCLC.[8]

**Precision medicine vs. personalized medicine**

Personalized medicine involves analyzing a patient's genetic information, and using diagnostic tests to identify medical treatments that may be effective for them. On the other hand, precision medicine takes into account molecular data to enhance the accuracy with which patients are diagnosed and treated. It encompasses various technologies beyond genomics, and clinical and molecular approaches, including patient engagement, digital health, and other molecular technologies. [9,3]

**Components of Precision Medicine Ecosystem**

The ecosystem of precision medicine involves a network connecting patients, researchers, and clinical laboratories. Electronic medical records (EMRs) and information technology (IT) systems support both research and healthcare systems, enabling the collection of more information from research participants and the sharing of their biospecimens. Precision medicine ecosystems also involve government sponsorship, industry partnerships, and society as enablers and policy analysts. These players contribute to the development of precision medicine.[3]

## AN OVERVIEW OF DISEASES

### LUNG CANCER

Lung cancer is one of the most deadly types of cancer and its death rate is more than that of other cancers of the colon breast and pancreatic. Non-small cell lung carcinoma (NSCLC) accounts for 85% of the total cases of lung cancer when compared to small cell lung carcinoma which accounts for 15%. NSCLC is again divided into squamous-cell carcinoma (25-35%), adenocarcinoma (40%), and large-cell carcinoma (5-10%).[10]

Adenocarcinoma is the most common type of cancer which occurs due to active or passive smoking. This type of cancer is found outside the lungs and spreads slowly. Large cell carcinoma occurs in patients who have a habit of smoking and starts in the central part of the lungs. Continuous exposure to gases, air pollution and family history contribute to the development of lung cancer.[10]

Personalized or precision medicine has helped to improve the survival rate of patients suffering from NSCLC. Mutations that were commonly observed included (KRAS) Kirsten rat sarcoma virus (KRAS, found in 24% of cases), epidermal growth factor receptor (EGFR, 17%), anaplastic lymphoma kinase (ALK, 3%), v-RAF murine sarcoma viral oncogene homolog B1 (BRAF, 2%), and c-ros oncogene 1 (ROS1, 1–2%).[11]

Surgery is one of the treatment options available for patients with stage I, II, IIIA NSCLC and which involves the surgeons removing the tumor from the lungs. Adjuvant therapy involves radiation, chemotherapy, and targeted therapies for resection therapy patients. and helps to reduce the relapse of cancer. Chemotherapy is given to patients suffering from

NSCLC stage IIA, IIB, and IIIA to prolong survival by remaining tumor cells. Radiotherapy damages the DNA present within the cells with the help of high-energy beams and helps to control/eliminate site-specific tumors in the body. This also helps patients who don't respond effectively to chemotherapy or surgery. Stereotactic body radiation therapy (SBRT) is a technique used in patients with early-stage NSCLC and it uses an advanced system to locate the tumor precisely and precise placement of tracking device.[12]

EFGR mutations occur in 10-35% of lung adenocarcinoma. Due to the mutations, constitutive activation of EGFR occurs due to stimulation of the proliferative signaling pathway. Three generations of tyrosine kinase inhibitors [TKIs] target mutated EGFR and include first-generation erlotinib and gefitinib, second-generation afatinib and dacomitinib, and third-generation Osimertinib (this is recognized as a go-to treatment for pretreated relapsed patients) The efficacy of these drugs by conducting clinical trials have proven that EGFR-TKI as the first-line treatment in EGFR-mutated stage IIIB and stage IV NSCLC and are less certain EGFR-TKI in adjuvant in stage II and stage IIIA.[12,13]

ALK gene rearrangements result from fewer mutations and result in chimeric protein (EML4-ALK) with constitutive ligand-independent tyrosine kinase activity. Crizotinib is developed as a specific agent against chimeric EML4-ALK protein. Newer generation ALK-TKI includes ceritinib, alectanib, and lorlatinib to treat tumors with acquired resistance to crizotinib. Other second and third-generation ALK inhibitors have shown improved CNS penetration with evident supporting superior outcomes. According to the ALEX study alectinib along with crizotinib as the first-line therapy and alectinib is associated with long median PFS and CNS progression time. ROS1 gene rearrangements occur for 1-2% of NSCLC and were also found in younger patients with a history of adrenocarcinoma but have minimal exposure to smoking. Due to the structural homology to ALK protein crizotinib and ALK-TKIs show activity against NSCLC with ROS1 rearrangements.[13]

KRAS mutations are among the most occurring types of oncogenic driver mutations and account for 25-34% of adenocarcinomas and 3-6% of squamous carcinomas. There are no specific treatments available and the recommended therapies available are similar to NSCLC without the identifiable driver mutations.[13]

BRAF mutations are observed in 1-2% of lung adenocarcinomas and V600E mutations are the common type of BRAF mutations. A combination of dabrafenib and trametinib (BRAF

inhibitor, MEK inhibitor respectively) was investigated in BRAF-positive NSCLC. In a study that involved 36 patients with metastatic BRAF V600E mutant lung cancer, partial or complete response was seen in 64% of the population.[13]

In immunotherapy, in NSCLC PD-1 and PD-L1 can be targeted with immune checkpoint inhibitors. These drugs have been investigated in all NSCLC subtypes and in first, second-line, and adjuvant therapy. Monoclonal anti-PD1 antibodies such as nivolumab, pembrolizumab and anti-PDLI antibody atezolizumab have been investigated for the treatment of NSCLC. Studies such as CheckMate-017 and CheckMate-057 have shown the use of second-line nivolumab in metastatic squamous and non-squamous NSCLC. Pembrolizumab is the first-line treatment for advanced-stage NSCLC. Another PD-L1 inhibitor durvalumab shows benefit in survival as adjuvant therapy. Small cell lung cancer (SCLC) therapy has developed slowly and the first-line standard therapy includes a combination of platinum with etoposide chemotherapy. Other drugs such as nivolumab, ipilimumab, pembrolizumab, durvalumab, and other immune checkpoint inhibitors have also been studied for SCLC.[13]

## DENTISTRY

Dentistry in precision medicine focuses on a way to identify possible ways to deliver personalized treatment for dental problems like tooth loss, oral cancer, and malocclusion.[14]

### Periodontal application:

Periodontitis is a polymicrobial infection that is largely preventable but can ultimately lead to loss of teeth. Periodontitis can vary due to genetic factors and elevated levels of interleukin-1 which is a proinflammatory cytokine and the presence of the IL-1 shows higher incidence and severity of the periodontal disease. IL-1 plays a role in bone reabsorption and has a role in the pathogenesis of periodontal disease. A commercial genetic susceptibility test under the name PerioPridict is used for periodontal disease that calculates the IL-1 levels.[14, 15]

### Dental caries

Dental caries or tooth decay is a common problem amongst children which is caused by the acids produced by the bacteria cause demineralization of tooth enamel, dentin which is present in the sugars present in the food which is the main source of energy for bacteria and it

ultimately may lead to loss of the tooth. Factors such as concentration of fluoride, salivary composition, oral care hygiene, and immune response affect dental caries. Research has shown that dental caries can be determined by genetic factors like a defect in the KLK4 gene which is responsible for enamel maturation, a mutation in single nucleotide polymorphism of Amel X which codes for enamel development, AJAP1 influences tooth development.[14, 15]

**Oral cancer**

Oral cancer is a common type of malignant cancer under the neck and head cancer caused due to tobacco, alcohol consumption, or HPV (human papillomavirus) infection. Squamous cell carcinoma (SCC) which constitutes about 90% followed by oral cancer in the tongue and floor of the mouth which constitutes up to 50% which is again followed by gingival, palatal mucosa, and buccal. The specific antibodies are produced to serve as a part of the immune reaction against the cancer-specific antigens which can serve as an early detection of head and neck cancer.

According to some articles it has been given that the detection of change in the chromosomal region can help in the cancer diagnosis. It has been given that in the chromosomal 3q26 region which consists of hTERC and SOX2 genes can serve as early detection for squamous cell carcinoma. It was also given that MYC and WISPI genes can serve as a diagnosis for tumors on the floor of the mouth.[16,17]

Treatment of oral squamous cell carcinoma (OSCC) is based on the stage of cancer when diagnosed. Targeted therapies have been introduced that increase survival rate with reduced side effects and toxicity which include cetuximab (monoclonal epidermal growth factor receptor [EGFR] antibody), bevacizumab (monoclonal vascular endothelial growth factor [VEGF] antibody), and rapamycin (mTOR) inhibitors. Monoclonal antibodies such as nivolumab, pembrolizumab which target PD-1(programmed cell death protein-1) are approved by the food and drug administration for recurrent/ metastatic head and neck cancer.[16,17]

**PARKINSONISM DISEASE**

Parkinsonism disease is a neurodegenerative disease that involves multiple motor and neuromotor circuits and is characterized by two pathological conditions; premature selective

loss of dopamine neurons and accumulation of Lewy bodies, which is composed of α-synuclein. It is also characterized by the early death of dopaminergic neurons in the substantial nigra (sNpc) and the widespread presence of α- synuclein(asyn). Dopamine deficiency can also lead to bradykinesia, tremor, rigidity, and later postural instability. Parkinsonism disease was previously considered as a sporadic disorder and the risk factors included environment and age factors. But it was found out that 15% of healthy patients and 5-10% of the patients followed the Mendelian inheritance pattern.[19]

Several genes such as SNCA, LRRK2, VPS35, PRKN, PINK1, GBA, and DJ-1 were linked to typical parkinsonism disease. But different alterations may be present in the same gene, for example, some point mutations in LRRK2 can be a cause for PD, while coding polymorphisms in the gene can be a strong risk factor and additional higher frequency variants at the LRRK2 locus contribute to the risk of developing PD.[18,19,20]

Also, it has been shown that mutations in arylsulfatase (ARSA) are linked to Parkinson's disease. Mutations in LRRK2 account for 5-15% of autosomal dominant Parkinsonism disease and 1-3% of sporadic Parkinsonism disease.[18,20]

Major risk factors for Parkinsonism disease are GBA (glucocerebrosidase) mutation, located on chromosome 1(1q21) which encodes glucocerebrosidase a lysosome enzyme involved in the metabolism of glucosylceramide. Mutations in the gene are said to increase the incidence of Parkinsonism disease in patients with Gaucher's disease and healthy patients and constitute 2-30% of PD patients.[21]

The pharmacogenomics of PD deals with the genes associated with dopaminergic activity, dopamine receptors, transporters, enzymes, and the genes involved in neurotransmission that influence the PD drug response.[19]

Age is also a factor that influences precision medicine strategies. It includes genetic factors which include telomeres and telomere length as a biomarker of biological aging; comorbidity either present or not present; imaging biomarkers include magnetic resonance imaging; DRT (Dopamine Replacement Therapy) related adverse events in younger patients and tolerability of DRT.

Another factor that affects Parkinsonism's disease is comorbidities. Examples such as severe hyperhomocysteinemia in levodopa therapy and risk of vascular dementia are associated with the cerebrovascular system so the appropriate strategies given are vascular risk factor management and the monitoring of plasma homocysteine levels in high levodopa patients. Another example involves the risk of cardiac dysrhythmia in the cardiovascular system and the personalized medicine strategy suggests avoidance of drugs that may increase the QTc interval and hyperthyroid, hypothyroid, diabetes, and testosterone deficiency is seen in the endocrine system, and accordingly the personalized medicine strategy is used.

Different biomarkers such as imaging, genetic, clinical can be used as an identification of neurotransmitter dysfunction-based syndrome, for example for cholinergic the neuromotor syndromes are park-cognitive which includes MCI, Apathy which can be both dopaminergic and cholinergic, RBD, postural instability. The clinical indications were high risk of dementia, cognitive dysfunction in patients. Cognitive decline, counselling-based lifestyle, and combining both DRT and cholinesterase inhibitor therapy were the suggested personalized treatment strategy. Similarly for noradrenergic, the clinical neuromotor syndromes involved park-autonomic, and symptoms were observed as pneumonia, poor DRT oral absorption. The personalized medicine strategy was given as non-oral DRT therapy, dietary and nutritional advice, and supplementation of DRT therapy with conventional management of postural hypotension and if the patient has osteoporosis, extra precaution must be taken for non-motor fall prevention.[22]

**ALZHEIMER DISEASE**

Alzheimer's disease (AD) is a progressive and neurodegenerative disorder that is characterized by several hallmarks such as extracellular deposition of amyloid-beta (Aβ); neurobillilary tangles (NFT) which are intracellular aggregates of tau proteins; neurodegeneration. Alzheimer's disease can be identified with the use of several biomarkers such as cerebrospinal fluid biomarkers in which the low amount of Aβ and a higher amount of total tau and phosphorylated tau (P-tau) proteins serve as an indication for AD. Positron emission tomography (PET) is a neuroimaging method in which cerebral activity and Aβ accumulation are studied with the help of radiotracers.[23,28]

This PET- Aβ is used to estimate the fibrillary form of accumulated amyloid-β Also in the PET technique, C-PIB is used as an amyloid-β marker as AD patients show a higher rate of

retention of 11C-PIB in the cortical regions. Along with these AD biomarkers also include protein, an inflammatory cytokine, proteolipid, chemokine, carbohydrate, and microRNA(miRNA). These biomarkers are helpful in the detection of illness and allow clinicians to monitor the responses of the AD patient. Advanced AD biomarkers include use of exosomes and extracellular microvesicles (EXs and EMVs) which contribute to the diagnosis of AD.[26, 27, 30]

Late-onset AD (LOAD) is caused due to complex genetic factors and it accounts for 95% of AD cases. Several common and rare genome-wide significant susceptibility (GWS) loci along with apolipoprotein E polymorphism are associated with LOAD. Early-onset AD (EOAD) is caused due to mutations in amyloid precursor protein (APP, located at chromosome region 21q21.2), presenilin 1 (PSEN1, located at 14q24.3), and presenilin 2 (PSEN2, located at 1q42.13).[27,31]

Genetic variations have been accounted for in the onset of EOAD and LOAD. Along with the three genes, researchers have identified about 21 genes that are a risk factor to AD out of which TREM2 has a role in increasing the risk of developing LOAD.[32]

The risk factors of Alzheimer's disease have helped to develop its preventive measures and some of these include diabetes, stress, oxidative stress, hypercholesterolemia, atrial fibrillation, alcohol, and smoking.

Diabetes type 2 there is an accumulation of Aβ and hyperinsulinemia due to the decrease in insulin signaling which tends to decrease in the production of the insulin-degradation enzyme. Hypertension may also lead to increased Aβ accumulation and tends to reduce the blood-brain barrier (BBB) vascular integrity and protein extravasation in brain tissues. Obesity and oxidative stress can also lead to a high risk of AD. In obesity, a high rate of cholesterol and saturated fats can enhance the risk of AD. Physical activity has been considered a strategy to treat different stages of AD. Physical activity tends to increase the production of neurotrophic factors such as brain-derived neuroprotective factor (BNDF). Also, physical exercise helps to increase and reduce the protein damage and also decreases the tumor necrosis factor-alpha (TNF-α), interleukin-1 alpha (IL-1α) and ultimately decreases the amyloid-β produced neuroinflammation of the brain and results in a positive effect on the brain.

The available pharmacotherapies suggest the use of acetylcholinesterase inhibitors and N-methyl-D-aspartate glutamate antagonists (NMDA antagonists). The acetylcholinesterase inhibitors act by reducing levels of amyloid β protein precursors, their production, and accumulation. Four acetylcholinesterase inhibitors namely tacrine, rivastigmine, donepezil, and galantamine are used in the treatment of AD. Memantine is an NMDA receptor blocker that is used for moderate to severe AD.[23]

## CYSTIC FIBROSIS

Cystic fibrosis is an inherited disease caused by mutations in CF transmembrane conductance regulator (CFTR). This causes impairment of CFTR mRNA and protein expression, function, and stability. CFTR mainly functions as a chloride and biocarbonate channel and functions by controlling the movement of fluid in and out of epithelial cells which line the respiratory tract, biliary, intestines, sweat ducts, and pancreatic ducts. Failure of the CFTR causes altered composition and amount of exocrine secretion which causes the formation of thick, hyper-viscous mucus which tends to obstruct sensory organs such as lungs, liver, pancreas, and increased amount of chloride in sweat. This inflammation, chronic infection can be a cause of death among patients.[30,31,33]

Over 1900 mutations in the CFTR gene have been identified and are classified into five types based on the effect of the mutation on the gene. Class I mutation results in deficient CFTR protein synthesis caused by a stop codon in the non-sense mutations. It also results in altered RNA processing. Class II mutations result in protein folding and cause the CFTR gene to get degraded before it reaches its functional site on the cell membrane. This mutation includes F508del leading to folding and maturation defects. Class III mutations result in nonfunctional CFTR protein which reaches the cell membrane and does not allow the movement of anions, and these are called gating mutations. Class IV and V either result in reduced chloride conductance through the reduced CFTR protein in the cell membrane or CFTR channel. Mutations of class I, II, and III are usually of classical and severe forms, and mutations of class IV, V, and VI are of a milder type and cover up to 5% of the CF-causing mutations. Out of the mutations of CF, F508del is the most occurring mutation which affects 82% and it leads to the CFTR protein mutations being degraded by proteosomes.[31,32,30]

Ivacaftor, a potentiator, was approved by the FDA as the first CFTR molecule that increases the activity of CFTR in the cell membranes. Long-term use has been associated with a

decreased need for a lung transplant and improved survival, along with less detection of pseudomonas aeruginosa and an increased chance of survival. Tezacaftor, a second-generation CFTR corrector shown to have improved tolerability when compared to lumacaftor, when it is used along with a combination of ivacaftor. In 2018, the combination of tezacaftor which is a corrector which has functions similar to lumacaftor was used with ivacaftor as a combination for the treatment of patients with two copies of Phe508del, along with patients carrying one of the 26 other ivacaftor-responsive CFTR mutations.[30,32,31]

## CONCLUSION

Precision medicine now is used to increase the lifespan of the patient. With the help of different methods of identification of genomic changes that help identify the causes of various diseases and also help to identify the possible treatment for the disease and in the future precision medicine can help to find the underlying cause and interconnection of the disease to the various factors associated with it. According to articles, CSER2 (Clinical Sequencing Evidence-Generating Research Consortium) aims to support the future discovery and interpretation of genomic variants and ensures that these discoveries are connected with the clinical medical practice. Along with these, IGNITE i.e., Implementing Genomics In practice projects improves investigation, development, and dissemination of genomic data and it also includes integration of genomic data into electronic health records of patients to allow creation of diagnostics and treatment of patients.

## ACKNOWLEDGEMENT

The authors thank the management and officials of G Pulla Reddy College of Pharmacy for providing us with all the facilities for the successful completion of the review article.

## CONFLICT OF INTEREST

There is no conflict of interest.

## ABBREVIATIONS

**PM**: precision medicine; **EHR**: electronic health records; **SNP:** single nucleotide polymorphism; **CNV**: copy number variations; **PMI**: precision medicine initiative; **CDS**: clinical-decision support; **NCI-MATCH**: Molecular Analysis for Therapy Choice;

**ALCHEMIST**: Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trial; **NSCLC**: non-small cell lung carcinoma; **EMR**: electronic medical records; **IT**: information technology; **KRAS**: Kirsten rat sarcoma virus; **EGFR**: epidermal growth factor receptor; **ALK**: anaplastic lymphoma kinase; **BRAF**: v-RAF murine sarcoma viral oncogene homolog B1; **ROS1**: c-ros oncogene 1; **SBRT**: Stereotactic body radiation therapy; **TKIs**: tyrosine kinase inhibitors; **EGFR-TKI**: epidermal growth factor receptor- tyrosine kinase inhibitors; **EML4-ALK**: echinoderm microtubule-associated protein-like 4- anaplastic lymphoma kinase gene; **PFS**: progression free survival; **CNS**: central nervous system; **MEK:** mitogen-activated protein kinase kinase; **PD-L1**: programmed death-ligand 1; **PD-1**: programmed cell death protein 1; **IL-1:** Interleukin-1; **KLK4:** Kallikrein Related Peptidase 4; **AJAP1:** Adherens Junctions Associated Protein 1; **SCC:** squamous cell carcinoma; **HPV**: human papillomavirus virus; **hTERC:** human telomerase RNA gene; **OSCC:** oral squamous cell carcinoma; **VEGF**: monoclonal vascular endothelial growth factor antibody; **mTOR:** Mammalian target of rapamycin; **sNpc:** substantial nigra; **asyn**: α- synuclein; **ARSA:** arylsulfatase; **GBA**: glucocerebrosidase mutations; **PD:** parkinsonism disease**; DRT:** Dopamine Replacement Therapy; **MCI** :Mild cognitive impairment; **RBD**:Rapid eye movement (REM) sleep behaviour disorder; **AD:** Alzheimer's disease; **Aβ** amyloid-beta; **NFT**:neurobillilary tangles; **P-tau:** phosphorylated tau; **PET:** Positron emission tomography; **EXs:** exosomes; **EMVs:** extracellular micro-vesicles; **LOAD**: Late-onset AD; **GWS**: genome-wide significant susceptibility; **EOAD**: Early-onset AD; **PSEN1**:presenilin 1; **PSEN2**: presenilin 2; **BNDF:** brain-derived neuroprotective factor**; TNF-α:** tumor necrosis factor-alpha**; IL-1α:** interleukin-1 alpha**;** **NMDA:** N-methyl-D-aspartate glutamate antagonist; **CFTR:** CF transmembrane conductance regulator; **CF:** cystic fibrosis; **CSER2**:Clinical Sequencing Evidence-Generating Research Consortium; **IGNITE:** Implementing Genomics into Clinical Practice.

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