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PRECISION MEDICINE IN TREATMENT OF NON-COMMUNICABLE DISEASES AND CANCER

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Abstract : Most deaths and disease burdens are caused by non-communicable diseases (NCDs). The primary cause of NCD-related deaths worldwide is cardiovascular disease (CVD), which is followed by various cancers, chronic obstructive pulmonary disease (COPD), and diabetes. To achieve the 25% reduction in NCD mortality target set by the World Health Organization (WHO) and the United Nations by 2025, many communities must embrace preventive measures. The purpose of the precision medicine approach is to provide patients with a better therapeutic goal to maximize benefits and minimize risks. The clinical advantages of this strategy are already evident in cancer targeted therapy, but additional research on its effects on other illnesses is required in many countries. In this review, we primarily discuss the idea of precision medicine in relation to NCDs and its potential for prediction, prevention, and individualized care.

IndexTerms **- Precision medicine, non-communicable diseases, type 2 diabetes, chronic obstructive pulmonary disease, cardiovascular diseases, cancer.**

1. Introduction

The practice of using cutting-edge molecular profiling in conjunction with more conventional techniques, for example, family history, to develop therapeutic and diagnostic approaches that are precisely tailored for each patient's needs is known as precision medicine, also known as precision medicine or individualized medicine. just genomic analysis, such as exome sequencing or genotyping, is heavily used for patient treatment, even though numerous molecular-profiling techniques accessible in research environments. This study discusses genomic databases that enable a contemporary precision medical practice that incorporates genomic data. specifically, the use of germline (rather than somatic) DNA to supplement a previous perspective paper on pharmacogenetic testing in primary care settings.[1]

In the past, diagnosing disease was done based on symptoms that may be caused by several different conditions. Because we can now test for genes known to be associated with the disease, several diseases can now be diagnosed with greater accuracy. This approach can precisely identify the subtype of the disease in addition to confirming the presence of a specific disease. The majority of medical practice throughout history has been reactionary. Even today, we have to wait until a disease manifest before attempting to treat or cure it. Because we are still learning about the genetic and environmental elements that contribute to the development of serious illnesses like cancer, Alzheimer's disease, and diabetes, our efforts to treat them are frequently erratic, unpredictable, and inefficient. [2]

It entails clearly defining drugs within the context of treatment that is customized for a specific patient, but it may also entail grouping people into stratified subpopulations that have different health statuses or treatment responses.[3]

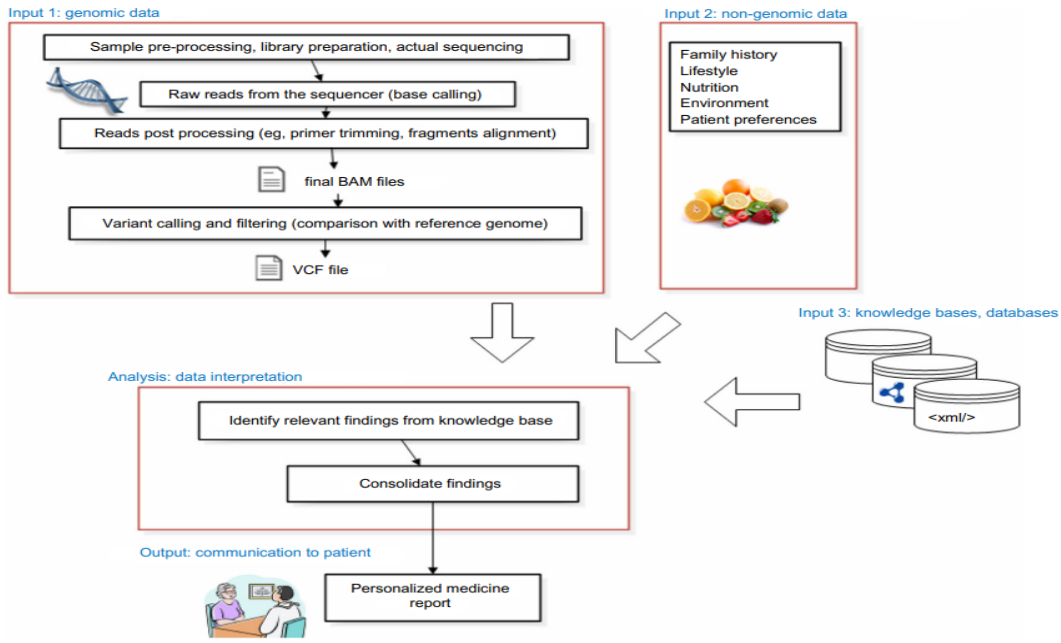

Fig. 1: Data flow in Precision medicine. [137]

Abbreviations: BAM -binary alignment/map,VCF- variant call file.

Maximizing treatment effectiveness and reducing the risk of drug toxicity for a specific patient are the two main objectives of Precision medicine. It demonstrates the proper use of pharmaceuticals with the appropriate patient, dosage, and timing. Individualized pharmacological therapy based on each patient's genetic makeup and molecular diagnosis is Precision medicine's main goal. Precision medicine's main promise is that genomics will increase the target selectivity of pharmaceuticals, the selection of volunteers and patients for clinical trials, and consequently the likelihood that many therapies will be effective for populations and individuals. This study's primary objective is to assess customized medicine in terms of its applications, advantages, drawbacks, and potential effects on healthcare. Actual clinical applications as well as perspectives for the future. With Precision medicine, illnesses can be predicted, prevented, and treated specifically for each patient's needs. Development of effective clinical diagnostic tools, high-throughput genome-wide screening for susceptibility to or protection from complex medical conditions, evaluation of a person's genomic profile for disease prediction/prevention, and the creation of vaccines and novel medications have all resulted from translational genetics and genomics research.[4]

2. Present and Future of Precision Medicine

A medical concept known as precision medicine suggests treating a person according to their genetic make-up. To determine a patient's genetic makeup, a variety of proper diagnostic tests must be performed on the patient. Molecular diagnostics, imaging, and analytics are just a few of the techniques used in precision medicine. Although there is no single, accepted definition of "precision medicine," the US National Institutes of Health's (NIH) definition is probably the most widely used. It describes the field as "an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person." This is occasionally used interchangeably with personalized medicine or tailored care.

Precision medicine is "an approach to disease treatment and prevention that seeks to maximize therapeutic effectiveness by taking into account the individual genetic, molecular, environmental, and lifestyle differences," according to the Precision Medicine Initiative Working Group of the National Institutes of Health.

Only about 40% of the medications we recommend are believed to be suitable or beneficial for the people in question. We currently conduct trial-and-error medicine, which ignores the individual variability that accounts for the variations in how well the effects of the pharmaceuticals vary from person to person. Instead of only treating the symptoms of an illness, precision medicine looks at its underlying causes. It considers the individual variation in genes, environment, and lifestyle for each person, as well as genotypic and phenotypic aspects. As a result, it uses focused therapy and is involved in finding relevant biomarkers. Every person is an island, and now that the molecular intricacy of disease has been uncovered, the contributions of genetics, environment, and epigenetics are blatantly informing us that every patient has to receive care tailored to their specific physiology and body type.

Numerous targeted medicines only function on individuals who have a certain genotype or genetic mutation; as a result, specific patients must be thoroughly evaluated before the therapy is recommended. Genetic testing is used to identify changes in chromosomes or genes in a variety of clinical and non-clinical contexts, such as diagnostic, predictive, and presymptomatic testing, carrier screening, preimplantation genetic diagnosis, prenatal screening, new-born screening, pharmacogenomic testing, etc.

A paradigm change in medicine has occurred with the introduction of precision medicine. With its help, specific treatment plans can be adapted for individual patients based on their genetic makeup. Thus, patients can take safe and effective medications. It prevents the needless administration of medications that may not only be ineffective in a certain patient but also endanger him or her. Healthcare professionals can customize therapy by changing the dose or medicine for each unique patient thanks to pharmacogenomic testing. Pharmacogenetics offers data that can be used to forecast how a person will react to the medication. Pharmacodynamics and pharmacokinetics are impacted by changes in specific genes. It is feasible to identify patients who are more prone to experience pharmacological side effects or who are more likely to not respond by noticing these changes. Pharmacogenomic testing enables medical professionals to customize therapy by changing the dosage or medication for each patient.

Only 30 pharmacogenomic medications that have been licensed for use in oncology as of today are helping the few patients who have cancer. Intratumor heterogeneity and poorly known resistance mechanisms also restrict the efficacy of these medications. Clinicians consider significantly more time to have passed between getting a patient's biopsy and beginning customized cancer treatment. Patients and doctors would both accept a 10- to 14-day delay in the start of tailored treatment. The situation is rapidly changing, and the adoption of Next Generation Sequencing (NGS) technology in the clinical setting has encouraged the creation of new laboratory best practices and standards for the generation, processing, and exchange of NGS data. These efforts have been made by numerous organizations and groups all over the world, and as a result, a large number of partially overlapping guidelines have been published. Some of these guidelines are very general, while others concentrate on particular diseases or steps in the process, such as providing patients and clinicians with results or creating specific bioinformatic pipelines for NGS data analysis. By lowering the price of hospital stays and the overall financial, physical, and psychological expenses of the trial-and-error method of medicine, precision medicine may provide a solution. It is comparable to the government of India's direct benefit transfer (DBT) program, which transfers subsidies directly to the linked bank accounts of intended individuals through the use of Aadhaar biometrics to achieve precise and targeted benefit delivery without any negative side effects or waste of tax dollars. Similar to this, precision medicine delivers the intended therapeutic drug directly to the targeted cells or tumor without causing collateral damage to normal cells or tissues, dramatically lowering morbidity and mortality. By implementing tailored therapy with a public health strategy, advancements in precision medicine are anticipated to benefit the health of the general population.

Precision medicine will use technology that goes beyond genes and disease. A new era of precision public health is being ushered in by the same technologies and big data that are advancing precision medicine. When it comes to public health, using techniques and technology to research different diseases, their infections, and their vulnerability at the community level will aid in creating accuracy in disease prevention. As the cost of genetic sequencing and data decreases over the coming years, precision medicine will overtake conventional medicine as the primary mode of therapy. Artificial intelligence (AI) will further change it by doing algorithm analysis and decision-making for the best drug selection, for more effective drugs, for a large number of patients in less time. This will make precision medicine genuinely a personalized treatment. In the meanwhile, nations must develop comprehensive and all-encompassing enabling legislation for DNA usage policy. Precision Medicine Initiative (PMI) [1] was previously launched in the US in 2015; it has subsequently been renamed "All of Us" to broaden its scope through federal financing and the involvement of numerous reputable universities. Similar efforts to develop more precise therapies have been made in the UK through the Medical Research Council's Stratified Medicine Initiative and significant collaborations between businesses and the country's National Health Service. These investments serve as a reminder of how precision medicine holds the potential to transform numerous other areas of medicine over the next several decades. Since malnutrition and poverty are two of the leading causes of death in a nation like India, the drive for precision medicine may be seen as an overly ambitious undertaking. However, a large number of inherited diseases are prevalent in this diversified nation, which has about 4000 different population groupings and a high proportion of consanguineous marriages. These diseases are caused by distinctive genetic traits in the subpopulations. With 1.3 billion people, there are a disproportionately high number of patients with genetically based disorders. India may seem perplexing to an outsider due to its disparate populations of billionaires and multimillionaires, underdeveloped infrastructure, top-four ranking in the fields of space and nuclear science, production of the greatest number of physicians and paramedics in the world, and state-of-the-art medical facilities, but people in rural areas cannot afford quality health care. Add to this the youthful middle class that is just beginning to emerge. The political leadership in India now, unlike in the past, is leapfrogging by making quantum leaps rather than small steps in all areas of growth. The Indian Prime Minister has declared that his country will make every effort to pass a complete DNA law after learning about the Precision Medicine Initiative. India will succeed in this area with perfection. Imagine that a patient undergoes a blood or saliva test at a lab and that at the ensuing appointment, his or her doctor is well-prepared with the medical horoscope, which includes information on chemical compounds or combinations of drugs that may be beneficial to or harmful to the patient, based on the reliable results of a genetic test. Although still in its infancy, precision medicine is being used in India in several medical disciplines, including oncology, cardiology, psychiatry, and diabetology. Oncology, however, appears to be the field where precision medicine is most progressed. To produce, share, and store the data necessary for precision medicine, infrastructure that uses high throughput computing systems is needed. Investment is also necessary for educating the general population, insurance providers, and medical professionals. Precision medicine cannot be achieved until appropriate training is provided to diverse stakeholders and transdisciplinary research is promoted or carried out.[5]

3. Advantages of Precision Medicine

1. Lower medical expenses
2. There will be a larger likelihood of achieving the intended results because of improved targeted therapy.
3. Place more emphasis on disease prediction and prevention than on disease response.
4. It is possible to lower the likelihood of adverse side effects.
5. Compared to the past, disease intervention will occur sooner.[6]

4. Disadvantages of Precision medicine

1. Huge data needs to be collected from the patient
2. The patient has to be aware of the family history
3. Time-consuming.[7]

Table 1: Precision Medicine Versus Traditional Medicine.[8]

Precision medicine	Traditional medicine
Liquid biopsy: non-invasive and captures more cancer characteristics that are not limited to a single area of the body	Prevents side effects, forecasts dosing, and boosts compliance Biopsy of a tumour: • invasive and does not capture cancer's heterogeneity • cancer metastasizes to only one area of the body
Individualized and genetically targeted medicine	Finding the right medication requires trial and error.
Identify patients who are most likely to respond to clinical trials.	Clinical trials' one-size-fits-all approach
Prevents side effects, forecasts dosing, and boosts compliance	A large percentage of patients do not benefit

5. Precision Medicine Used In Non-Communicable Diseases

The most common cause of death worldwide is non-communicable diseases (NCDs), including cancer, cardiovascular diseases (CVDs), type 2 diabetes mellitus (T2DM), and chronic respiratory diseases (CRDs).[9] NCDs cause more than 36 million deaths each year, or 63 percent of all fatalities worldwide.[9,10] Preventing premature death from the four major NCDs(malignancies, CRDs,CVDs, and diabetes) up to 25 percent relative to 2025, World Health Organization (WHO) produced a global NCD action plan with nine targets.[11] Considerable progress in medical practice is now possible because of significant advances to the basic science and the publication of human genome project data. Over the past ten years, hundreds of genes have had mutations that contribute to human disorders. Precision has always been a goal in medicine. Many doctors and academics have used the phrases "personalized," "precision," "stratified," "individualized," and "P4 medicine" interchangeably.[12] Precision medicine, often known as personalized medicine or tailored medicine, is not a recent development.[13] A novel taxonomy in the framework of In addition to the traditional signs and symptoms, precision medicine describes common diseases based on their molecular profile.[14] Precision medicine a new strategy to prognosis, early detection and therapy which considers each person's unique gene diversity. As soon as omics (genomic, transcriptomic, proteomic, and metabolomic) profiles are used to create tailored assessments of health and disease, this field of medicine is known as precision medicine.[15,16] When it comes to cancer, Precision medicine(PM) is far more popular than when it comes to diabetes, where omics sciences support personalized treatment.

Diabetes and cancer have very different genetic architectures because Both types of diabetes have genetic causes—type 1 (T1D) also type 2 (T2D) are germline mutations that have only a minor impact, whereas Cancer is caused by a specific somatic mutation in a specific cancer cell type.[15]

5.1 Precision medicine in type 2 diabetes

It is well acknowledged that diabetes poses a serious threat to human health on a global scale.[17] Therefore, it is vital to implement novel interventions that can predict and prevent diabetes. There is evidence to support the idea that prompt treatment is essential to preventing diabetes complications. Because of advanced diabetes's poor metabolic control, the current treatment guidelines are limited. Diabetes is a group of diseases that is far more diverse than the current classification of type 1 and type 2 diabetes. Even though it is related with insulin insufficiency , and increased blood glucose.

Clearly defined classification of diabetes, especially T2D, could be a powerful instrument to support the Precision medicine being used to improve diagnosis and to give treatment that works.[18] Five repeatable clusters of diabetes patients with varying Diabetic complications and disease progression were found In 2018, a data-driven cluster study was carried out. With the help of this new stratification, early treatments might finally be tailored to patients who would benefit from them the most, paving the way for precision medicine in the treatment of diabetes.[19] The American Diabetes Association (ADA) moves away from protocol-driven guidelines and highlights the value of a patient-centered approach. Care that recognises and responds to each patient's distinct preferences, needs, and values have been referred to as patient-centered care. Therefore, whether expert opinion or data is used, all clinical decisions are guided by patient values.[20] T2D have recently been divided into several unique diagnostic kinds (type 2A and type 2B).[21] When a clinician must make treatment suggestions for a patient who may not meet the eligibility criteria utilized in the guidelines on which we rely By using an evidence-based approach, medicine's science and art may coexist.. As a result, we must examine medical practice from the perspective of precision-based medicine, a cutting-edge strategy for customizing a focus on disease prevention and treatment surroundings, genetic composition, and lifestyles.[22] The ADA guidelines offer guidance regarding when and how to modify recommendations for an individual, acknowledging that one size does not fit all.[20] a majority prevalent diabetes type, T2DM, is a heterogeneous, difficult condition where hyperglycemia is caused by both inherited and environmental factors, which is its main identifying feature.[23] Exome, candidate gene, linkage analysis, and genome-wide association studies have all been used to look for the pathophysiology of T2DM-related risk genes (GWAS).[24] In 2007, the first GWAS for T2D were reported.[25] Upon completion of the Human Genome Project and affordable ‘genotyping techniques’ produced first GWAS successes, There was eagerness that the use of genomics had a significant influence on decisions about risk assessment, diagnosis, stratification, prevention, and treatment based on genetic variability in each patient. More than 300 loci that are strongly linked with T2DM have been found by GWAS.[26] Despite several GWAS that encompasses thousands of individuals in their hundreds and demonstrate genome-wide relevance, most of the polymorphisms collectively have a small impact on T2DM predisposition and only represent 10% of overall disease risk.[26,27,28] Numerous GWAS loci linked to T2DM have an impact on the pancreatic islet-specific insulin production pathway. Several genome-

based omics technologies have been used to construct gene expression maps of human islets, and T2DM risk mutations have been found to reside in active islet enhancers. One of the melatonin receptors is encoded by the melatonin receptor 1B (MTNR1B) gene, which is located near one of these crucial areas.

An islet enhancer contains a binding site for neurogenic differentiation 1 (NeuroD1), and changes to this site affect the expression of MTNR1B.[29] The genome, transcriptome, proteome, and metabolome have all received extensive knowledge thanks to high-throughput technology. These omics methods can aid in the identification of T2D subgroups that share particular biological traits.[15] However, only monogenic forms of diabetes have seen clinical use of genetics yet.[30]

5.1.1 Type 2 diabetes pharmacogenetics

Currently, there are 12 classes of medications available for the treatment of T2DM (Table 1).[20] Metformin is typically recommended as first-line treatment along with lifestyle/behavioural therapy. Several months into the course of treatment, metformin and a combination of treatments plus one or more additional oral diabetes drugs will be started If metformin is not tolerated well or the Haemoglobin A1C (HbA1c) target is still not achieved. Genetic variables account for roughly 20–40% of the variance between an individual's drug response and metabolism.[31] The main goals of pharmacogenomics studies are the stratification of patients, It attempts to group patients depending on their clinical reaction to the relevant medication or its toxicity, such as drug development by identifying the specific targets that arise from the GWAS.[32] Two categories of genetic polymorphisms (Table 1), the typical genes used in pharmacogenomics impacting pharmacodynamics /pharmacokinetics, also risk genes of T2DM, have been documented for the efficiency of oral drugs used in diabetes.[33,34,35] Individual differences in therapy response are not taken into account by the most recent standards.

Table 2 : Pharmaceutically important target genes, associated pathophysiological T2DM processes, and antidiabetic drugs.[136]

Drug.	Pathophysiological pathway.	Drug examples.	Gene (s).
.Biguanides	Insulin signaling. Gluconeogenesis Inhibition.	Metformin.	SLC22A2, SLC47A1, SLC47A2, SLC29A4, PRKAA1, PRKAA2, EF2D, HNF1B, HNF4A, ABCC8, KCNJ11, GCK, CAPN10, SLC22A3, ATM, LC2A2, SP1, AP2, PPARA, STK11, MEF2A, ATE2-K, SRR, TCF7L2, WFS1, ENPP1, TCF7L2, SLC22A1,
.Sulfonylureas	Increasing secretion of insulin.	Gliclazide. Glyburide. Glimepiride. Tolbutamide. Glipizide.	KCNJ11, CDKN2A/2B, KCNQ1, CYP2C9, CYP2C19, G6PD, ABCC8, TCF7L2, IRS1, CDKAL1,
.DPP4-inhibitors	inhibition of glucagon secretion (Glucose-dependent) and Stimulation of insulin secretion.	Alogliptin. Sitagliptin. Linagliptin. Vildagliptin. Saxagliptin.	KCNQ1, PRKD1, TCF7L2, CTRB1, CTRB2, GLP-1R, CNTN3, ASK, OC10537792, CYP3A4, CYP2C8,
.Meglitinides	Insulin secretion Enhancement.	Nateglinide. Repaglinide.	CYP3A4, UCP2, PAX4, NEUROD1/BETA2, SLCO1B1, OATP1B1, CYP2C9, CYP2C8, KCNJ11, SLC30A8, NAMPT, OS1AP, UCP2, KCNQ1, TCF7L2, IGFBP2, MDR1, PAX4.
.Thiazolidinediones	Sensitization of Insulin.	Troglitazone. Rosiglitazone. Ciglitazone. Pioglitazone.	CYP2C8, CYP2C9, PPARG2, ADIPOQ1, CYP3A4, PTPRD, ACE, KCNQ1, RBP4, MTHFR, SLC30A8, ABCA1.
.SGLT2 inhibitors	Excretion of Renal glucose.	Dapagliflozin. Canagliflozin. Empagliflozin.	No gene was described due to not responding to relevant effects with respect to treatment
.α-glucosidase inhibitors	Inhibition of intestinal glucosidase Resulting glucose absorption Inhibition.	Miglitol. Acarbose. Voglibose.	PPARA, HNF4A, LIPC, PPARG, PPARGC1A,
.Glucagon-like peptide-1(GLP-1) receptor agonists	decrease of glucagon secretion from pancreatic α-cells and increase of glucose-stimulated insulin secretion, functional pancreatic β-cell mass	Exenatide. Albiglutide. Dulaglutide. Liraglutide. Lixisenatide.	CNR1, GLP-1 R,
.Insulin	Decreasing hepatic glucose production and Increasing glucose disposal.	Glulisine. Inhaled insulin Lispro. Aspart.	DBH, PNPLA3, GLP1R, COMT, TM6SF2, ACE

		Human. Regular. Detemir. Degludec. Human NPH. Glargine. Peglispro. Basal insulin.	
.Bile acid sequestrants	lowering Glucose (which not known) hepatic glucose production(HGP) Decreases.	Colesevelam.	No gene was described due to not responding to relevant effects with respect to treatment
.Dopamine-2 agonists	.modulating hypothalamic regulation of metabolism and Increasing insulin sensitivity	Bromocriptine.	No gene was described due to not responding to relevant effects with respect to treatment
.Amylin mimetics	promoting satiety, reducingthe postprandial glucagons increase and Slows gastric emptying,	Pramlintide.	No gene was described due to not responding to relevant effects with respect to treatment

5.2 Precision medicine in cardiovascular diseases

CVD continues to be the world's number one killer.[9] 10% of the world's disease burden is caused by CVD.[36] The leading global cause of death and a significant hindrance to human healthcare are CVDs. all heart and circulatory system diseases are referred to as cardiovascular diseases (CVDs), including those caused by atherosclerosis, ischemic heart disease (IHD), or coronary artery disease (CAD) (e.g., heart attack), diseases of the aorta and arteries, cerebrovascular disease (e.g., stroke), including peripheral vascular disease and hypertension, as well as other CVDs like coronary heart disease (CHD), also known as CAD.[36] The world has made headway in reducing lifestyle behaviours like smoking and poor eating. However, CADs are complicated diseases that are brought on by numerous genetic and environmental variables working together. Between 40% and 60% of CAD, cases are heritable, according to estimates.[37] Because CVDs are incredibly avoidable, investing in prevention is the most long-term way to combat the disease. Due to a mix of preventative and control strategies, the mortality rate from CVDs has decreased in developed countries during the past 20 years.[36] Hypertension is one of the risk factors for CVDs. Controlling hypertension is crucial to preventing fatalities from CAD and stroke.[38] For cardiovascular precision medicine, a modern "omics" approach is appropriate. GWASs have shown to contribute significantly to the discovery of genetic loci for numerous complex disorders since 2007. Chromosome 9p21's common single nucleotide polymorphisms (SNPs) were confirmed to be associated with CAD in the first GWASs of the disease, which were published in 2007. This locus continues to have the strongest known connection with CAD.[39] In numerous GWAS for CADs, nearly 163 loci have now been significantly and genome-wide linked with CAD.[40] The current approach to lowering cardiovascular morbidity and death in high-risk individuals is built on evidence-based medicine. Evidence-based medicine, Which uses a "one size fits all" treatment approach and only assesses a small subset of a patient's complaints, has been used in clinical care for decades. Instead of focusing on individual variations, this approach places more emphasis on the etiology and pathophysiology of the disease.[41] New developments in omics methods (genomics, transcriptomics, and proteomics) and DNA technology have shown a profound understanding that the conventional medical approach is unable to take into account all factors contributing to the cause of CVD. Large amounts of data produced by the omics approach have an impact on precision medicine's capacity, as well as by merging their data sets with those from conventional clinical exams. Prediction, prevention, and customized treatment choices are all being revolutionized by the development of CVD precision medicine, and this is especially true for oncology.[42] Precision medicine for CVDs differs from other disorders since Numerous chronic conditions like obesity, diabetes, and hypertension contribute to CVDs. As a simple example, consider blood pressure (BP) or blood cholesterol values. The genetic profile of each person determines whether to use antihypertensive medication or drugs to decrease cholesterol or triglycerides, which should be taken into consideration by clinicians. Nearly 40 genes have been identified as contributing to the genetic makeup of hypertension, and each of these genes has a negligible impact on blood pressure (less than 1 mm Hg), indicating that hundreds of different gene variations might have minor effects on blood pressure.[43] Consequently, a number of genetic variants have been linked to CAD and hypertension, but their effects are similarly rather small.[44] Most known risk alleles are probably close to a variations that could be causal but are not. CAD GWAS research has proposed a novel target therapy based on the guanylate cyclase 1 soluble subunit alpha 1 (GUCY1A1) ,proteins proprotein convertase subtilisin/Kexin type 9 (PCSK9), and angiopoietin-like 3 and 4 (ANGPTL3, ANGPTL4).[40] CVD stratification is the process of identifying a group of patients who will benefit from a specific intervention in customised care (e.g., CAD, heart failure, CHD, etc.), and it is the other aspect of CVD personalized medicine.[45] CVD pharmacogenomics has introduced several key groups of CVD pharmaceuticals, such as - lipid-lowering therapies, adrenergic receptor blockers, angiotensin-converting enzyme inhibitors and antithrombotic agents.[46] Although proof of precision medicine's effectiveness as a treatment option is needed before it can be widely adopted, The potential of precision medicine for CVD is to alter modern medical practises. Clinicians need to be aware that the information from the omics approach will result in a concrete step that alters the alternatives for standard treatment.

5.3 Precision medicine in chronic obstructive pulmonary disease:

The prevalent lung condition known as chronic obstructive pulmonary disease (COPD) is impacted by a number of complex genetic and environmental factors. Airflow restriction, airway remodeling, and chronic inflammation are the typical symptoms of COPD, one of the top five causes of death and morbidity worldwide.[47,48,49] same clinical signs including dyspnea, cough, and wheezing are caused by COPD, a disorder with substantial molecular and cellular changes.[50] Considering how serious the problem is and previous therapeutic choices, the “Global Initiative for Obstructive Lung Disease (GOLD)” therapeutic strategy for COPD was proposed.[47,51] Therefore, no helpful advice was confirmed except for using some short-acting bronchodilators and/or theophylline and convincing the patient to stop smoking, which was regrettably linked to serious adverse effects.[51] We have gained a lot of knowledge on COPD, which is a heterogeneous and complex condition with many different phenotypes and endotypes thanks to recent advancements in our

understanding of the disease over the past two decades.[51] Not every one of these factors is present in every person at the same time due to the heterogeneity of COPD, Despite the complexity of COPD, which indicates that a substantial number of intrapulmonary and extrapulmonary components with non-linear dynamic interactions exist in COPD.[47] Thus, clinical management may benefit from knowledge of the genetics of COPD, which focuses on providing individualized care for each patient rather than grouping patients based on a specific clinical presentation.[51] Given the individual heterogeneity in each patient's genes, environment, and lifestyle, it means that the existing "one-size-fits-all" approach to COPD management must be changed immediately.[52] The precision medicine project, which was started in 2015, has provided fresh information on precision medicine management strategies for a variety of diseases, including COPD.[47] Biomarkers are used to support precision medicine by identifying patient subgroups that are most probably to gain from therapeutic decisions and those that are only likely to experience harm (predictive biomarkers, response biomarkers, and separating people with relatively stable illness from those at risk of bad outcomes) (prognostic biomarkers).[52] Precision medicine methods enhance evaluation, therapy, and outcomes in the areas of COPD cause and presentation.[50] The care of COPD in the future will undoubtedly be much more individualized than the recent developments in precision medicine. Precision medicine is anticipated to provide greater opportunities for managing COPD through the use of predictive biomarkers.[53,54] Personalized medicine The base of the COPD pathobiological process demands the identification of linked endotypes, whereas the disease's complicated and variable presentation makes it difficult to identify phenotypes.[48]

5.4 Precision medicine in cancer

In the world, cancer is the second biggest cause of mortality, making it a serious issue. Six malignancies, including colorectal (862 000 deaths), lung (1.76 million fatalities), stomach (783 000 deaths), breast (627 000 deaths), liver (782 000 deaths), and prostate, account for the majority of cancer-related mortality.[37,55] Thyroid cancer also has distinct biological traits and prognostic factors from other types of cancer.[56] Understanding tumour genetics has advanced significantly since the completion of the human genome project, which has been used in the clinical practice of precision medicine.[57] However, the development of targeted treatments in oncology has given rise to a novel cancer therapy strategy with the greatest impact (Figure 1). Precision medicine for the most prevalent cancer forms is reviewed here. Decision support systems (DSSs), developed as a result of the growth of precision medicine, use predictive models to assist radiation and clinical oncologists in making better decisions.[58]

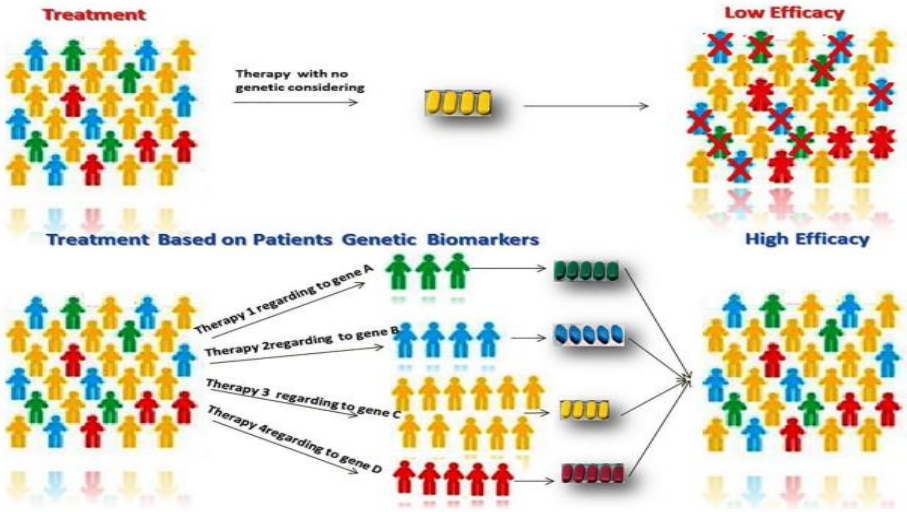

Fig 2: If patients are grouped according to their genetic data, cancer therapy may be more effective.[136]

5.4.1 Precision medicine in lung cancer

The most prevalent type of cancer worldwide, lung cancer has a high fatality rate in both sexes. The most advanced subtype of lung cancer, non-small cell lung cancer (NSCLC), accounts for 85% of cases and has a 5-year survival rate of less than 15%.[59] For patients with NSCLC stages I through IIIA, the conventional treatment options include extensive surgery and decisions depending mostly on the stage (extent) of the tumor[60] After that, adjuvant chemotherapy is used as part of the treatment plan in all resected instances other than stage IA.[61] Adjuvant chemotherapy using cisplatin is for individuals with stage II and stage IIIA NSCLC, the gold standard for entirely eliminating tumours is advised because it reduces the chance of non-brain metastases and local recurrence.[62] Additionally, individuals with two metastatic (N2) lymph nodes must have radiotherapy. Patients with advanced stage IIIB/IV or incurable NSCLC require multidisciplinary management with four cycles of cisplatin-based chemotherapy instead of a third-generation cytotoxic agent or a cytostatic (anti-vascular epithelial growth factor receptor (VEGFR) medication) therapy.[63] Before the precision medicine approach to cancer therapy, chemotherapy was administered to any patient with NSCLC, irrespective of histology or any additional genetic biomarker. The latest development in precision medicine is the combination of hereditary tumour data into potential patient diagnoses that have the lowest treatment toxicity and most treatment benefit.[64] For individuals with advanced NSCLC, anti-cancer medications like tyrosine kinase inhibitors (TKIs) and anti-EGFR are well-known treatments.[65] There are several classes of TKIs, including the most current one, osimertinib, whose effectiveness is reliant on the overexpression of the KRAS-like Kirsten rat sarcoma 2 viral oncogene or EGFR.[66] Now that the liquid biopsy technique has flourished, Using the plasma of cancer patients, it is possible to trace the tumour genetics and find the circulating EGFR mutation.. The first liquid biopsy test for NSCLC customized treatment approved by the U.S. Food and Drug Administration (FDA) is based on circulating-free tumor DNA EGFR mutation.[67] Additionally, it was demonstrated that cell-free DNA (cfDNA) and exosomal RNA (exoRNA) combined with standard circulating tumor DNA (ctDNA) improved the sensitivity of liquid biopsy for EGFR mutation detection in NSCLC alone.[68] Echinoderm microtubule-associated protein-like 4 (EML-4) and anaplastic lymphoma kinase (ALK) fusion, which is typically necessary for appropriate neuronal development and microtubule production, is another molecular route causing lung tumorigenesis.[69] Crizotinib is an ALK-

inhibitor that inhibits the activity of the 'EML4-ALK fusion protein's carcinogenic kinase'.[70] The alternative NSCLC treatment approach is based on FDA-approved monoclonal antibodies that traditionally target the interaction between the programmed death-ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) receptor.[71] Nivolumab, pembrolizumab, and atezolizumab are drugs that target the PD-L1 receptor and ligand.[72] Determining the levels of PD-L1 protein , Janus kinase 1 (JAK1), CD8, Janus kinase 2 (JAK2), and 2 microglobulins (B2M) expression is crucial for predicting the precise effectiveness of pembrolizumab in patients with NSCLC. Inactivating mutations in JAK2, JAK1, and B2M has been shown to reverse medication resistance in NSCLC patients, based on Zaretsky's research on patient models with pembrolizumab resistance.[73]

5.4.2 Precision medicine in colorectal cancer

Colon or rectum cancer, sometimes known as "colon cancer" or "rectal cancer," is also known as colorectal cancer (CRC). CRC is the second most prevalent cancer in women and the third most frequent in males.[74] CRC screening is an essential approach to find early-stage CRCs in older people and suspect cases with favourable family histories. However, 80% or more of CRC cases do not have a family history of the disease.[75] The most recent suggestion is to base the age at which CRC screening should begin on a person's lifestyle, environment, and genetics. utilising information from 14 population-based studies, Jeon et al. established this mode as the CRC risk prediction model using 63 shared genetic variants and 19 environmental and lifestyle factors that have been linked to the disease.[76] Additionally, Increased plasma levels of glypican-1 positive (GPC1+) exosomes and decreased expression of miR-96-5p and miR149 are diagnostic indicators for the diagnosis of CRC.[77] Regarding CRC treatment, two primary molecular pathways have been identified, with 85% of cases of chromosomal instability (CIN) and 15% of cases of microsatellite instability (MSI).[78] The use of molecular markers for precise CRC diagnosis and treatment has evolved as a result of genomics knowledge.

In reality, the primary cause of therapy failure for CRC may be the significant inter and intra-tumour heterogeneity.[79] To pick the targeted biological agents and spot CRC drug-resistant to the toxicity and effectiveness of particular medications, molecular testing should be carried out in clinical practice. Anti-EGFR monoclonal antibodies bevacizumab, cetuximab, aflibercept, regorafenib and panitumumab in combination with conventional fluoropyrimidines-based chemotherapy have been shown to improve the response rate and patient survival.[80] Additionally, the methylenetetrahydrofolate reductase (MTHFR) -1298 A>C (rs1801131) polymorphism may be a good predictor of stage II/III CRC patients' survival after adjuvant fluoropyrimidine treatment with or without oxaliplatin.[81] Inherited genetic modifications of the ATP-binding cassette (ABC) and solute carrier (SLC) drug transporter, as well as EGF and VEGF signalling pathways, have been linked to the patient's tumour sensitivity phenotype in CRC patients receiving fluoropyrimidines combined with either irinotecan or oxaliplatin therapy.[82] Nowadays, a reliable method of predicting tumour response to therapy involves computing clinical-pharmacogenetic algorithms that combine several SNPs with clinicodemographic landscapes.[83] In the treatment of CRC 5-fluorouracil and with platinum medicines, polymorphisms of the coding genes for dihydropyrimidine dehydrogenase (DPYD) and XPD (xeroderma pigmentosum complementation group D) are a key prognostic indicator.[84] Survivin, a member of the IAP (inhibitor of apoptosis) protein family that inhibits caspases and prevents cell death, may serve as a self-reflective prognostic factor and an appropriate target for 'CRC' patients undergoing chemotherapy and radiation treatment.[85]

5.4.3 Precision medicine in stomach/gastric cancer

Gastric cancer is another name for stomach cancer, is characterized as an aggressive, unchecked development of stomach cells. The third most frequent malignancy is stomach cancer -related cause of death worldwide and a disease that can be extremely deadly.[86] One of the challenges is that traditional diagnostic techniques are not as specific and sensitive as they should be for diagnosing stomach cancer. The early identification and individualised therapy of stomach cancer now have promising new opportunities because to recent advancements in biosensor technology.[87] Circulating tumor cells (CTCs), the main component of liquid biopsy, can provide a viable target for cancer detection using a nano biosensor device. Due to their properties that are similar to stem cells, CTCs may serve as a significant marker of gastric cancer stem cells.[88] CTCs were found in the peripheral blood, which demonstrated a clear correlation between the growth of secondary cancers and tissue metastasis.[89] CTCs or even 'one cell per 10 ml of blood' can therefore be a sign of a poor prognosis.[90] Molecular characterization of CTCs and their recruitment for individualized stomach cancer detection are both possible.[91] According to various research on the clinical effects of CTC, people with stomach cancer who have CTC may have a bad prognosis.[92] CTCs may serve as an alternative marker for assessing treatment response in individuals with advanced stomach cancer.[93] ACRG (Asian Cancer Research Group) presents a brand-new classification scheme based on MSI and gene expression profiles for various stomach populations.

Stomach cancer has four main molecular subtypes.: MSI, MSS/TP53 wild-type (MSS/TP53-), MSS/TP53 mutant (MSS/TP53+), and MSS/TP53 stable with epithelial- to- mesenchymal transition characteristics (MSS/EMT).[94] The molecular characterization of stomach cancer led to the identification of many subtypes, which included prognostic hypermethylated areas and new mutational signatures.[95] Despite the disease's early stages, the surgical approach seldom provides full recovery, and tumor recurrence frequently occurs.[96] multimodality therapy, target therapy and Chemotherapy are available treatment modalities for stomach cancer. The recommended first-line therapy for advanced stomach cancer with HER2-positive is trastuzumab (Herceptin®), a monoclonal antibody against 'human epidermal growth factor receptor 2' (HER2). However, There is no established second-line treatment therapy.[85] While many new drugs are still being researched for the treatment of gastric cancer, some ongoing clinical trials are presently focusing on cMET, STAT3, CLDN18.2, mTOR, and PD-1/PD-L1.[97] Pembrolizumab (KEYNOTE-012) was tested in a multicenter phase 1b trial and demonstrated significant decreases in a sample of patients with advanced gastric cancer that was PDL1-positive as determined by a prototype assay method.[98] Studies on the use of histone deacetylase inhibitor vorinostat in combination with radiotherapy to treat gastrointestinal cancer are examples of epigenetic targeting in cancer treatment.

5.4.4 Precision medicine in liver cancer

liver cancer, sometimes referred to as hepatic cancer, is one kind of cancer that originates in the liver cells or has metastasized there from another organ.[99] Although percutaneous liver biopsy is still a frequently performed diagnostic test, it has major side effects including bleeding after the biopsy.[100] Recent research suggested that hepatocellular carcinoma patients with next-generation sequencing of their cfDNA could receive a genetic analysis that could be used to guide their treatment (HCC).[101] A very diverse type of cancer is liver cancer, and this heterogeneity can be adjusted and refined to provide patients with individualized diagnoses and

treatments. By assessing the serum level of alpha-fetoprotein (AFP) level along with imaging methods including magnetic resonance imaging ultrasonography, and computed tomography, HCC can be diagnosed without pathologic confirmation.[102] Primary liver cancer includes HCC, intrahepatic cholangiocarcinoma (iCCA), and other uncommon cancers such fibrolamellar carcinoma and hepatoblastoma.[103] The targeted therapy of HCC patients has resulted from the discovery of new therapeutic targets based on the molecular pathways behind liver carcinogenesis.[104] focusing on the signalling pathways linked with different growth factors, including VEGF/VEGFR, EGF/EGFR, PDGF, IGF/IGFR, RAS/RAF/ERK/MAPK, FGF, Wnt/beta-catenin and PI3K/AKT/mTOR, has the potential to treat HCC more effectively using TKIs.[105] Over 60 elements are now being studied for the treatment of HCC, only sorafenib, which inhibits the PDGF, VEGF, and Raf receptor tyrosine kinase signalling pathways, is able to do this, has shown promising outcomes in patients with advanced HCC.[106] Other TKIs, including linifanib, sunitinib, regorafenib, and brivanib, block many signalling pathways associated with angiogenesis, including VEGFR, PDGFR, and FGFR.[107] Even though many clinical trials have been abandoned due to poor performance or These lines provide insight into the processes of targeted therapy for HCC despite its serious side effects. and may, at long last, enable precision medicine to enhance the efficacy of the present therapies for this devastating disease.

5.4.5 Precision Medicine in breast cancer

Breast cancer is the type of cancer that most commonly affects women. HER2-positive, Luminal A, Luminal B and triple-negative breast cancers are categorised into four subtypes based on key breast cancer-associated biomarkers such the progesterone receptor (PR), oestrogen receptor (ER) and Ki-67 (a protein marker with prognostic and predictive potential for adjuvant chemotherapy).[108] Breast cancer patients receive customised care still faces some challenges that lead to variations in how well they respond to a number of cancer therapy protocols (radiation, surgical procedures or chemotherapy), even though advances in precision medicine have largely increased overall patient survival.[109] Aged 40 or younger, premature menopause causes a decrease in estrogen production, therefore SNPs involved in its metabolism can provide information regarding breast cancer targeted therapy or 'chemotherapy-induced menopause' in breast cancer patients.[110,111,112] Brazilian population research found a link between polymorphisms in the estrogen receptor genes (ESR1 and ESR2) and 'premature ovarian failure', a symptom of early menopause.[113] In amenorrheic patients, chemotherapy led to better results and increased rates of overall survival and progression-free survival.[114] For patients with advanced breast cancer, finding the 'protein kinase B' point mutation (AKT1E17K/ PKB mutation) in plasma and tissue samples can aid in choosing the best course of rapamycin treatment to halt tumor growth.[83] HER2 is typically taken into account when choosing chemotherapeutic medications which take aim at this protein, like trastuzumab. Recent research has shown that HER2 expression can change at various points throughout the cancer progression, Consequently, HER2 in primary tumours cannot be the exclusive target of trastuzumab therapy.[115] Most frequent genetic changes that occur in people with breast cancer are mtDNA common deletions.[116] Some mtDNA deletions/insertions can play a significant part in the development of chemotherapeutic drug resistance and the outcome of treatment.[117]

5.4.6 Precision medicine in prostate cancer

Prostate cancer is the most typical malignancy in men and the main cause of mortality globally. The frequency of incidence instances of prostate cancer has increased during the previous fifteen years.[118] The start, progression, and metastasis of prostate cancer as well as the various treatment reactions that can be seen between patients may be affected by heterogeneous genetic abnormalities. Some transcription factors, including GATA-binding protein 2, octamer-binding protein 1 and Forkhead Box A1 are involved in the control of androgen receptor gene expression.[119] TMPRSS2 (Transmembrane serine protease) is another protein that is unique to the prostate. The transcriptional regulator Erg (ERG)-TMPRSS2, tumour protein 53 (TP53), ataxia telangiectasia mutant (ATM), speckled-type POZ protein (SPOP), phosphatase and tensin homolog (PTEN), and catenin 1 are the most frequently mutated cancer-causing genes in prostate cancer.[120] A broad family of transcription factors known as erythroblast transformation-specific is involved in the growth of several tissues as well as the progression of cancer (ETS). This family is demonstrated as the fusion form of ERGTMRPSS2 (ERG-transmembrane protease serine 2) in prostate cancer. Patients that have the ETS fusion mutation may be affected by medications that block fusion cofactors such as histone deacetylase and poly ADP-ribose.[121] For patients with PTEN deletion or mutation, rapamycin may be the best option because it targets the (Akt/ PI3K/mTOR) signalling pathway. In the care of prostate patients, FISH tests of ERG/ETV1 gene rearrangements and PTEN gene loss could be considered.[122] BRCA2 and ATM mutations may have greater sensitivity to therapy with poly ADP ribose polymerase inhibitors or platinum-based medicines.[123] In prostate tissue, several 'long noncoding RNAs' (lncRNAs) have been identified, and some investigations have shown that these lncRNAs exhibit altered expression patterns during prostate carcinogenesis.[124] Some epigenetic modifications, such as genomic global hypermethylation, are proposed as prostate cancer markers that go beyond genetic alterations.[125] Human castration-resistant prostate cancer has an overexpressed and hyperactivated androgen receptor (CRPC). "RAR-related orphan receptor gamma (ROR-)" was demonstrated to be a critical component of CRPC via the 'androgen receptor pathway' and is being investigated as a potential therapeutic target for advanced prostate cancer.[126] A response to enzalutamide and abiraterone can be developed when the androgen receptor and cytoplasmic CYP17 are overexpressed, especially in individuals with bone metastases.[127] Increased resistance to chemotherapy drugs like docetaxel is seen in cancers with 'high expression levels of the drug efflux transporter genes', such as particular -tubulin isotypes (III-tubulin) and multidrug resistance protein 1 (MDR1).[128] Taxane-resistance is a result of altered 'microtubule binding structure by isotype III-tubulin' or reduction of intracellular docetaxel due to MDR1's strong substrate affinity. Patients with down-regulated E-cadherin were linked to poor recurrence outcomes after radiation therapy, according to a prior archival cohort analysis.[129]

5.4.7 Precision medicine in thyroid cancer

A butterfly-shaped gland called the thyroid creates hormones needed for the body to function normally. It is located in the neck, slightly above the collarbone. There are multiple different kinds of thyroid cancer, including MTC (medullary thyroid carcinoma), which develops from follicular thyroid carcinoma (FTC), thyroid parafollicular (C) cells, papillary thyroid carcinoma (PTC) and anaplastic thyroid carcinoma (ATC).[130] As the fourth most prevalent cancer diagnosis by 2030, thyroid cancer is predicted to surpass colorectal cancer.[131] Ras-Raf-MEK-MAP-ERK kinase signaling is the most significant molecular process in thyroid carcinogenesis and is involved in the growth of both FTC and PTC. In PTC, constitutive activation of this cascade can be made by activating mutations in the gene encoding the serine/threonine kinase BRAF and RET tyrosine kinase rearrangements (PTC/RET oncogenes), which causes

thyroid cancer in the majority of populations.[132] patients with metastatic thyroid cancer that has spread or is progressed may now be prescribed some types of 'multitargeted kinase inhibitors', which have shown to have higher response rates than cytotoxic treatment.[133] Targeted thyroid cancer treatment can take some 'circulating cf DNA genetic and epigenetic' changes into consideration.[134] A non-randomized, open-label, multicentre, phase 2 trial conducted in 2016 by Brose et al. revealed that 'vemurafenib is effective in patients with metastatic or unresectable papillary thyroid cancer' that is positive to the BRAFV600E 'mutation' and is 'resistant to radioactive iodine' but who have never received TKI therapy.[135]

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