PHRAJ
Public Health Risk Assesment Journal
PHRAJ 3(1): 35–51
ISSN 3025-1109

Institute for Advanced Science, Social and Sustainable Future
MORALITY BEFORE KNOWLEDGE

Optimizing diabetic retinopathy therapy with precision medicine: Can we do that in Indonesia?

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Received Date: April 21, 2025 Revised Date: July 11, 2025 Accepted Date: July 31, 2025

ABSTRACT
Background: Diabetes is one of the most common diseases in the world, including in Indonesia. High blood sugar levels in diabetics can cause various complications, one of which is diabetic retinopathy. The treatment used in diabetic retinopathy does not fully provide the desired therapeutic effect in all patients. Therefore, a study was conducted on the prescription drug approach to optimize diabetic retinopathy therapy. **Methods:** This article was prepared using the literature review method by collecting and analyzing relevant literature sources. **Findings:** This study reveals that diabetic retinopathy is a complication of diabetes whose development can be influenced by genetic and environmental factors of the patient. Precision medicine can be applied in determining the best therapy for diabetic retinopathy by analyzing the clinical condition history, molecular and biochemical biomarkers of patients using artificial intelligence or machine learning. **Conclusion:** optimization of diabetic retinopathy therapy can be done with a precision medicine approach by analyzing genetic factors and patient environmental factors. However, there are still some challenges in its application in Indonesia. **Novelty/Originality of this article:** analysis of the application of precision medicine to provide the best therapy for patients in Indonesia.

KEYWORDS: diabetic retinopathy; precision medicine.

1. Introduction

In overcoming a disease, the treatment that is currently widely used is through a one-size-fits-all approach, where certain drugs are used in overcoming a disease in all patients. A treatment can be effective for some people but ineffective for others. Differences in response to treatment between individuals can be caused by age, race, comorbidities, concomitant medications, environmental factors, and genetic factors (Miller et al., 2015). A therapeutic approach that can be used to overcome this problem is precision medicine. Through precision medicine, a selection of therapy can be done by considering genetic, environmental, and lifestyle factors. The advantage of this precision medicine approach is that the risk of developing a disease can be done faster, diagnosis is more accurate and uses a molecular approach, and provides the best treatment options to achieve optimal therapy (Ginsburg & Phillips, 2018). Precision medicine uses omics technology approaches such as the genomics, the metabolomics, proteomics, transcriptomics in determining the best

Cite This Article:
Putri, N. S., & Barliana, M. I. (2025). Optimizing diabetic retinopathy therapy with precision medicine: Can we do that in Indonesia? *Public Health Risk Assesment Journal*, *3*(1), 35-51. https://doi.org/10.61511/phraj.v3i1.2025.1840

therapy for each patient's condition and can be a preventive approach to prevent and detect diseases early (Hasanzad et al., 2021).

Compared to conventional medicine that provides standardized treatment designed for a general group of patients, precision medicine offers treatment that is based on a patient's genetic profile, providing specific, targeted therapy. In addition to genetics, precision medicine also considers lifestyle factors, unlike conventional medicine that focuses on relieving symptoms. Diagnosis using precision medicine approach is based on biomarkers and combines various data that can be analyzed with an algorithm such as AI, unlike conventional diagnosis that relies on sophisticated tools such as X RAY. While conventional medicine focuses on diagnosis and pharmaceuticals, precision medicine can provide customized treatment plans according to the patient's condition (Molla & Bitew, 2024). Although the application of precision medicine is costly, treatment based on precision medicine can reduce costs because it can maximize treatment and prevent other ineffective effects (Stefanicka-Wojtas & Kurpas 2023).

One of the non-communicable diseases that pose a global health threat is diabetes mellitus (DM). Diabetes mellitus is defined as a metabolic disease in which hyperglycemia occurs as a result of abnormalities in insulin secretion, insulin action, or a combination of both (Antar et al., 2023). Diabetes mellitus is one of the diseases that is the biggest problem in Indonesia. The prevalence of diabetes mellitus of 9.19% in 2020 is expected to increase to 16.09% in 2045 or equivalent to 40.7 million cases. Deaths caused by diabetes are expected to increase to 944,468 in 2045 from 433,752 in 2020 (Wahidin et al., 2024). In patients with diabetes mellitus, metabolic disorders occur due to chronic hyperglycemia conditions which, if uncontrolled, can cause organ damage through complications. One of the microvascular complications caused by DM is diabetic retinopathy (DR). Diabetic retinopathy is one of the major neurovascular complications of DM and is the leading cause of blindness in adults. According to the latest epidemiological data shared by the American Academy of Ophthalmology, the number of people with DM in the world is 387 million, which is expected to increase to 592 million by 2035. Ninety-three million people worldwide are affected by DR. The prevalence of DR is 77.3% in patients with type 1 diabetes and 25.1% in patients with type 2 diabetes, of which approximately 25% to 30% are expected to develop vision-threatening diabetic macular edema (Shukla & Tripathy, 2023). Blindness caused by DR worldwide was estimated at 51% with 56% of DR sufferers with visual impairment coming from Asia Pacific (Chua et al., 2018). In one study, it was reported that the prevalence of DR in Indonesian adults with type 2 diabetes was 43.1% (Sasongko et al., 2017).

The initial pathophysiology of DR is vascular endothelial cell damage and loss of pericytes. The resulting hypoxic response then triggers the expression of vascular endothelial growth factor (VEGF) and other pro-angiogenic factors. Currently, the most effective treatment for DR and diabetic macular edema (DME) is to control blood glucose levels. More advanced cases require laser, anti-VEGF therapy, steroids and vitrectomy (Tomita et al., 2021). There are various factors ranging from HbA1C, fasting blood glucose levels, total cholesterol levels, triglyceride levels, hypertension, duration of diabetes diabetic foot ulcers, diabetic nephropathy, diabetic neuropathy, age, to male gender into risk factors that trigger the occurrence of DR (Yin et al., 2020). In a study conducted in Vietnam on 140 patients with type 2 diabetes, it was stated that other factors such as uric acid, serum creatinine levels, glomerular filtration rate (eGFR), red blood cells levels, and Hb levels were risk factors for DR. Diabetic patients who had diabetes for more than 15 years had a risk factor for DR 8.319 times higher than patients with less time with diabetes (Nga et al., 2023). In addition to these factors, there are several genetic variants that are influential in angiogenesis and inflammatory pathways that affect the development of DR (Cabrera et al., 2020). Currently, the use of anti-VEGF agents is the standard of care for DR. However, among patients with DR, there is great variation in clinical response with many patients not showing satisfactory levels of visual acuity improvement (Agarwal et al., 2014). Diabetic retinopathy is a complex disease that can be influenced by both genetic and environmental factors. Therefore, this article will analyze the approach of diabetic retinopathy therapy

using precision medicine by discussing the genetic and environmental factors, the components needed, and opportunities for implementation in Indonesia.

2. Methods

This article is organized through a literature review approach. This article is organized through a literature review approach with six steps described by Templier and Paré (2015) in Paré and Kitsiou (2017). Formulating the research question(s) and objective(s): This step is carried out to direct researchers to explore the information needed, select and determine relevant reference sources, and direct the next stage of analysis. In this step, the purpose of the research is to find out whether the precision medicine approach can be done to optimize DR therapy in Indonesia. Questions were formulated such as, what are the components needed in the implementation of precision medicine? How to apply precision medicine in DR? Do genetic and environmental factors affect the prevalence and development of DR? and several other questions. Searching the extant literature: Data searches were conducted using the Google search engine, Google Scholar and PubMed with the keywords "Precision Medicine", "Personalized Medicine", "Diabetic Retinopathy", and "Precision Medicine in Diabetic Retinopathy". Screening for inclusion: The references obtained were then determined by inclusion and exclusion criteria. The inclusion criteria were national and international journals containing precision medicine, diabetic retinopathy, and precision medicine approaches in diabetic retinopathy therapy published after 2014. Meanwhile, the exclusion criteria were invalid sources and journals published before 2014. Assessing the quality of primary studies: This step was done in addition to screening with inclusion criteria. This step is done by assessing the rigor and research methods so that the data included in the article is valid. Extracting data: In the next step, the data obtained from the references were collected and screened regarding the method, time of implementation, researchers who conducted the study, and the results obtained. Analyzing and synthesizing data: In the final step, all the data that has been collected is summarized, combined and connected. Then, it is analyzed to answer the objectives of the research conducted.

3. Result and Discussion

3.1 Pathophysiology of diabetic retinopathy

Based on data published by the International Diabetes Federation (IDF) in 2021. As many as 10.5% of the world's population, which is around 537 million people, have diabetes (Hossain et al., 2024). In diabetics, hyperglycemia conditions occur which can cause both microvascular and macrovascular vascular damage. This occurs because hyperglycemia conditions cause factors that normally protect blood vessels to decrease, while there is an increase in factors that cause blood vessel damage. Microvascular complications occur in arterioles, venules, and capillaries where these blood vessels function to maintain systemic blood pressure and maintain vascular flow and permeability so that proper nutrients can be delivered. In the retina, there are several types of nerve cells that receive nutrients and oxygen from two different blood vessels. Microvascular complications in DR begin with decreased perfusion and function of the blood vessels that deliver nutrients to the retina. Diabetes also causes significant changes in the structure of the blood vessels that line and support normal blood vessel function, called the endothelial lining (Wright et al., 2023).

Diabetic retinopathy is a complication of DM due to chronic hyperglycemia. Hyperglycemia leads to activation of alternative pathways of glucose metabolism, including the polyol pathway. These alternative pathways lead to cytokine activation along with growth factors and vascular endothelial dysfunction, ultimately leading to increased vascular permeability and microvascular occlusion. Retinal ischemia, which occurs due to microvascular occlusion, leads to the formation of IRMA (intraretinal microvascular abnormalities) and neovascularization. In the polyol pathway, glucose is reduced to sorbitol

by the enzyme aldose reductase. The inability to sorbitol leads to accumulation of sorbitol in all retinal cells causing osmotic damage to the cells. In hyperglycemia conditions, there is an increase in reactive oxygen species (ROS) levels resulting in oxidative stress that can cause cell damage. In addition, there is activation of protein kinase C which causes changes in the basement membrane and vascular changes such as increased vascular permeability, release of angiogenic growth factors, vascular stasis, and capillary occlusion. Hyperglycemia also causes the release of growth factors such as vascular endothelial growth factor (VEGF) as well as the release of cytokines/chemokines such as tumor necrosis factor-α (TNF-α) (Shukla & Tripathy, 2023). In a review conducted by Safi et.al in 2014, the molecular and biochemical pathophysiology of diabetic retinopathy occurs due to increased glucose levels through the polyol and hexosamine pathways, increased formation of advanced glycation end products, and activation of protein kinase C.

DR can be classified based on clinical conditions, namely nonproliferative DR characterized by intraretinal vascularization changes, and proliferative DR where neovascularization is found due to ischemia (Elvira & Suryawijaya, 2019). The International Clinical Diabetic Retinopathy (ICDR) gives the following severity scale of DR: Mild Non Proliferative Diabetic Retinopathy (NDPR), which is a condition where only microaneurysm occurs. Moderate NDPR, conditions where any of the following occur, i.e. microaneurysms, retinal dots or hard exudate spot hemorrhages or cotton wool spots, and there are no signs of severe NPDR. Severe NDPR, a condition where there are more than twenty intraretinal hemorrhages in all four quadrants, obvious venous beads in 2 or more quadrants, prominent intraretinal microvascular abnormalities (IRMA) in 1 or more quadrants, and no signs of proliferative retinopathy. Proliferative DR (PDR), conditions where one or both of the following occur: neovascularization (new blood vessels) or vitreous/preretinal hemorrhage (Cleland, 2023).

In general, the order of occurrence of DR is absence of DR, then mild to moderate NDPR, followed by PDR to longer duration of PDR. In some patients with NDPR, lipid (hard exudates) and plasma (edema) leakage may occur until diabetic macular edema develops. However, the study mentioned that DR is a heterogeneous disease where the sequence of DR disease progression to PDR stage or progression to diabetic macular edema is not the same for each patient (Das et al., 2015). Management for NPDR in patients without diabetic macular edema can include systemic management and ophthalmic management. Systemic management consists of blood sugar control, blood pressure control, blood lipid control, dietary modification and management of anemia and vitamin D deficiency, as well as smoking cessation. Ophthalmic management may include laser photocoagulation. Laser photocoagulation can be beneficial for preventing the progression of DR to PDR. However, in one study it was reported that treatment of severe NDPR using laser can lead to decreased visual acuity due to reduced ocular blood flow. In addition, the management of NDPR may utilize intravitreal injection of anti-VEGF (Arabi et al., 2022). Management of PDR patients may include intravitreal injection of anti-VEGF. Anti-VEGF can also be given to DR patients with diabetic macular edema and vitreous hemorrhage. In addition, the treatment can be laser photocoagulation called pan retinal photocoagulation (PRP) (Kansora & Goldhardt 2019).

3.2 Genetic and environmental factors of diabetic retinopathy

The core of the therapeutic approach through precision medicine is genomics. The effectiveness and metabolism of a drug can be affected by gene mutations or variations that can differ from one individual to another. Therefore, it is important to examine the genomics of a patient by studying genomics, genetics, and biomarkers (Su et al., 2024). Genetic factors play a role in the development of DR. In a study conducted on DR patients in Han China, it was stated that the proliferation of the aldose reductase (ALR2 rs759853) and sorbitol dehydrogenase (SDH rs2055858) genes was associated with the development of DR through the polyol pathway (Li et al., 2019). In addition, there are genetic markers involved in the progression of DR, including VEGF which plays a role in the angiogenesis process in the

development of DR as well as TNF-α and IL-6, which are associated with inflammatory responses. Another study mentioned that there are several DR-related genes that fail to replicate in some populations such as Aldo-Keto Reductase Family 1 Member B (AKR1B1), Vascular Endothelial Growth Factor A (VEGFA), Advanced Glycosylation End-Product Specific Receptor (AGER), erythropoietin (EPO), and Nitric Oxide Synthase 3 (NOS3) (Bhatwadekar et al., 2021). The development of diabetic retinopathy is influenced by inflammation and oxidative stress, and the progressivity of these mechanisms can be influenced by epigenetic factors. These epigenetic factors are influenced by several genes that can be modified by the environment and lifestyle (Kowluru, 2023). In a literature study conducted by Sienkiewicz-Szłapka, it was mentioned that there are genes that play an important role in DR. These genes can be polymorphic located on chromosomes 1-22, except chromosomes 5, 8, 11, 12, 14, 18, 21, X/Y with the largest number of genes found on chromosomes 1 and 7 (Sienkiewicz-Szłapka et al., 2023). In a literature review conducted by Cabrera and colleagues, it was suggested that genetics not only plays a role in the development of DR but also in the response to therapy. The effectiveness of anti-VEGF injections is thought to be influenced by specific molecular pathways or genetic factors. In major clinical trials (DRCR, RIDE/RISE, VISTA), in diabetic macular edema patients given anti-VEGF injections, patients who showed an improvement in three-line visual acuity were only 27-45%. Therefore, DR is said to have a heterogeneous phenotype.

In addition to taking genetic factors into account for optimization of therapy, it is also important to consider triggers and/or cofactors as influences from environmental factors. Inappropriate results may result from predicting the response of a treatment based on genetic factors alone without taking into account environmental factors (Agyeman & Ofori-Asenso, 2015). Environmental factors are also influential in the development of DR. The main environmental factor that plays a role in the risk of developing DR is uncontrolled blood glucose levels. Other factors include hypertension, dyslipidemia, and obesity (Schreur et al., 2018). In a study conducted by Zhang et al, it was found that blood pressure above 120/80 mmHg significantly increased the prevalence of DR by 10-20% in diabetic patients with and without hypertension (Zhang et al., 2023). In a large population-based study of patients with diabetes and hypertension in Asia, treated but poorly controlled hypertension and untreated hypertension were significantly associated with DR (Liu et al., 2020). In a hospitalized based therapy study conducted by Ezhilvendhan on patients in a tertiary care hospital in Salem from September 2018 to March 2020, it was found that there was a significant relationship between dyslipidemia and the degree of severity of DR in patients with type 2 diabetes mellitus (Ezhilvendhan et al., 2021). A study conducted by Sebastian et al., at Sanglah Hospital in Denpasar, Bali, Indonesia, found that the prevalence of diabetic retinopathy patients with dyslipidemia in the 2021-2022 period was quite high. (Sebastian et al., 2023). In a meta-analysis study conducted, it was mentioned that there is an association between obesity and increased DR (Zhu et al., 2018). Another study also mentioned that unhealthy lifestyles such as smoking, as well as high body mass index and waist-to-hip ratio also play a role in the development of DR (Su et al., 2023). The interaction between genetic factors, environmental factors, and lifestyle plays an important role in DR risk assessment and management that can be done through a precision medicine approach (Pei et al., 2024).

3.3 Detection of diabetic retinopathy

Symptoms that may be felt for people with DR can include blurred vision, impaired vision, partial or total loss of vision, small shadows that are seen moving in the field of vision, such as spots, lines, webs, or blobs called floaters (Shukla and Tripathy, 2023). In a review conducted by Safi et al, it was mentioned that the symptoms and clinical signs of DR in the early stages are not visible. Therefore, it is necessary to detect DR in a timely manner. The general examination of DR that can be done is by funduscopy method, but retinal damage due to microvascular complications before DR occurs cannot be restored. In retinal imaging using conventional funduscopy, there are several stages in the diagnosis, namely retinal

blood vessels, optic disc, macula, and retinal periphery. Current research on funduscopic imaging is that it can be combined with a smartphone-based camera and connected with artificial intelligence-based devices to facilitate analysis during diagnosis (Vaughan, 2024). In addition to funduscopy, there is also a diagnostic method that can also be used to monitor the patient's retina, which is fundus photography. Through fundus photography, retinal imaging can be monitored over time. In addition, there is also B-scan ultrasonography that can show the presence of hemorrhages that can cause opacities in the eye media (Sal & Witkin, 2015). Another DR diagnostic tool is using Optical Coherence Tomography Angiography (OCTA). Through OCTA, the retinal blood vessels can be seen in three dimensions with good resolution. In addition, through OCTA, early detection of DR can be done. OCTA can also provide an overview and analysis of the stages of DR (Wijesingha et al., 2024).

There are currently several alternative methods for detecting and diagnosing DR that are more cost-effective and accessible. These methods can detect DR at an early stage and can improve diagnostic accuracy, thereby speeding up treatment. In a comprehensive review conducted by Kąpa and colleagues, these methods use technological innovations such as Teleophthalmology that allow ophthalmologists to focus on the therapeutic intervention stage with remote treatment and detect DR through imaging more effectively and accurately in a cost-effective manner. The sensitivity of teleophthalmology reaches an average of 90.0% and specificity of 84.6%. Another method is ultrawide imaging called Ultra-widefield photography. This method allows for more accurate detection as it provides up to 80% comprehensive imaging of the retina. This method is also beneficial for people with mydriasis as it performs retinal imaging without causing pupil dilation. Furthermore, there is a nanotechnology diagnostic method that can detect DR early, with the help of fluorescein angiography. There are also several artificial intelligence-based methods that have been approved by the FDA, namely AEYE Diagnostic, EyeArt, and LumineticsCore™ which have high sensitivity and selectivity in detecting DR. Good diagnostic methods will help improve the effectiveness in therapeutic approaches using precision medicine. The information provided by diagnostic tools contributes to providing precise results in precision medicine.

3.4 Treatment for diabetic retinopathy

Lifestyle modification: Treatment for DR can start with controlling risk factors such as blood sugar control, blood pressure, and lipid levels. Patients with DR who are still in the early stages can achieve recovery by controlling blood sugar levels. In a comprehensive review conducted by Rodríguez-Gutiérrez and Montori in 2016, it was stated that the HbA1C level that must be maintained to prevent complications of nephropathy, retinopathy, and neuropathy due to diabetes is below 7%. Another important risk factor to control to prevent further progression of DR is blood pressure. People with type 2 diabetes tend to suffer from hypertension with a three times higher risk than those without diabetes. Vascular damage due to hypertension also increases the risk of DR (Rajalakshmi et al., 2016). The American Diabetes Association recommends blood pressure control with target systolic blood pressure levels of <140 mm Hg and diastolic blood pressure levels of <90 mm Hg. Meanwhile, for high-risk patients, the recommended blood pressure target is <130/80 mmHg (Kim & Kim, 2022). The benefit of lowering blood pressure is that it can prevent DR for up to 4 to 5 years (Do et al., 2015). In addition to controlling blood sugar and blood pressure levels, it is also important to control cholesterol levels in the blood to prevent further progression of DR. In a study conducted on young type 1 diabetics, it was found that there was an association between elevated cholesterol levels and a higher risk of developing retinopathy (Rathsman et al., 2020). Anti vascular endothelial growth factor (anti-VEGF): Further therapy can use anti-VEGF injections such as bevacizumab, ranibizumab, and aflibercept. The aim of anti-VEGF is to inhibit the increase in VEGF concentration and restore the intactness of the blood retinal barrier (Gonzalez-Cortes et al., 2022). Anti-VEGF is given to DR patients who have entered the proliferative DR stage. Anti-VEGF administration is

done through intravitreal injection which can be repeated once a month (Bahr & Bakri, 2023). In a RECOVERY trial to determine the effectiveness of anti-VEGF in the progressivity of DR, in 40 eyes of 40 proliferative DR patients for 12 months, 2 mg aflibercept was injected every three months or every month. From the test, it was found that the improvement in DR severity indicator called Diabetic Retinopathy Scale Score (DRSS) in the quarterly group was 67% and in the monthly group, it was 74% (Wykoff et al., 2019). In a study of 850 patients with type 1 and 2 DM who developed PDR, the effectiveness of one of the anti-VEGF injectables, bevacizumab, was determined by documenting vitreous hemorrhage in real-life data over 5 years. From the study, it was found that out of 336 vitreous hemorrhages in 140 eyes of 103 patients documented, in less than 3 months intravitreal injection of bevacizumab was effective in healing vitreous hemorrhages in 92%. In addition, intravitreal injection of bevacizumab is superior as it provides a shorter duration of treatment in cases of vitreous hemorrhage compared to other methods. Intravitreal injection of bevacizumab can also prevent recurrent and presistent vitreous hemorrhage and can reduce the need for costly pars plana vitrectomy (Wirkkala et al., 2019).

Steroids: Other pharmacological therapies can use steroids such as triamcinolone acetonide and dexamethasone. Steroids work as anti-inflammatories that are involved in the pathogenesis of DR by reducing the concentration of arachidonic acid and indirectly reducing the concentration of VEGF by reducing the synthesis of thromboxane, prostaglandins, and leukotrienes. Corticosteroids may be an alternative option for patients who are contraindicated with anti-VEGF or patients who do not respond to anti-VEGF therapy (Gonzalez-Cortes et al., 2022). Steroids can be used for DR patients who have progressed to diabetic macular edema. Corticosteroids can delay the neurodegenerative process in the retinal nerves. Corticosteroids have a longer duration of action than anti-VEGF. However, there are some side effects that result from administering steroid injections, such as intraocular hypertension and cataract formation and progression (Chawan-Saad et al., 2019). Other treatments: In a review conducted by Wang et al., several other drugs that can be used in DR therapy are senolytic drugs, retinal ganglion cell injury and regeneration-related drugs, and fenofibrates. Apart from injection, there is also therapy using laser photocoagulation which can reduce neovascularization and reduce VEGF levels in retinal tissue. Surgery may also be an option to prevent blindness for patients with advanced stages of intravitreal hemorrhage and retinal detachment. It was also mentioned that gene therapy as an alternative therapy has several advantages but further research is still needed (Wang et al., 2024). Gene therapy for DR has also been investigated with two mechanisms which protect retinal blood vessels and nerve cells from damage and target abnormal blood vessel growth and hyperpermeability of existing blood vessels. However, there are still obstacles in clinical trials due to the complex pathophysiology of DR, patient recruitment and measuring outcomes (Wang et al., 2020).

3.5 Precision medicine in diabetic retinopathy

Precision medicine (PM) is an approach that considers subpopulation variability in genetic, socio-environmental, and lifestyle factors to propose appropriate therapies. PM comes as a solution to traditional medicine that uses the concept of one size fits all where all patients suffering from a disease are given the same treatment. PM uses Big Data where large amounts of data are collected and by linking with clinical, pharmacological, and socio-economic information, analysis can be done using data sets integrated with various computer-based algorithms. With these measures, patterns of effectiveness of certain treatments can be observed and optimal treatment options can be provided (Naithani et al., 2021). To develop precision medicine as a solution to health problems, we need a complete population genome database from various ethnicities and knowledge of how to process the data so that it can be used to diagnose and analyze the right treatment for patients. In addition, the ability to operate AI is also needed to be able to combine genetic and environmental data in order to provide the right predictions for patients. Knowledge of the ethics of using genomic data is also required. To tailor treatment according to the patient's

genomic condition in order to achieve optimal therapy and minimal side effects, pharmaceutical companies can also prioritize drug development that leads to pharmacogenomics (Molla & Bitew, 2024). In applying prescription medicine in the ophthalmic field, ophthalmologists can determine the best treatment for a patient by compiling a genomic study of the patient and combining the genetic information with other factors such as the patient's medical history, family history, lifestyle and environmental factors, the patient's eye health condition and medical history, and the results of the patient's eye examination. From all this information, a preliminary diagnosis will be made by estimating the risk factors that the patient has in order to determine the best treatment to maintain, enhance and improve vision (Straatsma, 2018).

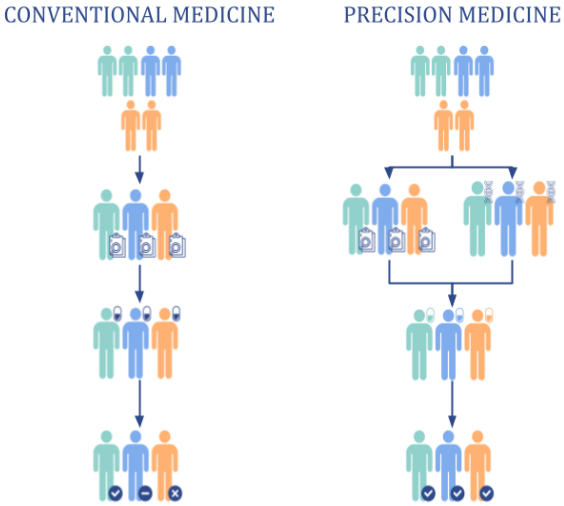

Fig. 1. Comparison between conventional and precision medicine

In people with diabetes, the progression of DR can vary, including the rate of progression of DR as well as the specific symptoms experienced. In some patients, DR may progress to proliferation diabetic retinopathy and in others it may progress to diabetic macular edema. In addition, there are also differences in the effectiveness of the therapy provided. In DR patients who are given anti-VEGF therapy, there are patients who get moderate effects and even patients feel worse effects (Ashraf et al., 2016). In one study, it was mentioned that the difference in the therapeutic outcome of anti-VEGF was related to gene variations associated with VEGF (Sajovic et al., 2019). The precision medicine approach in optimizing DR therapy aims to improve the efficacy of treatment and reduce side effects on patients. By analyzing the genetic and environmental factors of the patient, the best DR therapy for that patient can be recommended. Variations in the VEGF gene may affect anti-VEGF therapy. Therapy using anti-inflammatory agents such as steroids is also affected by the proliferation of inflammation-related genes such as TNF-α and IL-6. In addition, by analyzing environmental factors that increase the progression of DR, therapeutic recommendations and lifestyle changes can be made to improve therapeutic outcomes (Pei et al., 2024).

3.6 Components in precision medicine for diabetic retinopathy

The components used to analyze the best therapy for DR using precision medicine are as follows. Clinical condition history: The implementation of PM can be established through anamnesis. Anamnesis in general can be done by recording age, type of diabetes, duration of diabetes, family history, and risk factors such as blood pressure. Anamnesis can also be done by examining clinical conditions related to the patient's ocular condition. The examination can include identifying the stage of retinopathy (e.g. Early Treatment Diabetic Retinopathy Study, visual acuity), Optical Coherence Tomography examination (e.g. retinal thickness), retinal blood vessel calipers, retinal blood vessel geometry, corneal and lens

autofluorescence, corneal confocal microscopy (CCM), and electroretinogram (Jenkins et al., 2015). In the application of precision medicine, patient health information can be collected and managed in a health service called electronic health records (EHR). In the EHR, patient data ranging from age, gender, vital signs ranging from height, weight, body temperature, heart rate, and other data such as immunization and medication history are provided (Abul-Husn & Kenny, 2019). Molecular biomarkers: The more or less constant genome that we are born with can undergo chemical modifications during our lifetime due to diet, environment and lifestyle. In this component, a sample of the patient's blood is examined for genetic conditions. Molecular biomarkers can be analyzed based on the patient's DNA, epigenetics, RNA, and lipidomic conditions (Jenkins et al., 2015). Molecular biomarkers can be RNA, genes, proteins, or metabolites that can be useful in detecting, diagnosing, and also play a role in the treatment of a disease. Molecular biomarker is a single molecule or a group of molecules whose expression or concentration is different from normal conditions when a disease occurs (Liu et al., 2014). One of the molecular biomarkers associated with the pathogenesis and progression of DR is VEGF. High VEGF levels are associated with increased severity of DR. In addition, increased VEGF can also affect the response of anti-VEGF therapy given to patients due to the role of polymorphisms in the VEGF gene. Some of the pathways that can affect the response to anti-VEGF therapy due to increased or resistant VEGF are high risk human leukocyte antigen (HLA), single nucleotide polymorphisms, micro RNAs, mutated VEGF, and phenotypic variations (Agarwal et al., 2014).

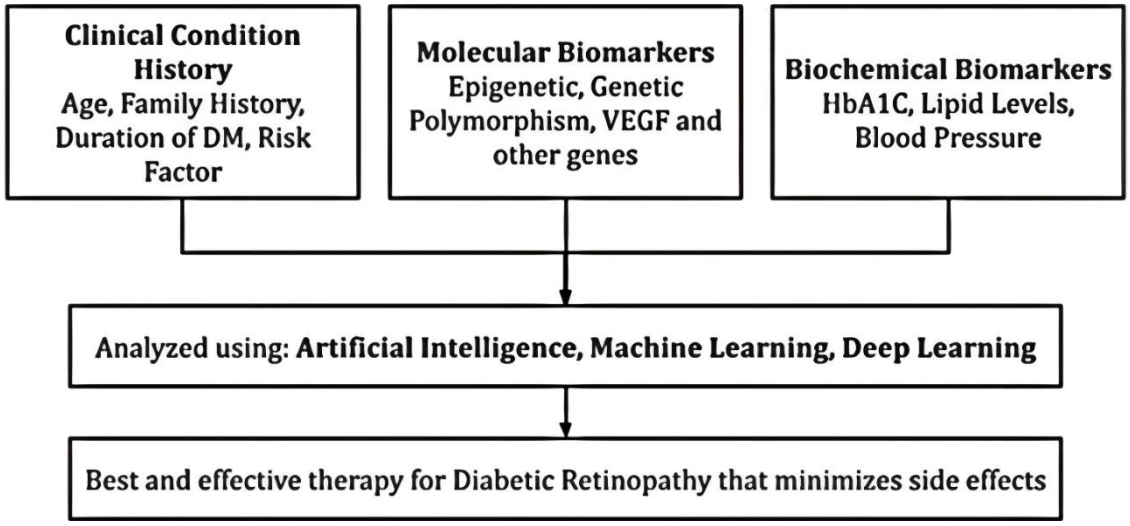

Fig. 2. Components in precision medicine for diabetic retinopathy

Biochemical biomarkers: Biomarkers are important in diagnosis as markers of a disease. In addition, biomarkers can also be used to predict and assess the progression of a disease. To optimize a therapy and minimize side effects, biomarkers can guide the selection of therapy and can be used to monitor the effectiveness of the therapy (Drugan & Leucuța 2024). One of the biochemical biomarkers that can be analyzed is HbA1C. HbA1C is an examination based on non-enzymatic glycation of hemoglobin, and reflects the average blood glucose level over the previous 2-3 months. There is a relationship between HbA1C and the risk of developing DR where the higher the HbA1C value, the higher the risk of developing DR. In addition, blood lipid levels can also be tested. Although blood lipid levels are somewhat associated with diabetic retinopathy, lipoproteins in the retina, particularly modified lipoproteins identified in the circulation using newer techniques, may play an important role in retinopathy, and may be targeted for therapy. Blood pressure checks can also be performed where high blood pressure may increase the risk of developing DR (Jenkins et al., 2015). Artificial intelligence (AI), machine learning (ML), and deep learning (DL): AI and ML can process volumes of data in a timely manner through bioinformatics systems. AI and ML can integrate and transform data into useful diagnostic and therapeutic interventions. Data storage, handling, and analysis are best done using AI and ML. By

fostering various clinical, diagnostic, and therapeutic algorithms through flowcharts, these methods enable clinicians to make various quick decisions in the treatment of DR (Naithani et al., 2021).The use of AI in the ophthalmic field is helpful in the diagnostic process as well as in the analysis for the next stage of treatment in several diseases such as glaucoma, age-related macular degeneration (AMD), cataract, including DR (Jin & Zhang, 2023). The use of AI in optimizing DR therapy can be used both for diagnosis and for monitoring the development and progressivity of DR. In a comprehensive review conducted by Kąpa et al., it was mentioned that there are AI systems that are sensitive and specific to DR, for example VoxelCloud in Shanghai, China with a sensitivity of 83.3%. In addition, there is also DeepDR plus developed by Dai et al which can extend the DR screening interval by an average of 12 months to almost 3 years (Kąpa et al., 2024). In a study on DM patients undergoing dilated ophthalmoscopy aged 18 years and above, it was shown that the EyeArt Artificial Intelligence (AI) system had a higher sensitivity in detecting more than mild diabetic retinopathy (mtmDR) than both general ophthalmologists and retina specialists (Lim et al., 2022). In a systematic review conducted by Senapati et al in 2024, several studies were written about the application of ML techniques in DR where the accuracy rate varied from 75-97.8%. Besides using AI and ML, there is also an approach using deep learning in DR identification using retinal fundus images. However, this research is still less accurate in detecting DR symptoms in the early phase (Chetoui & Akhloufi, 2020). In a study using deep learning methods, it was mentioned that the DeepDR Plus System can be used to predict the risk and progression of DR within 5 years using fundus imaging (Dai et al., 2024).

3.7 Challenge in the implementation of precision medicine in Indonesia

The application of precision medicine is based on pharmacogenetics where pharmacogenetics studies the role of genetics and its interaction with the environment that can vary the effectiveness or side effects of a therapy (Ortega & Meyers, 2014). Precision medicine has many benefits in providing the best therapy for patients by minimizing the side effects of treatment and increasing the effectiveness of the drugs used. In addition to direct benefits for patients in terms of toxicity and effectiveness, the application of precision medicine in optimizing therapy is also useful as a facility to discover, research, and develop new drug discoveries and can play a role in balancing the health care system. However, there are some challenges in its application. This is because the biotechnology process is costly and can be a problem of social inequality for some countries. Likewise, pharmacogenomic testing requires a lot of evidence and skills. The application of precision medicine in Europe, still has several challenges ranging from licensing for testing and pharmacogenomic development. In addition, privacy and data protection issues are also still a challenge in the implementation of precision medicine in Europe (Stefanicka-Wojtas & Kurpas 2023). Countries in Southeast Asia that have adopted precision medicine are Thailand and Singapore where pharmacogenomic networks have been established. Some of the obstacles in the application of precision medicine range from limited costs, limited political support such as investment, to low public awareness of precision medicine. To increase resources to achieve the goals of precision medicine, multi-country cooperation is needed (Chong et al., 2018).

Currently, the Ministry of Health of the Republic of Indonesia is developing biomedical genetics studies in an effort to support precision medicine. Indonesia has begun to develop the Biomedical Genome-based Science Initiative (BGSi) in several hospitals where this system is achieved through an integrated health data governance system (big data) and an artificial intelligence-based health analysis system. However, there are still several challenges in the development of precision medicine, namely in terms of cost, limited social health insurance which makes it difficult to equitable distribution of genomic health services, and limited information and communication technology (Kamelia & Putri, 2023). There are several ethical and regulatory issues related to the application of precision medicine such as the need for clear regulations or regulations related to the use, research, and testing of genomic therapies that are ethical and safe. Access to technology must be fair,

which should be based on need not finance. The use of genomic information must also be used fairly and must be able to guarantee the security and privacy of the information. Psychological support is also needed in case of misunderstandings in taking action based on genomic information. Supportive infrastructure is also needed for genomic testing (S & R, 2024). Another challenge that must be prepared by Indonesia if it wants to implement precision medicine is the ability to manage Big Data. Indonesia should invest more in biostatistics, biomathematics, and bioinformatics in order to increase the number of data sets in big data. In addition, the patient's EHR data must be supplemented with genomic data so that analysis can be carried out linking genetic, environmental and lifestyle factors. Therefore, Indonesia needs to know more about how to collect, analyze, and process large amounts of data, how to integrate and intervene, and prepare the costs for the process (Alyass et al., 2015). To support the successful implementation of PM in Indonesia, adequate information technology is needed to store and process data. To ascertain the genetic profile and biomarkers of a disease, Indonesia must have adequate laboratory facilities. In addition, to ensure that the treatment needed is adequate, the role of the pharmaceutical industry in providing drugs is also needed. From all these components, cooperation from various fields of science is needed, from doctors and biomedical experts to information technology experts who can analyze large amounts of data (Haque et al., 2020).

Indonesia, as a low- and middle-income country, must take extra steps to implement treatment with a pharmacogenetic approach. There are several limitations to adopting pharmacogenetics such as technological resources where technology is needed for bioinformatics data management and analysis. Inadequate human resources are also an obstacle in the implementation of pharmacogenetics. In addition, there is also limited access to health services due to inadequate costs in health care. Cost also has a big role in the implementation of pharmacogenetics ranging from infrastructure costs, human resource development, and testing costs. Therefore, low- and middle-income countries, including Indonesia, can collaborate with other countries and share resources to jointly develop infrastructure, formulate policies, and improve human resources through education on pharmacogenetics in order to achieve optimal therapy through the application of pharmacogenetics (Ausi et al., 2024).

In a review conducted by Hisan and Amri, several steps that can be taken by Indonesia in implementing precautionary medicine are outlined. First, the government is needed to fund genomic research or research that will be used to support precision medicine. In addition, the government must also ensure the quality and equitable distribution of research, as well as provide a standardized medical practice and facilities for EHR provision. The government must also be a provider of quality and safe health services. Second, Indonesia must conduct research that supports the application of precision medicine such as research in pharmacogenomics. In this research, it is also necessary to develop facilities and equipment to process the data obtained so that it can be used in diagnosis, prognosis, and treatment. Third, in terms of education. Indonesia must develop education in molecular, genetic and other sciences to understand the field of pharmacogenomics in the application of precision medicine. Fourth, the role of medical institutions. Medical institutions play a role in facilitating the implementation of EHRs that can be used by doctors. The system should also be able to implement pharmacogenomics. Fifth, the pharmaceutical industry, acting as a facility for the development and discovery of new drugs. Sixth, the role of patients and communities who must participate in health development and initiatives. Finally, Indonesia must provide other supporting bodies that play a role in data protection and privacy, ethics committees, and network infrastructure. The aim is to ensure that the patient data collected is used properly and protected.

4. Conclusion

Diabetic retinopathy is one of the complications of diabetes whose development can be influenced by genetic and environmental factors. Patients with DR can have different conditions ranging from genetic factors and risk factors such as a blood sugar levels, blood

pressure, and blood lipid levels. DR management can start from lifestyle changes, then further therapy using anti-VEGF injections, steroids, other drugs, to a performing surgery or laser. However, treatment outcomes and side effects may vary from patient to patient due to genetic and environmental factors. Precision medicine approach in a optimizing diabetic retinopathy therapy can be done by analyzing genes related to a DR and combined with the review of other risk factors with the help of AI. Through the precision medicine approach, the best treatment recommendations can be given with minimal side effects in a various conditions that are specific to a each patient. However, for its application in Indonesia, there are still limitations both in terms of cost and technology. To develop precision medicine in determining the best therapy for DR, further research is needed on pathogenesis, diagnostic techniques, and genomic studies in DR. In addition, adequate human resources and cooperation with various parties are also needed. The role of other parties such as the government is also needed.

Acknowledgement
The authors express their gratitude to the reviewers for their valuable and constructive feedback on this article.

Author Contribution
N.S.P and M.I.B., contributed to the literature search, interpretation, writing, and proofreading of the manuscript. All authors have read and agreed to the published version of the manuscript.

Funding
This research did not use external funding.

Ethical Review Board Statement
Not available.

Informed Consent Statement
Not available.

Data Availability Statement
Not available.

Conflicts of Interest
The authors declare no conflict of interest.

References
Abul-Husn, N. S., & Kenny, E. E. (2019). Personalized Medicine and the Power of Electronic Health Records. *Cell*, *177*(1), 58–69. https://doi.org/10.1016/j.cell.2019.02.039.

Agarwal, A., Soliman, M. K., Sepah, Y. J., Do, D. V., & Nguyen, Q. D. (2014). Diabetic Retinopathy: Variations in Patient Therapeutic Outcomes and Pharmacogenomics. *Pharmacogenomics and Personalized Medicine*, *7*, 399-409. https://doi.org/10.2147/PGPM.S52821.

Agyeman A. A., Ofori-Asenso R. (2015). Perspective: does personalized medicine hold the future for medicine? *J. Pharm. Bioallied. Sci*, *7*, 239–244. https://doi.org/10.4103/0975-7406.160040.

Antar, S. A., Ashour, N. A., Sharaky, M., Khattab, M., Ashour, N. A., Zais, R. T., Roh, E. J., Elkamhawy, J., & Al-Karmalawy, A.A. (2023). Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments. *Biomedicine and Pharmacotherapy*, *168*, 115734. https://doi.org/10.1016/j.biopha.2023.115734.

Arabi, A., Tadayoni, R., Ahmadieh, H., Shahraki, T., & Nikkhah, H. (2022). Update on Management of Non-proliferative Diabetic Retinopathy without Diabetic Macular Edema; Is There a Paradigm Shift?. *Journal of ophthalmic & vision research*, *17*(1), 108–117. https://doi.org/10.18502/jovr.v17i1.10175.

Ashraf M, Souka A, & Adelman R. (2016). Predicting outcomes to anti-vascular endothelial growth factor (VEGF) therapy in diabetic macular oedema: a review of the literature. *Br J Ophthalmol*, *100*(12), 1596–1604. https://doi.org/10.1136/bjophthalmol-2016-308388.

Ausi, Y., Barliana, M. I., Postma, M. J., & Suwantika, A. A. (2024). One Step Ahead in Realizing Pharmacogenetics in Low- and Middle-Income Countries: What Should We Do?. *Journal of multidisciplinary healthcare*, *17*, 4863–4874. https://doi.org/10.2147/JMDH.S458564.

Bahr, T. A., & Bakri, S. J. (2023). Update on the Management of Diabetic Retinopathy: Anti-VEGF Agents for the Prevention of Complications and Progression of Nonproliferative and Proliferative Retinopathy. *Life (Basel, Switzerland)*, *13*(5), 1098. https://doi.org/10.3390/life13051098.

Bhatwadekar, A. D., Shughoury, A., Belamkar, A., & Ciulla, T. A. (2021). Genetics of Diabetic Retinopathy, a Leading Cause of Irreversible Blindness in the Industrialized World. *Genes*, *12*(8), 1200. https://doi.org/10.3390/genes12081200.

Cabrera, A. P., Monickaraj, F., Rangasamy, S., Hobbs, S., McGuire, P., & Das, A. (2020). Do Genomic Factors Play a Role in Diabetic Retinopathy? *Journal of Clinical Medicine*, *9*(1), 216. https://doi.org/10.3390/jcm9010216.

Chawan-Saad, J., Wu, M., Wu, A., & Wu, L. (2019). Corticosteroids for Diabetic Macular Edema. *Taiwan journal of ophthalmology*, *9*(4), 233–242. https://doi.org/10.4103/tjo.tjo_68_19.

Chetoui, M., & Akhloufi, M. A. (2020). Explainable end-to-end deep learning for diabetic retinopathy detection across multiple datasets. *Journal of medical imaging (Bellingham, Wash.)*, *7*(4), 044503. https://doi.org/10.1117/1.JMI.7.4.044503.

Chong, H. Y., Allotey, P. A., & Chaiyakunapruk, N. (2018). Current landscape of personalized medicine adoption and implementation in Southeast Asia. *BMC medical genomics*, *11*(1), 94. https://doi.org/10.1186/s12920-018-0420-4.

Chua, J., Lim, C. X. Y., Wong, T. Y., & Sabanayagam, C. (2018). Diabetic Retinopathy in the Asia-Pacific. *Asia-Pacific journal of ophthalmology (Philadelphia, Pa.)*, *7*(1), 3–16. https://doi.org/10.22608/APO.2017511.

Cleland C. (2023). Comparing the International Clinical Diabetic Retinopathy (ICDR) severity scale. *Community eye health*, *36*(119), 10. https://pubmed.ncbi.nlm.nih.gov/37600672/

Dai, L., Sheng, B., Chen, T., Wu, Q., Liu, R., Cai, C., Wu, L., Yang, D., Hamzah, H., Liu, Y., Wang, X., Guan, Z., Yu, S., Li, T., Tang, Z., Ran, A., Che, H., Chen, H., Zheng, Y., Shu, J., … Jia, W. (2024). A deep learning system for predicting time to progression of diabetic retinopathy. *Nature medicine*, *30*(2), 584–594. https://doi.org/10.1038/s41591-023-02702-z.

Das, A., McGuire, P. G., & Rangasamy, S. (2015). Diabetic Macular Edema: Pathophysiology and Novel Therapeutic Targets. *Ophthalmology*, *122*(7), 1375–1394. https://doi.org/10.1016/j.ophtha.2015.03.024.

Do, D. V., Wang, X., Vedula, S. S., Marrone, M., Sleilati, G., Hawkins, B. S., & Frank, R. N. (2015). Blood pressure control for diabetic retinopathy. *The Cochrane database of systematic reviews*, *1*, CD006127. https://doi.org/10.1002/14651858.CD006127.pub2.

Drugan, T., & Leucuța, D. (2024). Evaluating Novel Biomarkers for Personalized Medicine. *Diagnostics*, *14*(6), 587. https://doi.org/10.3390/diagnostics14060587.

Elvira, E., & Suryawijaya E. E. (2019). Retinopati Diabetes. *Continuing Medical Innovation*, *46*(3), 220-224. https://doi.org/10.55175/cdk.v46i3.514.

Ezhilvendhan, K., Sathiyamoorthy, A., Prakash, B. J., Bhava, B. S., & Shenoy, A. (2021). Association of Dyslipidemia with Diabetic Retinopathy in Type 2 Diabetes Mellitus Patients: A Hospital-Based Study. *Journal of pharmacy & bioallied sciences*, *13*(2), S1062–S1067. https://doi.org/10.4103/jpbs.jpbs_164_21.

Ginsburg, G. S., & Phillips, K. A. (2018). Precision Medicine: From Science To Value. *Health affairs (Project Hope)*, *37*(5), 694–701. https://doi.org/10.1377/hlthaff.2017.1624.

Gonzalez-Cortes, J. H., Martinez-Pacheco, V. A., Gonzalez-Cantu, J. E., Bilgic, A., de Ribot, F. M., Sudhalkar, A., Mohamed-Hamsho, J., Kodjikian, L., & Mathis, T. (2022). Current Treatments and Innovations in Diabetic Retinopathy and Diabetic Macular Edema. *Pharmaceutics*, *15*(1), 122. https://doi.org/10.3390/pharmaceutics15010122.

Haque, M., Islam, T., Sartelli, M., Abdullah, A., & Dhingra, S. (2020). Prospects and Challenges of Precision Medicine in Lower- and Middle-Income Countries: A Brief Overview. *Bangladesh Journal of Medical Science*, *19*(1), 32-47. https://doi.org/10.3329/bjms.v19i1.43871.

Hasanzad, M., Sarhangi, N., Ehsani Chimeh, S., Ayati, N., Afzali, M., Khatami, F., Nikfar, S., & Aghaei Meybodi, H. R. (2021). Precision medicine journey through omics approach. *Journal of diabetes and metabolic disorders*, *21*(1), 881–888. https://doi.org/10.1007/s40200-021-00913-0.

Hisan, U. K., & Amri, M. M. (2023). Recommendation of precision medicine application in Indonesia from multiple perspective: a review. *International Journal of Public Health Science (IJPHS)*, *12*(1): 225-238. https://doi.org/10.11591/ijphs.v12i1.22010.

Hossain, M. J., Al-Mamun, M., & Islam, M. R. (2024). Diabetes mellitus, the fastest growing global public health concern: Early detection should be focused. *Health science reports*, *7*(3), e2004. https://doi.org/10.1002/hsr2.2004.

Jenkins, A. J., Joglekar, M. V., Hardikar, A. A., Keech, A. C., O'Neal, D. N., & Januszewski, A. S. (2015). Biomarkers in Diabetic Retinopathy. *The review of diabetic studies : RDS*, *12*(1-2), 159–195. https://doi.org/10.1900/RDS.2015.12.159.

Jin, K., & Zhang, C. (2023). Personalized Medicine in Ophthalmic Diseases: Challenges and Opportunities. *Journal of personalized medicine*, *13*(6), 893. https://doi.org/10.3390/jpm13060893.

Kamelia, T., and Rahayu, N. A. (2023). Perkembangan Precision Medicine di Indonesia. *Indonesia Journal Chest*, *10*(1), 1-12. https://www.indonesiajournalchest.com/index.php/IJC/issue/view/223.

Kansora, M. B., & Goldhardt, R. (2019). Decision Making in Proliferative Diabetic Retinopathy Treatment. *Current ophthalmology reports*, *7*(1), 45–50. https://doi.org/10.1007/s40135-019-00198-w.

Kim, H. J., & Kim, K. I. (2022). Blood Pressure Target in Type 2 Diabetes Mellitus. *Diabetes & metabolism journal*, *46*(5), 667–674. https://doi.org/10.4093/dmj.2022.0215.

Kowluru R. A. (2023). Cross Talks between Oxidative Stress, Inflammation and Epigenetics in Diabetic Retinopathy. *Cells*, *12*(2), 300. https://doi.org/10.3390/cells12020300.

Kąpa, M., Koryciarz, I., Kustosik, N., Jurowski, P., & Pniakowska, Z. (2024). Modern Approach to Diabetic Retinopathy Diagnostics. *Diagnostic*, *14*(17), 1846. https://doi.org/10.3390/diagnostics14171846.

Li W, Chen S, Mei Z, Zhao F, Xiang Y. (2019). Polymorphisms in Sorbitol-Aldose Reductase (Polyol) Pathway Genes and Their Influence on Risk of Diabetic Retinopathy Among Han Chinese. *Med Sci Monit*, *20*(25), 7073-7078. https://doi.org/10.12659/MSM.917011.

Lim, J. I., Regillo, C. D., Sadda, S. R., Ipp, E., Bhaskaranand, M., Ramachandra, C., & Solanki, K. (2022). Artificial Intelligence Detection of Diabetic Retinopathy: Subgroup Comparison of the EyeArt System with Ophthalmologists' Dilated Examinations. *Ophthalmology science*, *3*(1), 100228. https://doi.org/10.1016/j.xops.2022.100228.

Liu, L., Quang, N. D., Banu, R., Kumar, H., Tham, Y. C., Cheng, C. Y., Wong, T. Y., & Sabanayagam, C. (2020). Hypertension, blood pressure control and diabetic retinopathy in a large population-based study. *PloS one*, *15*(3), e0229665. https://doi.org/10.1371/journal.pone.0229665.

Liu, R., Wang, X., Aihara, K., & Chen, L. (2014). Early diagnosis of complex diseases by molecular biomarkers, network biomarkers, and dynamical network biomarkers. *Medicinal research reviews*, *34*(3), 455–478. https://doi.org/10.1002/med.21293.

Miller N.A., Farrow E.G., & Gibson M. (2015) A 26-hour System of Highly Sensitive Whole Genome Sequencing for Emergency Management of Genetic Diseases. *Genome Med*, *7*, 100. https://doi.org/10.1186/s13073-015-0221-8.

Molla, G., & Bitew, M. (2024). Revolutionizing Personalized Medicine: Synergy with Multi-Omics Data Generation, Main Hurdles, and Future Perspectives. *Biomedicines*, *12*(12), 2750. https://doi.org/10.3390/biomedicines12122750.

Naithani, N., Sinha, S., Misra, P., Vasudevan, B., & Sahu, R. (2021). Precision medicine: Concept and tools. *Medical journal, Armed Forces India*, *77*(3), 249–257. https://doi.org/10.1016/j.mjafi.2021.06.021.

Nga, V.V., Minh, N.T.B., Dung, D.T.M., Anh, N.T.L., Huu, N.C., Anh, B.T.V., Hiep, N. X., Ha, H.T.T., Khanh, T.V., Thom, V.T., & Thanh, L.C. (2023). Risk factors related to diabetic retinopathy in Vietnamese patients with type 2 diabetes mellitus. *Endocrine and Metabolic Science*, *13*(1), 100145. https://doi.org/10.1016/j.endmts.2023.100145.

Ortega, V. E., & Meyers, D. A. (2014). Pharmacogenetics: implications of race and ethnicity on defining genetic profiles for personalized medicine. *The Journal of allergy and clinical immunology*, *133*(1), 16–26. https://doi.org/10.1016/j.jaci.2013.10.040.

Paré G., & Kitsiou, S. (2017). *Chapter 9 Methods for Literature Reviews. In: Lau F, Kuziemsky C, editors. Handbook of eHealth Evaluation: An Evidence-based Approach [Internet]*. Victoria (BC): University of Victoria. https://www.ncbi.nlm.nih.gov/books/NBK481583/

Pei, X., Huang, D., & Li, Z. (2024). Genetic insights and emerging therapeutics in diabetic retinopathy: from molecular pathways to personalized medicine. *Frontiers in genetics*, *15*, 1416924. https://doi.org/10.3389/fgene.2024.1416924.

Rajalakshmi, R., Prathiba, V., & Mohan, V. (2016). Does tight control of systemic factors help in the management of diabetic retinopathy?. *Indian journal of ophthalmology*, *64*(1), 62–68. https://doi.org/10.4103/0301-4738.178146.

Rathsman, B., Haas, J., Persson, M., Ludvigsson, J., Svensson, A. M., Lind, M., Andersson Franko, M., & Nyström, T. (2021). LDL cholesterol level as a risk factor for retinopathy and nephropathy in children and adults with type 1 diabetes mellitus: A nationwide cohort study. *Journal of internal medicine*, *289*(6), 873–886. https://doi.org/10.1111/joim.13212.

Rodríguez-Gutiérrez, R., & Montori, V. M. (2016). Glycemic Control for Patients With Type 2 Diabetes Mellitus: Our Evolving Faith in the Face of Evidence. *Circulation. Cardiovascular quality and outcomes*, *9*(5), 504–512. https://doi.org/10.1161/CIRCOUTCOMES.116.002901.

S, D., & R, K. (2024). A Review of the Regulatory Challenges of Personalized Medicine. *Cureus*, *16*(8), e67891. https://doi.org/10.7759/cureus.67891.

Safi, H., Safi, S., Hafezi-Moghadam, A., & Ahmadieh, H. (2018). Early detection of diabetic retinopathy. *Survey of ophthalmology*, *63*(5), 601–608. https://doi.org/10.1016/j.survophthal.2018.04.003.

Safi, S. Z., Qvist, R., Kumar, S., Batumalaie, K., & Ismail, I. S. (2014). Molecular mechanisms of diabetic retinopathy, general preventive strategies, and novel therapeutic targets. *BioMed research international*, *2014*, 801269. https://doi.org/10.1155/2014/801269.

Sajovic, J., Cilenšek, I., Mankoč, S., Tajnšek, Š., Kunej, T., Petrovič, D., et al. (2019). Vascular endothelial growth factor (VEGF)-related polymorphisms rs10738760 and rs6921438 are not risk factors for proliferative diabetic retinopathy (PDR) in patients with type 2 diabetes mellitus (T2DM). *Bosn. J. Basic Med. Sci*, *19*(1), 94–100. https://doi.org/10.17305/bjbms.2018.3519.

Salz, D. A., & Witkin, A. J. (2015). Imaging in diabetic retinopathy. *Middle East African journal of ophthalmology*, *22*(2), 145–150. https://doi.org/10.4103/0974-9233.151887.

Sasongko, M. B., Widyaputri, F., Agni, A. N., Wardhana, F. S., Kotha, S., Gupta, P., Widayanti, T. W., Haryanto, S., Widyaningrum, R., Wong, T. Y., Kawasaki, R., & Wang, J. J. (2017). Prevalence of Diabetic Retinopathy and Blindness in Indonesian Adults With Type 2 Diabetes. *American journal of ophthalmology*, *181*, 79–87. https://doi.org/10.1016/j.ajo.2017.06.019.

Schreur V, van Asten F, Ng H, Weeda J, Groenewoud JMM, Tack CJ, Hoyng CB, de Jong EK, Klaver CCW, & Jeroen Klevering B. (2018). Risk factors for development and progression of diabetic retinopathy in Dutch patients with type 1 diabetes mellitus. *Acta Ophthalmol*, *96*(5), 459-464. https://doi.org/10.1111/aos.13815.

Sebastian, P. A. W., Kusumadjadja, M. A., Juliari, I. G. A. M., & Suryaningrum, I. G. A. R. (2023). Karakteristik Pasien Diabetic Retinopathy. *Intisari Sains Mediaa*, *14*(1): 59-63. https://doi.org/10.15562/ism.v14i1.1576.

Senapati, A., Tripathy, H. K., Sharma, V., & Gandomi, A. H. (2024). Artificial Intelligence of Diabetic Retinopathy Detection: A Systemic Review. *Informatics in Medicine Unlocked*, *45*(2024): 101445. https://doi.org/10.1016/j.imu.2024.101445.

Shukla UV, & Tripathy K. (2023). *Diabetic Retinopathy*. Treasure Island (FL): StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK560805/.

Sienkiewicz-Szłapka, E., Fiedorowicz, E., Król-Grzymała, A., Kordulewska, N., Rozmus, D., Cieślińska, A., & Grzybowski, A. (2023). The Role of Genetic Polymorphisms in Diabetic Retinopathy: Narrative Review. *International Journal of Molecular Sciences*, *24*(21), 15865. https://doi.org/10.3390/ijms242115865.

Stefanicka-Wojtas, D., & Kurpas, D. (2023). Personalised Medicine-Implementation to the Healthcare System in Europe (Focus Group Discussions). *Journal of personalized medicine*, *13*(3), 380. https://doi.org/10.3390/jpm13030380.

Straatsma B. R. (2018). Precision medicine and clinical ophthalmology. *Indian journal of ophthalmology*, *66*(10), 1389–1390. https://doi.org/10.4103/ijo.IJO_1459_18.

Su, J., Yang, L., Sun, Z., & Zhan, X. (2024). Personalized Drug Therapy: Innovative Concept Guided With Proteoformics. *Molecular & cellular proteomics : MCP*, *23*(3), 100737. https://doi.org/10.1016/j.mcpro.2024.100737.

Su, Z., Wu, Z., Liang, X., Xie, M., Xie, J., Li, H., Wang, X., & Jiang, F. (2023). Diabetic retinopathy risk in patients with unhealthy lifestyle: A Mendelian randomization study. *Frontiers in endocrinology*, *13*, 1087965. https://doi.org/10.3389/fendo.2022.1087965.

Tomita Y, Lee D, Tsubota K, Negishi K, & Kurihara T. (2021). Updates on the Current Treatments for Diabetic Retinopathy and Possibility of Future Oral Therapy. *Journal of Clinical Medicine*, *10*(20), 4666. https://doi.org/10.3390/jcm10204666.

Vaughan N. (2024). Review of smartphone funduscopy for diabetic retinopathy screening. *Survey of ophthalmology*, *69*(2), 279–286. https://doi.org/10.1016/j.survophthal.2023.10.006.

Wahidin, M., Achadi, A., Besral, B., Kosen, S., Nadjib, M., Nurwahyuni, A., Ronoatmodjo, S., Rahajeng, E., Pane, M., & Kusuma, D. (2024). Projection of diabetes morbidity and mortality till 2045 in Indonesia based on risk factors and NCD prevention and control programs. *Scientific reports*, *14*(1), 5424. https://doi.org/10.1038/s41598-024-54563-2.

Wang, J. H., Roberts, G. E., & Liu, G. S. (2020). Updates on Gene Therapy for Diabetic Retinopathy. *Current diabetes reports*, *20*(7), 22. https://doi.org/10.1007/s11892-020-01308-w.

Wang, Z., Zhang, N., Lin, P., Xing, Y., & Yang, N. (2024). Recent advances in the treatment and delivery system of diabetic retinopathy. *Frontiers in endocrinology*, *15*, 1347864. https://doi.org/10.3389/fendo.2024.1347864.

Wijesingha, N., Tsai, W.-S., Keskin, A. M., Holmes, C., Kazantzis, D., Chandak, S., Kubravi, H., & Sivaprasad, S. (2024). Optical Coherence Tomography Angiography as a Diagnostic Tool for Diabetic Retinopathy. *Diagnostics*, *14*(3), 326. https://doi.org/10.3390/diagnostics14030326.

Wirkkala, J., Bloigu, R., & Hautala, N.M. (2019). Intravitreal bevacizumab improves the clearance of vitreous haemorrhage and visual outcomes in patients with proliferative diabetic retinopathy. *BMJ Open Ophthalmology*. 4:e000390. https://doi.org/10.1136/bmjophth-2019-000390.

Wright, W. S., Eshaq, R. S., Lee, M., Kaur, G., & Harris, N. R. (2020). Retinal Physiology and Circulation: Effect of Diabetes. *Comprehensive Physiology*, *10*(3), 933–974. https://doi.org/10.1002/cphy.c190021.

Wykoff C.C., Nittala M.G., Zhou B., Fan W., Velaga S.B., Lampen S.I.R., Rusakevich A.M., Ehlers J.P., Babiuch A., & Brown D.M. (2019). Intravitreal Aflibercept for Retinal Nonperfusion in Proliferative Diabetic Retinopathy: Outcomes from the Randomized RECOVERY Trial. *Ophthalmol. Retin*. *3,* 1076–1086. https://doi.org/10.1016/j.oret.2019.07.011.

Yin, L., Zhang, D., Ren, Q., Su, X., & Sun, Z. (2020). Prevalence and risk factors of diabetic retinopathy in diabetic patients: A community based cross-sectional study. *Medicine*, *99*(9), e19236. https://doi.org/10.1097/MD.0000000000019236.

Zhang, M., Wu, J., Wang, Y., Wu, J., Hu, W., Jia, H., & Sun, X. (2023). Associations between blood pressure levels and diabetic retinopathy in patients with diabetes mellitus: A population-based study. *Heliyon*, *9*(6), 16830. https://doi.org/10.1016/j.heliyon.2023.e16830.

Zhu, W. M D., Wu, Y. M. D., Meng, Y. F. M . D., Xing, Q. M. D., Tao, J. J. M D., & Lu, J. M. D. (2018). Association of obesity and risk of diabetic retinopathy in diabetes patients: A meta-analysis of prospective cohort studies. *Medicine*, *97*(32), e11807. https://doi.org/10.1097/MD.0000000000011807.

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