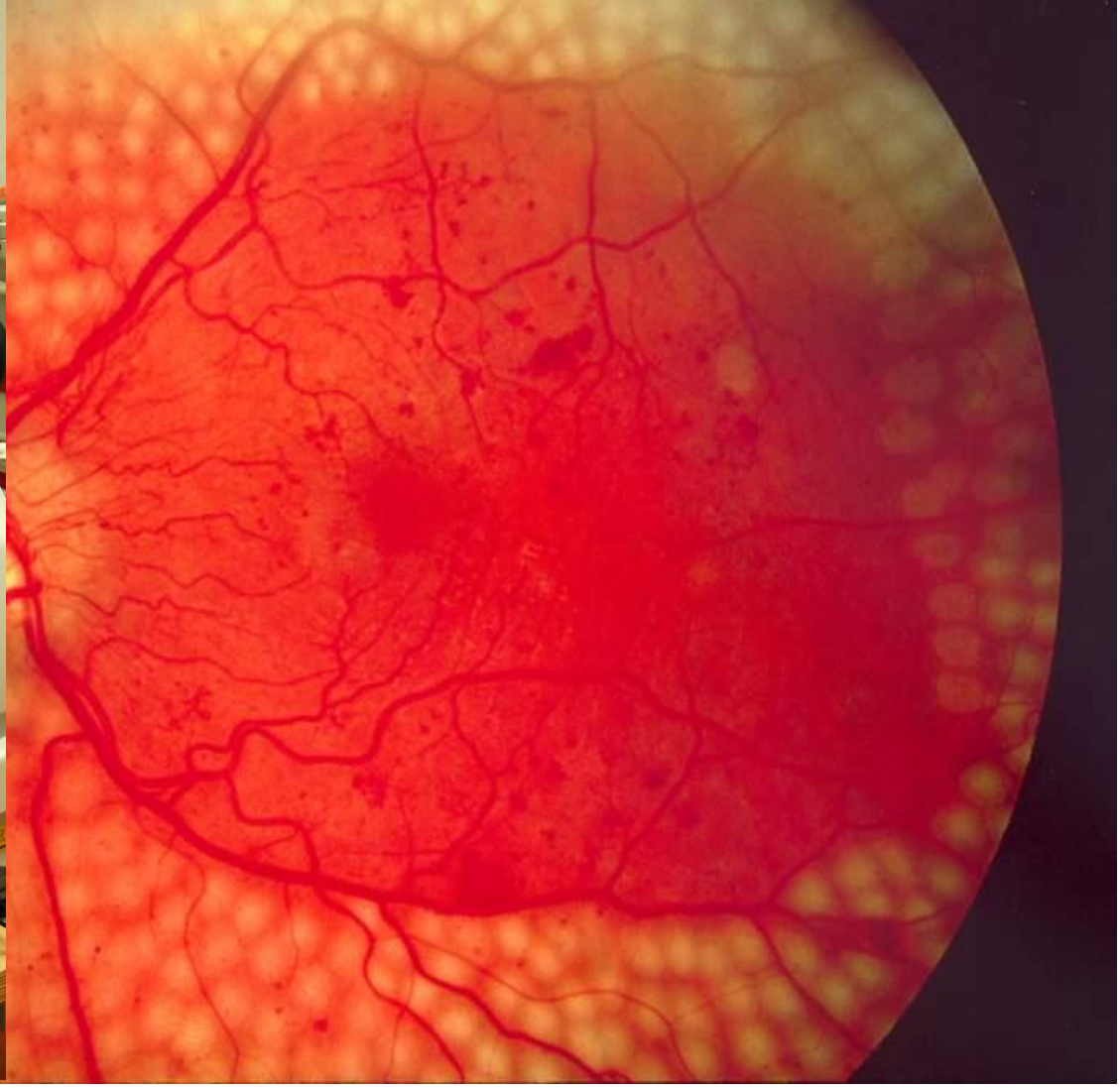

Available Technologies for Detection of Diabetic Retinopathy from Colour Fundus Photographs to Prevent Blindness in India

HTA Report by

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Regional Technical Resource Centre for Health Technology Assessment

(RTRC-HTA)

AMCHSS, SCTIMST, Thiruvananthapuram.

HTA REPORT

On

Available technologies for detection of diabetic retinopathy from colour fundus photographs to prevent blindness in India

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ABBREVIATIONS

Abbreviations.

BIA	Budget Impact Analysis
CT-HMM	Continuous-time Hidden Markov Model
DALY	Disability Adjusted Life Years
DM	Diabetes Mellitus
DME	Diabetic Macular Edema
DR	Diabetic Retinopathy
ETDRS	Early Treatment Diabetic Retinopathy Study
FHC	Family Health Centre
GRADE	Grades of Recommendation Assessment Development&Evaluation
HBP	Health Benefit Packages
HTA	Health Technology Assessment
HMA	Haemorrhages and Microaneurysms
HR	Human Resources
ICER	Incremental Cost Effectiveness Ratio
IRMA	Intra Retinal Microvascular Abnormalities
LMIC	Low-Middle Income Country
NCD	Non-communicable diseases
NCDC	Non-Communicable Diseases Clinics
NPDR	Non-proliferative Diabetic Retinopathy
NVD	Neo Vascularization of the Disc
NVE	Neo Vascularization Elsewhere
PICO	Population Intervention Comparator Outcome
PDR	Proliferative Diabetic Retinopathy
PHC	Primary Health Centre

PRP	Pan Retinal Photocoagulation
QALY	Quality Adjusted Life Years
RIO	Regional Institute of Ophthalmology
RR	Relative Risk
VTDR	Vision Threatening Diabetic Retinopathy
VRS	Vitreo Retinal Surgery

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EXECUTIVE SUMMARY.

INTRODUCTION.

Diabetic Retinopathy (DR), the common microvascular complication of diabetes mellitus, has a high prevalence in India, varying from 18% to 34%. The burden of retinopathy is expected to increase globally as diabetes is projected to increase from 285 million in 2010 to 439 million in 2030. Between 2000 and 2030, the prevalence of diabetes in India is expected to increase by 150%. Currently, 30% (28/93 million) of those with DR have vision-threatening diabetic retinopathy.

Diagnosis of diabetic retinopathy in the early stages can have a significant effect on its prognosis. Currently, the uptake of screening is low as the services of an ophthalmologist is required, and various barriers exist which prevent the patient from availing it. Tele-screening for DR, where a trained optometrist takes fundus photographs with a specialized camera at the primary level, which are forwarded to a higher centre for analysis, is a promising technology for improving uptake of screening.

The study compares two scenarios; one the existing one, where diabetic patients attending the Non-Communicable Disease (NCD) clinics are advised to undergo annual screening by an ophthalmologist; and a tele-screening model where all NCD attendees are subjected to fundus photography which is analyzed centrally at a higher centre, categorized into stages, and the patient is managed as per their category.

OBJECTIVES.

(i) To develop an economic model to compare the cost-effectiveness by calculating the ICER of tele-screening and non-screening scenarios for diabetic retinopathy aided by reviews of recent literature to bring out the prevalence, disease progression and risk profiles of diabetic retinopathy and screening strategies relevant to a resource-poor setting.

(ii) To evaluate the budget impact of implementing systematic teleophthalmology-based screening to the whole state.

METHODOLOGY.

A decision tree combined with a Markov model was developed to analyze the screening process, its effect on disease progression and to calculate the costs and QALYs associated with each stage of diabetic retinopathy. An initial cohort of 10,000 patients enters the cycle in both arms. Both health system and societal perspectives were adopted for the study, and a time horizon of 5 years was chosen. The ICER (Incremental Cost-Effectiveness Ratio) estimates were generated for both the scenarios along with sensitivity analyses and budget impact analysis.

RESULTS.

Tele-screening for diabetic retinopathy using fundus photography was cost-saving in the health system perspective with an ICER/QALY gained of -717 and cost-effective from the societal perspective. However, the study pointed to considerable out of pocket expenditure and loss of labour associated with screening. On doing one-way sensitivity analysis, ICER in health system perspective was highly influenced by treatment uptake and cost of screening. Societal perspective ICER by utility values of late stages of DR. The budget impact analysis showed that scaling up the program to all Family Health Centers (FHCs) in Kerala burden 16 crore rupees on the exchequer. However, the net impact will be saving around eight crore rupees by reducing the number of patients requiring expensive management in the late stages.

RECOMMENDATIONS.

Scaling up Nayanamritham like tele-screening model to the whole of Kerala is recommended as it is beneficial to the patient and the health system. However, ensuring that district-level hospitals can absorb the patient yield from screening who require specialized ophthalmic care is important.

1. INTRODUCTION.

1.1. DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is one common microvascular complications of diabetes mellitus, characterized by hyperglycaemia induced damage to the retinal microvasculature.[1] It is a significant cause of blindness in developing nations, among both type 1 and type 2 diabetes.[2]

THE BURDEN OF DIABETIC RETINOPATHY

The prevalence of diabetic retinopathy across different states in India varies from 18% - 34%. The global burden of diabetes is expected to rise from 285 million in 2010 to well over 439 million in 2030, thus increasing the burden of diabetic retinopathy.[3] Currently, India has around 72 million diabetics out of a population of approximately 1.3 billion. This number is estimated to rise to 135 million by 2045.[4] Between 2000 and 2030, the prevalence of diabetes in India is expected to increase 150%. Currently, 30% (28/93 million) of those with DR have vision-threatening diabetic retinopathy (VTDR).[5]

In 2019, China led the global top ten countries with the highest diabetic population (116.4 million), followed by India (77 million).[6] Developing countries account for seven of the world's top ten countries with the maximum diabetic population.[7] With the diabetic population expected to increase in the coming decades, India will have to incur huge expenditures on health in the future. Twenty years ago, diabetic retinopathy was the 17th leading cause of blindness in India.[8] Today, diabetes-related blindness ranks sixth among the leading causes of blindness in India.[9]

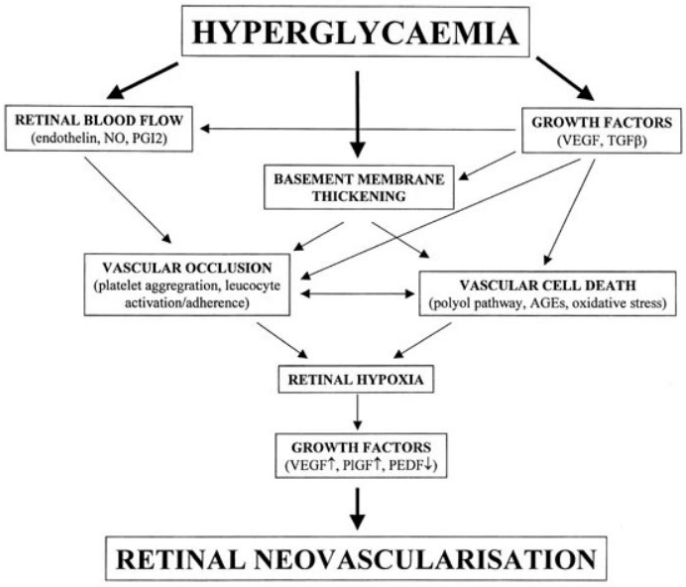
The prevalence of diabetes among the urban Indian population is 28.2%, and the prevalence of diabetic retinopathy is 14.9% (10.7–19.0%) among known diabetics aged ≥30 years and 18.1% (14.8–21.4) among those aged ≥50 years.[10] According to the same report, every fourth individual, more than 40 years in urban India, has diabetes, and every sixth diabetic has diabetic retinopathy.[11,12] In rural India, the prevalence of diabetic retinopathy is 17.6%, and in persons with newly detected diabetes is 10.2%. The prevalence of referable (sight-threatening) diabetic retinopathy is 5.3%.[13]

The state of Kerala has been undergoing a rapid epidemiological transition, and the prevalence of NCDs are increasing in Kerala. A report from 2006 suggested that one in five of the Kerala adult population may have diabetes.[14] However the National Family Health Survey round five (NFHS 5) estimates that 25-30% of the population of Kerala aged more than fifteen years have high or very high blood sugar levels or are taking medication for controlling blood sugar.[15] Hence, it may be safely assumed that at least a third of the adult population of Kerala are diabetic.

Etiopathogenesis of Diabetic Retinopathy

Patients with either Type 1 or Type2 diabetes are at risk of developing neurovascular complications of diabetes that can lead to diabetic retinopathy or Diabetic Macular Edema (DME). It is characterized by hyperglycaemia, basement membrane thickening, pericyte loss, microaneurysms, Intra Retinal Microvascular Abnormalities (IRMA) and pre-retinal neovascularisation, which can eventually lead to blindness through haemorrhage and tractional retinal detachment.[2]

The incidence of proliferative diabetic retinopathy varies from 2% in those who had diabetes for less than five years to 15.5% in those who had diabetes for fifteen or more years.[16] The onset and duration of diabetic retinopathy occurs more rapidly in type 2 diabetics compared to type 1.



: Etiopathogenesis of Diabetic Retinopathy

1.2. Staging and Prognosis of Diabetic Retinopathy.

Clinical staging.[17]

1. Background retinopathy

Microaneurysms start to appear in the retinal vasculature. There is no vision impairment in this stage, and no treatment is required. The patient needs stringent blood sugar control and frequent screening as the chances of progression to advanced stages within three years is more than 25%.

2. Pre-proliferative Retinopathy.

More severe and widespread changes, including aneurysms and exudates, venous bleeding etc., are seen. There is a high risk of patients developing vision impairment in future. Screening frequency is increased to three-month intervals.

3. Proliferative Retinopathy.

This is characterized by neovascularisation of the retina, leading to significant bleeding and retinal detachment. Patient's might have lost vision.

Microscopic staging of Diabetic Retinopathy[16]

Table 1: Microscopic Staging of Diabetic Retinopathy

Microscopic Stage	Definition	Clinical stage
DR Absent	All Diabetic Retinopathy features absent	No DR
Mild NPDR	Microaneurysms plus retinal haemorrhages and/or hard exudates and/or cotton wool spots.	Background Retinopathy
Moderate NPDR	Lesions above+ either extensive or severe Haemorrhages and Micro Aneurysms (HMA) or Intra Retinal Microvascular Abnormalities (IRMA) are present.	Pre-proliferative Retinopathy
Severe NPDR	Extensive and severe HMA, IRMA and/or venous bleeding	Pre-proliferative Retinopathy
Proliferative DR	Neo Vascularisation of the Disc (NVD) and/or Neo Vascularisation Elsewhere (NVE) without or with complications.	Proliferative retinopathy

1.3. Screening principles of Diabetic Retinopathy.

The principles of screening

The principles for screening for human disease derived from the public health papers produced by the WHO[18] in 1968 are:

1. The condition sought should be an important problem.
2. There should be an accepted treatment for patients with recognized diseases.
3. Facilities for diagnosis and treatment should be available.

4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The condition's natural history, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of the case-finding programme (including early diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care.
10. Case-finding should be a continuing process and not a 'one-time' project.

Screening for diabetic retinopathy

People with Type 1 diabetes should have annual examinations for diabetic retinopathy beginning five years after the onset of their disease, while those with Type 2 diabetes should have a prompt examination at the time of diagnosis, then at least yearly examinations thereafter. Women who develop gestational diabetes do not require an eye examination during pregnancy and do not appear to be at increased risk for developing diabetic retinopathy during pregnancy. However, people with diabetes who become pregnant should be examined soon after conception and early in the first trimester of the pregnancy. The recommended follow-up is every 3-12 months for no retinopathy or moderate non-proliferative diabetic retinopathy (NPDR), or every 1-3 months for severe NPDR, respectively.

Conventional Model.

Under the conventional model, patients diagnosed with diabetes and those under treatment for diabetes are advised to undergo timely screening at a speciality centre where an ophthalmologist is available. The ophthalmologist is physically present at the screening venue, and they screen the population themselves by performing dilated retinal evaluation by indirect ophthalmoscope/ direct ophthalmoscope/ slit lamp bio-microscopy.

Tele-screening model.

The facilities for fundus photo capture, including camera, paramedical staff etc., are available at peripheral centres permanently or on designated days. The images acquired when diabetic patients visit the centres are transferred by electronic means to the base hospital, where the ophthalmologist or a trained optometrist interprets the images. Mobile tele-screening (Phone-based non-Mydriatic) is an ophthalmologist-led screening program that takes eye care facilities to the rural population.

In addition, there are variants of these two broad models that are in use in various parts of India. In the 'ophthalmologist based' model, the ophthalmologist visits the PHC on designated days to conduct the screening. By and large, the different approaches used for screening of DR include telemedicine; eye camps for diabetes; mobile screening with or without training and treatment; screening in clinics for diabetics and hospitals providing large community-based screening programs for DR etc.

Is Mydriasis Needed While Using Nonmydriatic Camera?

Pupillary dilatation improves the gradability of a single-field 45° digital fundus image during tele-screening of diabetic retinopathy. It was reported that after pupillary dilatation, the non-gradability of digital fundus images reduced from 29.1% to 8.6%.[19] But more recent studies have shown that with improvements in the camera, non-mydriatic fundus retinography is also very useful in DR screening in the primary healthcare setting.[20,21]

Need for Tele-screening

In India, 66% of the population resides in rural areas[22], whereas 70% of healthcare resources are urban. It has been estimated that the ophthalmologist to patient ratio is at a dismal 1:100,000 for the Indian population and that 70% of the ophthalmologists' practice in urban areas.[23] This is well below the World Health Organization's recommended ratio of 1 ophthalmologist per 20,000 population[24], a severe shortage of specialists. At the same time, currently, few ophthalmologists in India have been trained to diagnose and treat diabetic retinopathy. The limited number of ophthalmologists available in the country adversely affects conducting an ophthalmologist-based screening

service in India. As a result, the optimal screening model in India may be an "ophthalmologist-led" system. Establishing mechanisms to reach populations with geographic and financial barriers to access is essential to prevent visual disability globally. The technology to facilitate this type of service is telemedicine.

Typically, automated detection of DR analyses retinal colour images obtained by fundus cameras and triages those who have DR and require referral to an ophthalmologist from those who can be screened again safely. Telemedicine includes assessing and analyzing patient information and interaction by a health professional who is separated temporally and/or spatially from the patient.[25] Table 2 shows the difference between these models. A tele-screening technology with a high-speed internet connection between the peripheral health and wellness centre/ health camp and the leading medical centre enables ophthalmologists working in the main medical centres (district/ taluk hospitals) to screen the rural population. This minimizes the number of unnecessary referrals to the main centre for diagnostic investigation and treatment and reduces the cost of the screening program.

Table 2: Comparison of Tele-screening model and current scenario

	Tele-screening model	Current Scenario
Feasibility	Yes, with less HR	Needs trained expert
Dilatation	May not be required	Needed (improvements in cameras have made it possible to take non-mydriatic images)
Maintenance	Required (if we include medical camps and on-site visits)	No
Capital expenditure	More	Less
Revenue expenditure	Less	More

Working Model of DR Tele-screening Program

The "Telehealth Practice Recommendations for Diabetic Retinopathy" divide DR telehealth program into four elements of care:

1. Image acquisition
2. Image review and evaluation
3. Patient care supervision
4. Image and data storage

These components require personnel with specific duties and qualifications, equipment and data transfer, legal requirements, validation, and quality control. The data collected include patient examination findings (identification, demographic, and medical information) and fundus images. These images are taken by a trained technician using a fundus camera. Images of both eyes of the patient are acquired under a fixed and predetermined protocol. Mydriasis using tropicamide may be required in some patients to obtain an image of sufficient quality.[19] The data are then encrypted to protect patients confidentiality and transmitted to the central server via the Internet or satellite. At the reading centre, an ophthalmologist or a specially trained staff member performs image grading and interpretation and then decides about the treatment plan and referral to a higher centre. A report comprising findings and any medical advice by the specialist is made available to the patient at the peripheral imaging site itself.

1.4. Tele-screening in Kerala.

Need for Kerala.

Kerala has 35 million people, and one in five residents of urban Kerala have diabetes. The diabetic retinopathy screening in the state has been undergoing for some time now. In the private sector, DR screening for DM patients has been routinely done in specialized centres. In the government sector, the ophthalmologist-based model was pursued in most of the districts. The ophthalmologist would visit the peripheral on predesignated days (once a month), and the known cases of diabetes mellitus patients would be screened. Patients who needed further evaluation, including expert care, surgical intervention, were referred to the apex centres (Regional Institutes, Medical colleges etc.).

The Nayanamritham Project.

The Nayanamritham project has been implemented in the Indian state of Kerala following a research project led by a Moorfields Eye Hospital clinician. The Government of Kerala has introduced diabetic retinopathy screening because of the ORNATE India project, led by Moorfields's consultant surgeon Sobha Sivaprasad. The project aims to develop systematic diabetic retinopathy screening in the country by enhancing research capacity and capability in the country.

Currently, the project has been rolled out in a pilot mode in the district of Thiruvananthapuram. The state government is scaling up this intervention to all the fourteen districts of the state. The project is also expected to bring out evidence on the potential use of innovative technologies, such as handheld cameras with smartphone technology and automated grading, in addressing the burden of diabetic eye disease in India. The new policy will involve screening all people with diabetes who are registered in primary care clinics for diabetic retinopathy

1.5. THE RATIONALE OF THIS HTA

The burden of diabetes in lower-income countries is growing even faster than in higher-income countries, and this will increase the need for effective, low-cost screening programs for DR. Regular eye examinations are necessary to diagnose diabetic retinopathy at an early stage when it can be treated with the best prognosis, thus delaying, or deferring visual loss. Though treatment interventions at the early stages of DR and management of risk factors can reduce the burden of blindness due to DR by up to 90%, such early interventions remain a challenge for health care providers in India. In the context of the increasing prevalence of diabetes, the key to such early intervention would be annual screening for DR by an expert human and the grading of retinal images by trained grading personnel. The services of such personnel for DR screening and grading could reduce the need for trained ophthalmologists, thereby improving access to accurate diagnosis and subsequent diabetic eye care.

We hypothesize is that this study will improve health care processes for DR screening by integrating teleophthalmology within the existing health care system, will achieve and

maintain increased DR screening rates, and will be cheaper than utilizing ophthalmologists alone as human expert graders

2. *Research Question.*

The effectiveness and cost-effectiveness of tele-screening of diabetic patients for diabetic retinopathy in peripheral centres using fundus camera by trained technicians.

3. *Objectives.*

i. To develop an economic model to compare the cost-effectiveness by calculating the ICER of tele-screening and non-screening scenarios for diabetic retinopathy aided by reviews of recent literature to bring out the prevalence, disease progression and risk profiles of diabetic retinopathy and screening strategies relevant to a resource-poor setting.
ii. To evaluate the budget impact of implementing systematic teleophthalmology-based screening to the whole state.

4. METHODOLOGY

4.1. ECONOMIC EVALUATION

Framework

P(Population): Diabetic patients (an individual with a random blood glucose measurement ≥140 mg/dl was considered suspect for diabetes) who have not been previously screened for DR

I(Intervention): Tele-screening for diabetic retinopathy using a fundus camera

C(Comparator): Current scenario.

O(Outcome): ICER (Incremental Cost Effectiveness Ratio) per QALY gained.

Study perspective.

The study was conducted from both the Health System perspective and the Societal perspective.

From the Health system perspective, the expenses incurred by the system for screening and management of diabetic retinopathy patients in the intervention and comparator arm were compared.

From the societal perspective, the direct and indirect costs incurred by the patient were included in the analysis.

Time Horizon.

A time horizon of five years is chosen for this study, considering the lifespan of the imaging technique under study and the duration by which a sizeable proportion of patients progress from the stage of No Diabetic Retinopathy to Blindness.

STUDY SETTING.

The study was set in Thiruvananthapuram, the southern-most and capital district of the state of Kerala. The district has an area of 2,189 sq.km and a population of 33.01 lakhs at

a density of 1508/sq.km. The district holds close to 10% of the population of Kerala. The sex ratio is 1087 females per 1000 males, and the average literacy of the district is 93.022%.[26]

The district has a well-oiled three-tier health care delivery system with fifty Primary Health Centres (FHCs), sixteen of which have been upgraded to Family Health Centres (FHCs) constituting the primary level. The secondary level has four District/General hospitals, eight Taluq hospitals and 22 Community Health Centres (CHCs). The tertiary level includes a medical college, a regional institute of ophthalmology and several centres specializing in managing TB, leprosy, psychiatric and women& child health. While all the tertiary care centres are in urban areas, more than 90% of secondary and tertiary care centres are rural.[27]

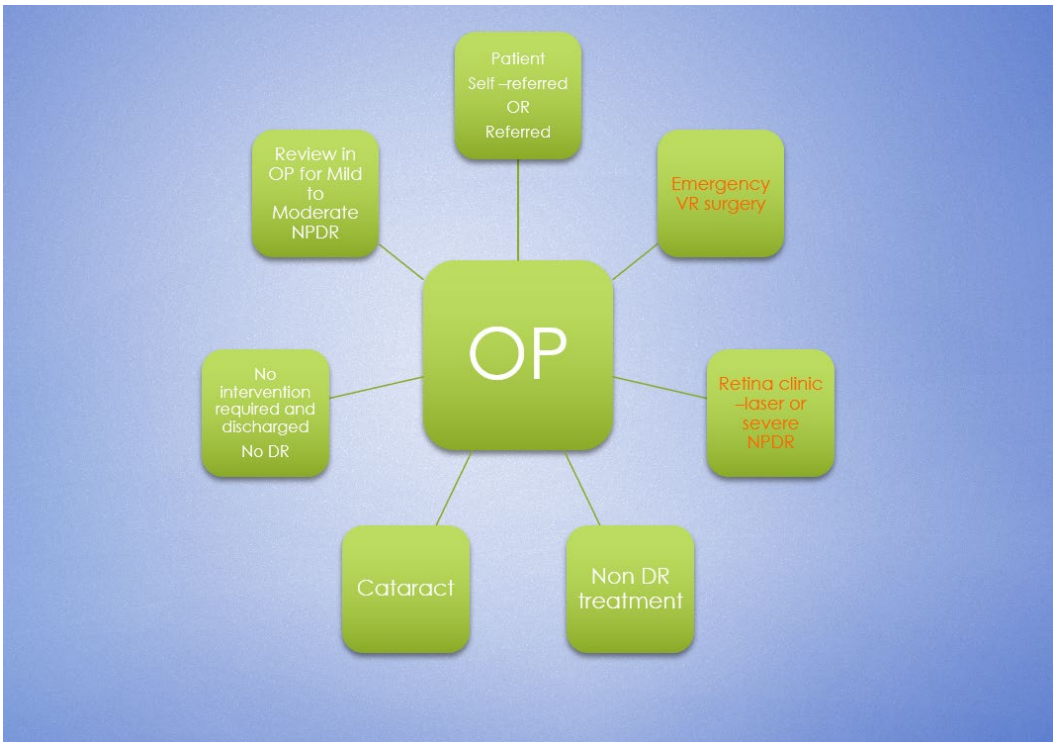
Diagnosis and management of diabetes are carried out primarily through Non-Communicable Disease (NCD) clinics that operate three days a week in the primary care centres. Patients registered are given medication free of cost for fifteen days to one month period. Hence around fifty per cent of patients with chronic conditions rely on government facilities for management, although in general, the public-private split in health care utilization is 30% and 70%, respectively.

COMPARATOR: CURRENT SCENARIO.

Type 1 and 2 diabetic patients are undergoing treatment through the NCD Clinics conducted at PHCs, and FHCs are advised to undergo yearly screening by an Ophthalmologist at district hospitals or above. The ophthalmologist is physically present at the screening venue, and they screen the population themselves by performing dilated retinal evaluation by indirect ophthalmoscope/ direct ophthalmoscope/ slit lamp bio-microscopy.

However, the take-up of screening at district hospitals is very low, and effectively, there is no functioning pathway for identification and management of early stages of diabetic retinopathy, patients self-represent to the Regional Institute of Ophthalmology (RIO) when vision is affected, usually in the later stages of DR.

Figure 2: Patient Flow in Current Scenario



INTERVENTION: NAYANAMRITHAM LIKE MODEL.

Under the project, sixteen FHCs in the district of Thiruvananthapuram have been provided with state-of-the-art non-Mydriatic fundus cameras, and optometrists trained at handling the fundus camera have been appointed at each FHC. The doctors and staff nurses working in the said FHCs are given training to orient them to the care pathway for diabetic retinopathy patients and prepare the patient for fundus photography. In addition to this, Asha workers have been trained on the purpose and functioning of the program to promote its uptake in the diabetic population of the concerned F.H.Cs.

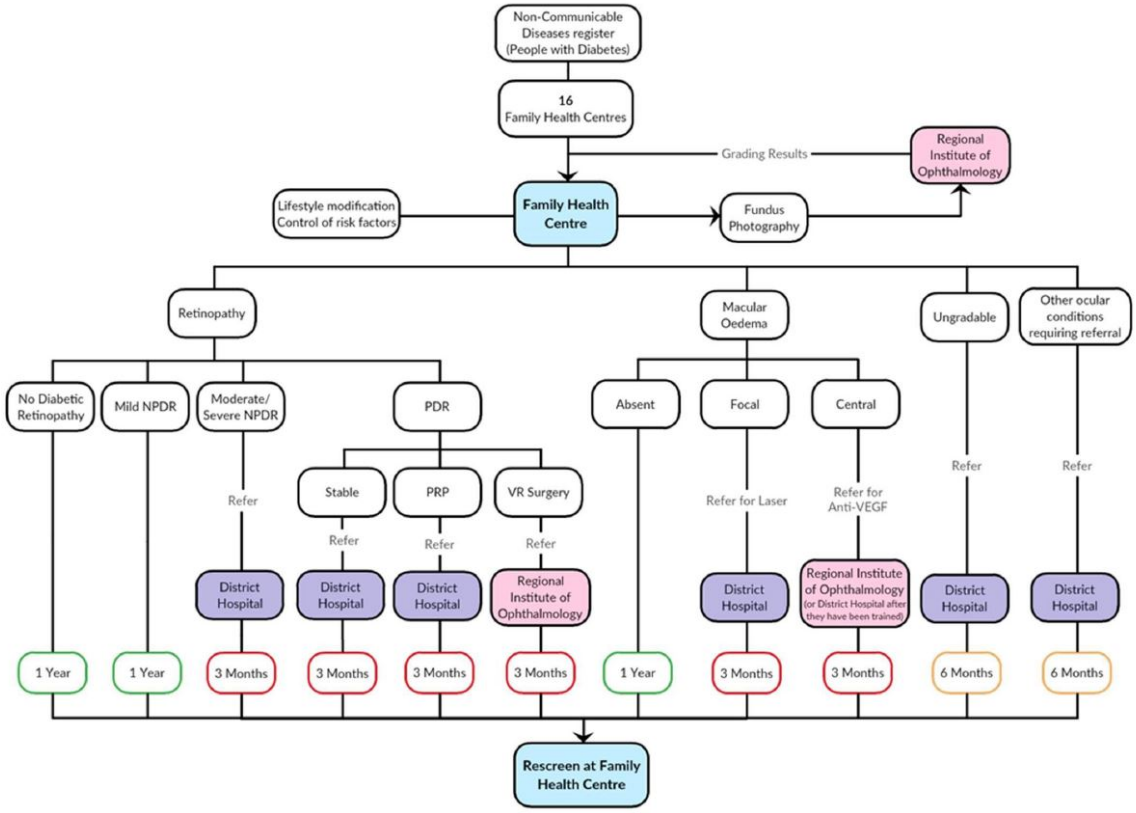
Diagnosis and Management Pathway Under Nayanamritham.

1. The capture of fundus photograph at FHC:
   Diabetic patients under treatment from NCD clinics in the concerned FHC are redirected to the Nayanamritham pathway. The trained optometrist captures the fundus images of the patient annually, and the captured images are forwarded to the unit at the Regional Institute of Ophthalmology (RIO), Thiruvananthapuram.
2. Grading of images at RIO

A trained optometrist, certified as having competency comparable to an ophthalmologist, grades the captured images into Ungradable, No DR, Mild NPDR, Mod NPDR, Severe NPDR and PDR. PDR patients are further classified into Stable, requiring Pan Retinal Photocoagulation and requiring Vitreoretinal surgery. The presence or absence of Diabetic Macular Edema is also assessed by the ophthalmologist. The results are returned to the respective FHCs

3. Management.
    i. No DR: Continue with annual screening.
    ii. Mild DR: Reduced screening interval to six months.
    iii. Moderate/Severe DR, Stable PDR: Reduced screening interval to three months
    iv. PDR requiring PRP: Referred to District Hospital for PRP, reduced screening interval to three months.
    v. PDR requiring VRS: Referred to Regional Institute of Ophthalmology for VRS, reduced screening interval to three months.

Figure 3: Nayanamritham Model



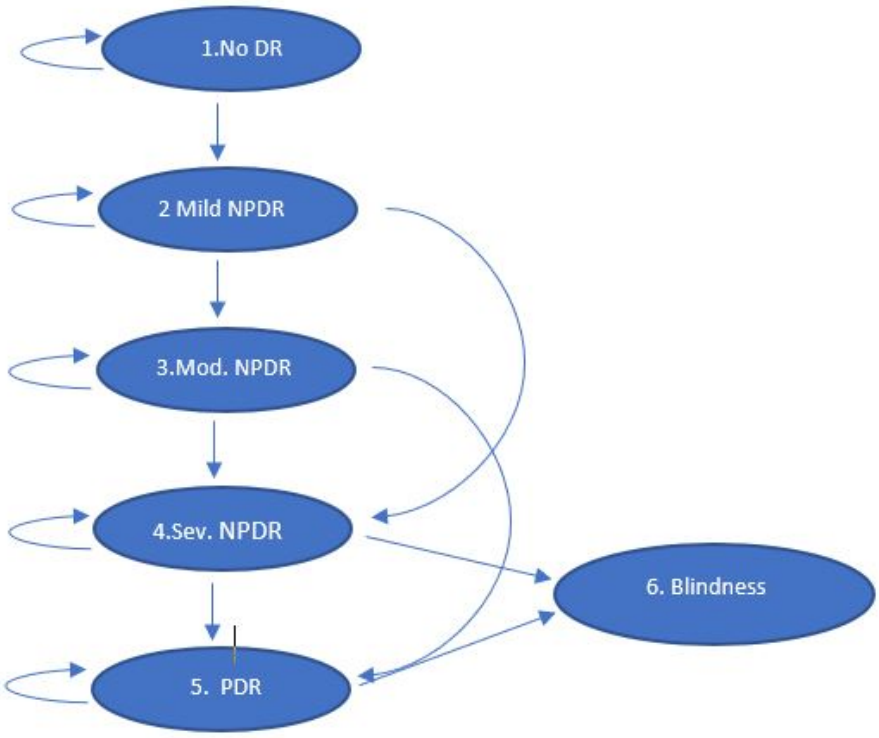
The state health department already has the pilot project data on screening results from sequential screening visits for individuals who had at least one screening exam between 2017 and 2019. They also collect the number of screening visits and the median interval between visits. In addition to the information on screening outcomes, the dataset also contains clinical and demographic variables, including the type of diabetes, diagnosis date, sex, and age. Under these circumstances, the state government necessitates a full health technology assessment on Tele-ophthalmology for Diabetic Retinopathy Screening to prevent blindness in Kerala.

4.2. MODEL OVERVIEW AND CEA

A decision tree cum Markov model was created to compare the tele-screening arm with the current scenario. The model depicts the costs and consequences associated with each stage of diabetic retinopathy.

Figure 4: Decision Tree

Figure 5: Markov Model



The cohort enters Markov stimulation with six health states in tele-screening and non-screening scenarios-No Diabetic Retinopathy, Mild Non-Proliferative Diabetic Retinopathy, Moderate Non-Proliferative Diabetic Retinopathy, Severe Non-Proliferative Diabetic Retinopathy, Proliferative Diabetic Retinopathy and Blindness. Cohort size is assumed to be ten thousand, which is the approximate number of adult diabetics seeking care at the NCD clinic of one FHC.

In the screening scenario, diabetic patients undergo screening at a frequency determined by their stage at the previous screening. Those with no diabetic retinopathy undergo screening yearly, mild DR every six months, moderate DR and upwards every three months.

Those categorized as having No DR, Mild NPDR, Moderate NPDR and Severe NPDR do not receive any ophthalmic treatment. Advice for systemic management of glycemia, including pharmaceutical and dietary modifications, are given.

In the non-screening scenario, patients self-report to an ophthalmologist when they experience problems with vision and are then managed identically to tele-screening patients. The model assumes that this self-reporting happens in the PDR stage.

4.3. Data collection and model inputs

The initial prevalence and utility values of diabetic patients in each stage and the transition probabilities in screening and non-screening scenarios were obtained through a targeted literature search.[28–30] Costs of procedures, screening, out of pocket expenditures etc. were taken from HBP packages, expert opinion or arrived at through investigators' calculation.

Cycle Length and Input Parameter Conversions.

The cycle length in Markov simulation was taken as three months, as it is the interval at which Moderate NPDR to PDR patients screened. The appropriate conversion was applied to all input parameters.

Transition Probabilities.

The annual transition probabilities obtained from literature were first converted to annual rates, which in turn are converted to cycle probabilities.

The equation used for converting probabilities to rate

$r = -[\ln(1-P)]/t$. [31]

Where r is the rate, P is the probability, and t is the time period of interest.

The rate was converted to probability using the equation

$p = 1 - \exp\{-rt\}$.

Utility values.

The annual utility values were converted into utility values for the cycle length by multiplying with the factor *3/12.*

Discount rate

The annual discount rate is taken and 3%. This was into a discount rate for the cycle length by multiplying with the factor *3/12.*

Costs

Capital costs were annuitized assuming a five-year life span and multiplied with the factor of 3/12 to convert them into per-cycle costs. Monthly recurring costs such as salary and overheads were multiplied by the factor 12/4 to convert them into per-cycle costs. All costs were finally converted to per-patient per-cycle cost by dividing by 10000, which is the assumed capacity of the system.

Table 3: Input parameters

Parameters	**Actual**	**Modified**	**References**
Initial prevalence of No Diabetic Retinopathy	0.6460	0.6460	[29] Nguyen et al
Initial prevalence of Mild NPDR	0.2115	0.2115	
Initial prevalence of Moderate NPDR	0.0755	0.0755	
Initial prevalence of Severe NPDR	0.0670	0.0670	
Initial prevalence of PDR	0	0	
Initial Prevalence of Blindness	0	0	
Proportion of PDR patients receiving treatment	0.25	0.25	K.I.I.
Proportion of Patients Requiring PRP among PDR	0.95	0.95	
Proportion of Patients Requiring VRS among PDR	0.05	0.05	
TP in NS: No DR to No DR	0.87	0.965784	[28] Srikant et al
TP in NS: No DR to Mild NPDR	0.13	0.034216	
TP in NS: Mild NPDR to Mild NPDR	0.8	0.947917	
TP in NS: Mild NPDR to Moderate NPDR	0.12	0.031453	
TP in NS: Mild NPDR to Severe NPDR	0.08	0.02063	
TP in NS: Moderate NPDR to Moderate NPDR	0.44	0.842178	
TP in NS: Moderate NPDR to Severe NPDR	0.3	0.085308	
TP in NS: Moderate NPDR to PDR	0.26	0.072512	
TP in NS: Severe NPDR to Severe NPDR	0.46	0.830743	
TP in NS: Severe NPDR to PDR	0.5	0.159104	
TP in NS: Severe NPDR to Blindness	0.04	0.010154	
TP in NS: PDR to PDR	0.88	0.968547	
TP in NS: PDR to Blindness	0.12	0.031453	
TP in NS: Blindness to Blindness	1	1	
TP in TS: No DR to No DR	0.94	0.98465	
TP in TS: No DR to Mild NPDR	0.06	0.01535	
TP in TS: Mild NPDR to Mild NPDR	0.75	0.933333	
TP in TS: Mild NPDR to Moderate NPDR	0.19	0.051317	

TP in TS: Mild NPDR to Severe NPDR	0.06	0.01535	[29] Nguyen et al
TP in TS: Moderate NPDR to Moderate NPDR	0.405	0.955678	
TP in TS: Moderate NPDR to Severe NPDR	0.17	0.033523	
TP in TS: Moderate NPDR to PDR	0.425	0.010799	
TP in TS: Severe NPDR to Severe NPDR	0.46	0.820798	
TP in TS: Severe NPDR to PDR	0.5	0.159104	
TP in TS: Severe NPDR to Blindness	0.04	0.020098	
TP in TS: PDR to PDR	0.88	0.979902	
TP in TS: PDR to Blindness	0.12	0.020098	
TP in TS: Blindness to Blindness	1	1	
Utility of No DR	0.87	0.2175	[30] Rachepelle et al
Utility of Mild NPDR	0.79	0.1975	
Utility of Moderate NPDR	0.79	0.1975	
Utility of Severe NPDR	0.7	0.175	
Utility of PDR	0.7	0.175	
Utility of Blindness	0.7	0.175	
Cost of Camera	3,50,000	1.910602	K.I.I.
Cost of Furniture	15000	0.081883	
Cost of Room	2000	0.6	
Cost of Electricity	500	0.15	
Cost of Training	40000	1	
Cost of Pan Retinal Photocoagulation	8500	8500	[32] H.B.P.2
Cost of Vitreo Retinal Surgery	35800	35800	
Cost of Hospitalisation			
Cost of Travel for patient+ bystander	200	200	Investigator Calculation
Cost of wage loss of patient + bystander per day	2000	2000	

4.4. Cost and QALY estimation

Estimation of Cost.

The total cost of screening was computed by multiplying the number of patients in each stage of Markov trace by the frequency of screening in each stage and the screening cost per patient per cycle. Since the cycle length was taken as three months and the cost of screening does not go up for the cohort of 10000 despite the number of visits, the screening frequency was taken as ¼ for the screening arm. Screening frequency in the non-screening arm is taken as zero.

The cost of treatment only applied to PDR stage, and each patient is assumed to undergo treatment only once. Hence, the additional number of patients in PDR in each cycle was determined by subtracting the value from the previous cycle and multiplying by the

proportion of patients undergoing PRP/VRS and the cost of PRP/VRS to arrive at the total treatment cost.

Estimation of QALYs.

Total QALYs in each arm was calculated by multiplying the number of patients in each stage of the Markov cycle by the utility values of the respective stage.

4.5. ICER ESTIMATION

The Incremental Cost-Effectiveness Ratio (ICER) was calculated through the following steps.

Incremental cost = Total Cost of Screening arm- Total Cost of Non-screening arm.

Incremental Effectiveness = Total QALYs of Screening Arm- Total QALYs of Non-Screening Arm.

ICER= Incremental Cost/Incremental Effectiveness.

Since the study considers both Heath System and Societal perspectives, ICERs were calculated independently for both.

SCOPING REVIEW

A scoping review was conducted to identify articles on the following areas relevant to this study.

i. Etiopathogenesis of Diabetic Retinopathy including stages and progression.
ii. Data on effectiveness and cost – effectiveness of tele-screening methods for diabetic retinopathy
iii. Cost of treatment of various stages of diabetic retinopathy and utilities associated with each stage.

4.7. SENSITIVITY ANALYSIS

The robustness of the model and parameters used in the model were assessed through one-way sensitivity analysis (OWSA), which was carried out in R. Base R, and *hesim* packages were used in the analysis.

4.8. BUDGET IMPACT ANALYSIS

A budget impact analysis (BIA) over a time horizon of five years was conducted to assess the financial implications of expanding the Nayanamritham Like Model to all the FHC.s in Kerala. The BIA model was based on the above cost-effectiveness model for the intervention and the comparator scenarios of DR tele-screening among patients with diabetes. Only health-system costs were considered in the BIA.

The following assumptions were made in the BIA.

i). The annual economic model holds true for five years.

ii) The annual budget is based on the unit cost of Camera, Salaries, Overheads, PRP, VRS etc. assumed in the Health System Perspective CEA model for DR.

iii) The uptake of screening is fixed at 100 %. Uptake of PRP/VRS assumed to be 25% for base-case analysis. The uptake was varied from 20% to 60% at 10% increments to account for uncertainty.

5. RESULTS.

5.1. DETERMINISTIC RESULTS.

Health System Perspective.

Costs borne by the health system for screening of Diabetic retinopathy and treatment of identified PDR patients were compared for tele-screening and non-screening arms. The discounted total cost incurred for tele-screening of a cohort of 10000 diabetic population was Rs. 4,721,715, which is lower compared to the non-screening arm for which the total cost is 5,241,721. The discounted QALY gained was 724.67, yielding an ICER/QALY gained of -717, making tele-screening a cost-saving intervention.

Table 4: ICER - Health System Perspective

Strategy	Costs	QALYs	Incremental Costs	Incremental QALYS
Non-Screening	5,241,721	37121.11		
Tele-screening	4,721,715	37845.78	-520,006	724.67
ICER	**-717**			

Note: Costs and QALYs are discounted at 3% per annum.

Societal Perspective.

Costs borne by the society for screening of Diabetic retinopathy and treatment of identified PDR patients were compared for tele-screening and non-screening arms. The discounted total cost incurred for tele-screening of a cohort of 10000 diabetic population was Rs. 105,213,355, which is higher compared to the non-screening arm for which the total cost is 6,518,391. The discounted QALY gained was 724.67, yielding an ICER/QALY gained of 1,36,192.

Table 5: ICER- Societal Perspective

Strategy	Costs	QALYs	Incremental Costs	Incremental QALYS
Non-Screening	6,516,950	37121.11		
Tele-screening	105,213,355	37845.78	98,696,405	724.67
ICER	**136,194**			

Note: Costs and QALYs are discounted at 3% per annum.

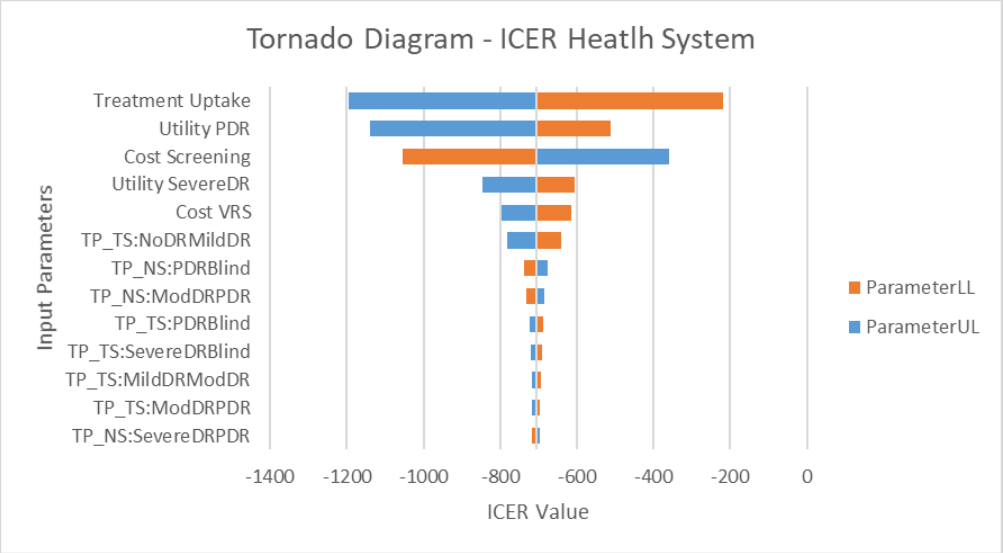
5.2. SENSITIVITY ANALYSIS

One way sensitivity analysis was carried out for Health system and Societal perspectives by varying the input parameters by 20% in both directions.

Health System Perspective.

Variations in Health System perspective ICER obtained by varying model input parameters by ±20% is demonstrated in the graph below. Maximum variation was caused by variations in Treatment Uptake, Utility values of PDR stage and cost of screening. Transition probabilities between stages caused minimal variations in health system ICER

Figure 6: Tornado Diagram; Health System ICER

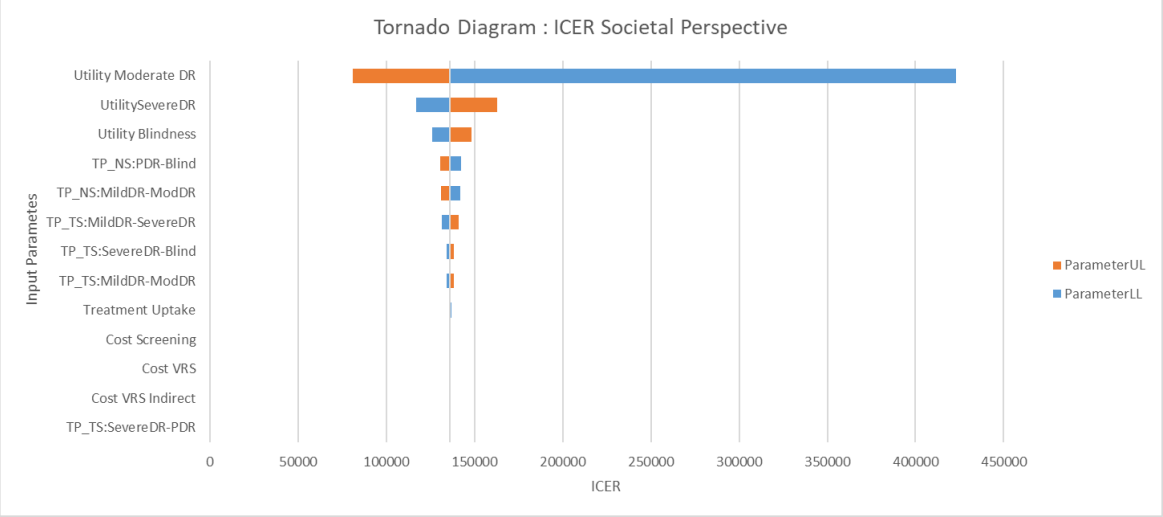


TP_TS: Transition Probability tele-screening arm; TP_NS: Transition Probability Non-screening arm

Societal Perspective.

Variations in Societal perspective ICER obtained by varying model input parameters by ±20% is demonstrated in the graph below. Maximum variation was caused by variations in Utility values of Moderate DR, Severe DR and PDR stages, and the cost of screening. Transition probabilities had some influence on ICER variation, and the cost of various parameters had negligible influence.

Figure 7: Tornado diagram: ICER FROM Societal Perspective



TP_TS: Transition Probability tele-screening arm; TP_NS: Transition Probability Non-screening arm

5.3. BUDGET IMPACT ANALYSIS.

A budget impact analysis was done for upscaling the project to the whole of Kerala, and cost from a health system perspective was considered. The cost of tele-screening obtained from the cost-effectiveness analysis was Rs.47,07,417 for a cohort of 10000 belonging to a single FHC over a five-year period.

This brings the annual cost of a single FHC for this screening to Rs.9,41,483.

The total number of FHCs in Kerala is 170.[27] Hence, assuming the same uptake of screening and treatment, the annual budget for expanding the project to all FHCs in Kerala comes to Rs. 160052178 ~ 16 crore rupees.

The cost savings from one FHC is Rs. 5,12, 006 and for 170 FHCs. Rs.8,70,41,020~ 8.7crore rupees.

Figure 8: Incremental Cost and QALYs

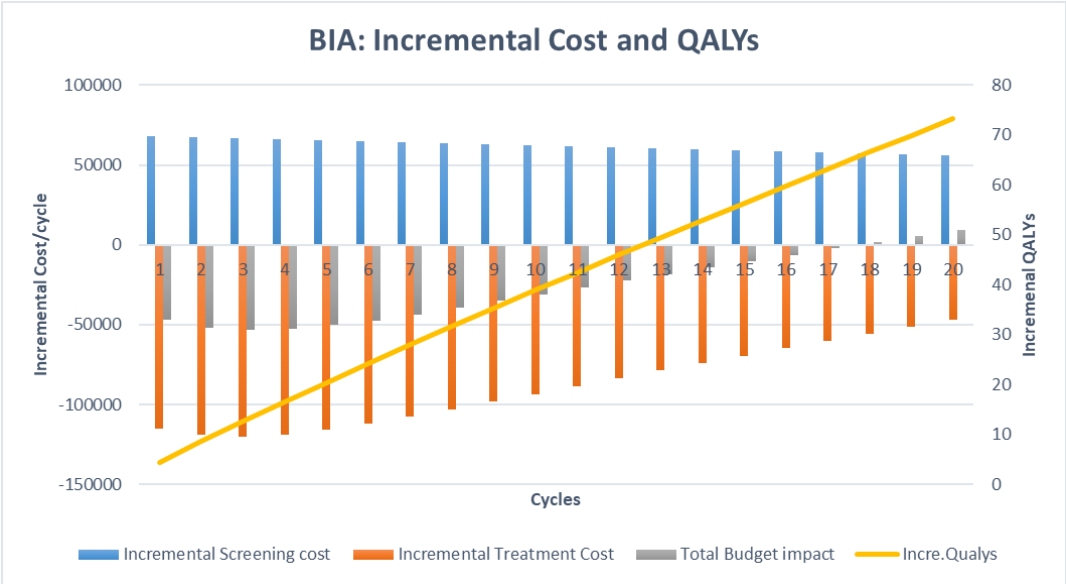
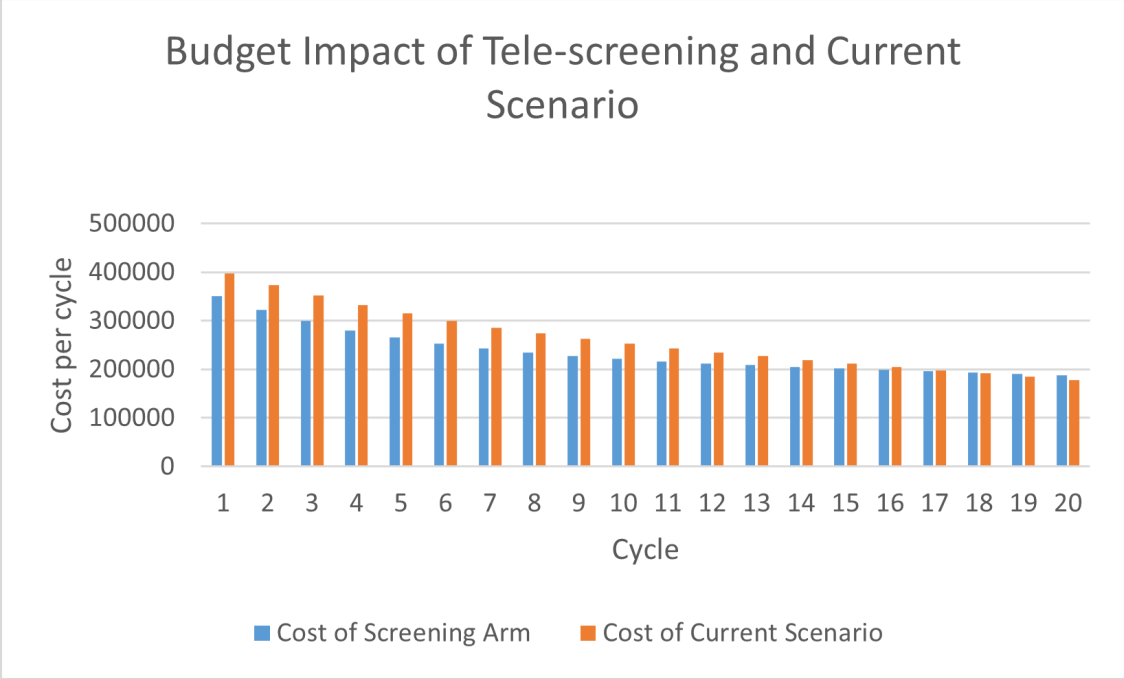


Figure 9: Budget Impact of Tele-screening and Current Scenario



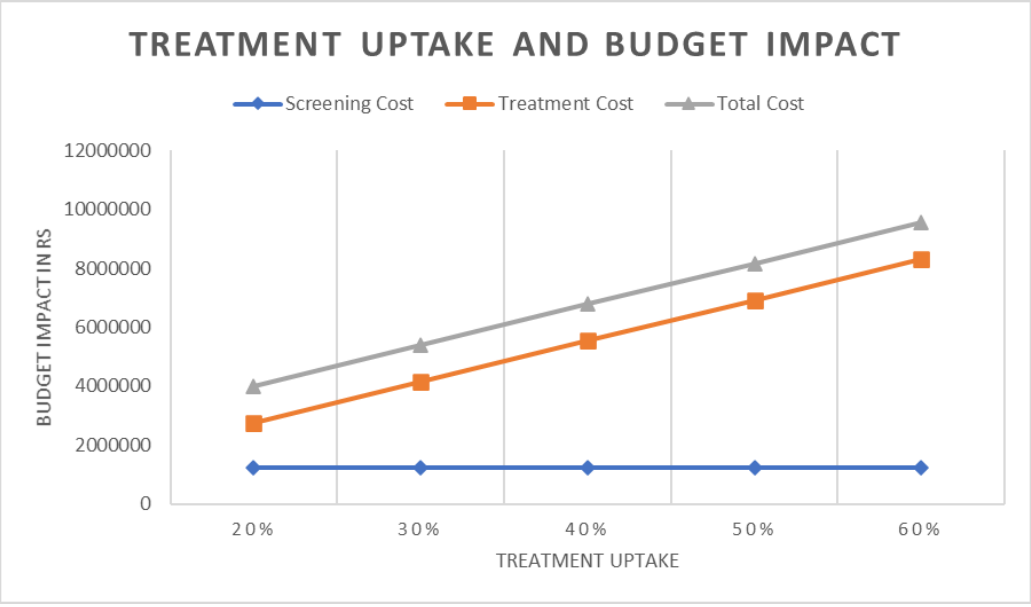
BIA: Uncertainty analysis

Variation in treatment uptake in PDR stage is the primary determinant of budget impact. Hence, the budget impact was calculated by varying treatment uptake from 20% to 60% in increments of 10%. The results are displayed in table number 6. The cost of treatment for the cohort of 10000 in each FHC for five years increases by nearly 14 lakh rupees for every 10% increment in treatment uptake, which translates to nearly five crore rupees increment in annual budget impact for the state of Kerala. The budget impact of implementing the screening program to all FHCs in Kerala is 13.64 crores at treatment uptake of 20% and 32.49 crores at treatment uptake of 60%.

Table 6: Treatment Uptake and Budget Impact

Treatment Uptake	Treatment Cost (Rs)	Total Cost/FHC(Rs)	Annual Cost/FHC(Rs)	Annual Cost for Kerala(Rs)	Percentage of State Health Budget
20%	27,72,099	40,14,264	8,02,852	13,64,84,976	0.19
30%	41,58,149	54,00,314	10,80,062	18,36,10,676	0.25
40%	55,44,198	67,86,364	13,57,272	23,07,36,376	0.32
50%	69,30,248	81,72,413	16,34,482	27,78,62,042	0.38
60%	83,16,298	95,58,463	19,11,692	32,49,87,742	0.45

Figure 10: Treatment Uptake and Budget Impact



6. Discussion.

The prevalence of diabetes and its complications are bound to increase globally and in India in the coming decades. Diabetic retinopathy, a major microvascular complication of diabetes mellitus, is one of the leading causes of blindness in third world countries. Hence, cost-effective methods for screening of diabetic retinopathy, which are suitable for the Indian context, is the need of the hour.

The cost-effectiveness analysis in the health system perspective in the current study yielded a deterministic ICER value of -717 and a QALY gain of 725, implying that adopting tele-screening of diabetic retinopathy through fundus photography by a trained optometrist is a cost-saving intervention. The primary driver of cost, as revealed by the study, is the treatment given to PDR patients, which include Pan Retinal Photocoagulation and Vitreoretinal surgery. The simulations reveal that timely screening along with modification of lifestyle and prescription reduces the incidence of diabetic retinopathy and delays the progression of patients from its early stages to PDR and blindness. It is important to note that a robust NCD-screening mechanism like that of Kerala is essential for tele-screening of DR to be cost-effective.

The ICER value from a societal perspective was much higher at 136,194. Although it is still lower than India's per capita GDP at current prices (Rs.1,58,573), this shows a considerable burden on patients and society via travel expenses, other Out of Pocket Expenditures, and wage/labour loss. The cost of tele-screening arm doubles when these expenses are included. Hence, streamlining of the screening process to minimize loss of working days and reimbursement of travel costs for the patient should be considered.

One way sensitivity analysis showed that input parameters with maximum influence on cost-effectiveness from a health system perspective were treatment uptake, the utility of PDR stages and cost of screening. On the other hand, the cost had negligible influence on Societal perspective cost-effectiveness, which was swayed largely by utility values of Moderate NPDR, PDR and Blindness stages. Transition probabilities had minimal

influence on the health system perspective ICER value and some influence on the societal perspective.

The stated assumption in the model that all patients in non-screening arm self-report to the health system only at PDR stages may be problematic since some patients may report in earlier stages. This can delay their progression to later stages and negatively influence ICER values. However, the sensitivity analysis (OWSA) shows that transition probabilities have only minimal influence on ICER values. Hence, uncertainty regarding the stage at reporting in the non-screening arm should not be a significant concern.

Budget impact analysis shows that to scale up the tele-screening model to the entire state of Kerala, the burden on the exchequer will be to the tune of 16 crores. This is just 0.2% of Kerala's annual health budget of 7227 crores.[33] Further, it is important to remember that the intervention was cost-saving from a health system perspective and reducing the number of PDR patients requiring expensive procedures saves close to 9 crore rupees. The annual budget impact is heavily influenced by treatment uptake and varies from 13.64 crores to 32.49 crores when the treatment uptake increases from 20% to 60%.

7. Conclusion and Recommendations.

1. Tele-screening for diabetic retinopathy by fundus photography is a cost-effective and cost-saving tool compared to the current scenario from a health system perspective.
2. It is cost-effective relative to the threshold of Indian GDP per capita, even from a societal perspective.
3. The indirect expenses such as travel and wage loss cost more than the expenses of screening, hence streamlining of screening and reimbursement of travel expenses of patients need to be considered.
4. As per the current model, the effectiveness of screening is dependent on the proportion of patients in PDR stage receiving PRP/Vitreoretinal surgery. Hence, ensuring that district/subdistrict level referral hospitals can absorb the additional caseload is important to its success.

8. LIMITATIONS OF THE STUDY.

1. There was scarce literature on the progression of diabetic retinopathy through different stages; hence the assumptions on transition probabilities may not be accurate.
2. The study was based in the capital district of Kerala, which has one of the best health infrastructures in the country. Hence, the model may not be reproducible across the state/country.
3. Easy access to the Regional Institute of Ophthalmology is a significant factor in the number of patients undergoing VRS/PRP treatment from the study cohort. Hence, the assumption used in the model may not be appropriate for upscaling the project.
4. Due to the lack of data, the model assumes that under the current scenario, no patients undergo screening in the early stages of DR. Data regarding the number of patients undergoing screening in the study setting will improve the model.
5. The societal costs of managing blindness have not been included in the model.

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ANNEXURE-I.

Scoping Review Protocol.

OBJECTIVE

i. To ascertain the prevalence of various stages of diabetic retinopathy and the probability of progression from No DR to Blindness across various stages.
ii. To ascertain the utility values of each stage of diabetic retinopathy.
iii. To determine the effectiveness and cost-effectiveness. of tele-screening in the detection of Diabetic Retinopathy

METHODOLOGY

Search Framework:

- Population – Adult diabetics who have not been previously screened for DR.
- Intervention – Tele- Screening for Diabetic Retinopathy
- Comparator – Non-screening scenario
- Outcome – Effectiveness and Cost Effectiveness.

A targeted PubMed search was conducted with search strings tailored to each of the objectives mentioned. The search was limited to include only studies published in the last ten years and those conducted in India for objectives i. and ii. Two investigators conducted title and abstract screening in parallel, and full article reading was carried out to extract data relevant to stated objectives.

Sl. No	Query	Filters	Results
1.	((Diabetic Retinopathy) AND (((Stages) OR (Grades) OR (Severity)))) AND (((Prevalence) OR (Progression) OR (Probability) OR (Risk))) AND (India)	10 yrs.	189
2	((Diabetic Retinopathy) AND ((Stages) OR (Grades) OR (Severity))) AND ((utility) OR (QALY) OR (HRQoL) OR (Quality of life)) AND (India)		97
3	((Diabetic Retinopathy) AND ((Tele-screening) OR (Tele-ophthalmology) OR (Tele-retinal screening))) AND ((Effectiveness) OR (Cost-effectiveness) OR (cost-benefit) OR (Cost utility))	10 yrs.	26

ANNEXURE II. Transition Probability Matrices

1. Tele-screening Scenario.

Annual Probabilities.

	No DR	MildNPDR	ModerateNPDR	SevereNPDR	PDR	Blindness
No DR	0.94	0.06	0	0	0	0
MildNPDR	0	0.75	0.19	0.06	0	0
ModerateNPDR	0	0	0.83	0.1275	0.0425	0
SevereNPDR	0	0	0	0.422	0.5	0.078
PDR	0	0	0	0	0.922	0.078
Blindness	0	0	0	0	0	1

3 Month Cycle Probabilities.

	No DR	MildNPDR	ModerateNPDR	SevereNPDR	PDR	Blindness
No DR	0.9846	0.0153	0	0	0	0
MildNPDR	0	0.9333	0.05132	0.0153	0	0
ModerateNPDR	0	0	0.9557	0.0335	0.0108	0
SevereNPDR	0	0	0	0.8207	0.1591	0.02009
PDR	0	0	0	0	0.9799	0.02009
Blindness	0	0	0	0	0	1

2. Non-screening Scenario.

Annual Probabilities.

	No DR	MildNPDR	ModerateNPDR	SevereNPDR	PDR	Blindness
No DR	0.88	0.12	0	0	0	0
MildNPDR	0	0.8	0.12	0.08	0	0
ModerateNPDR	0	0	0.44	0.3	0.26	0
SevereNPDR	0	0	0	0.46	0.5	0.04
PDR	0	0	0	0	0.88	0.12
Blindness	0	0	0	0	0	1

3 Month Cycle Probabilities.

	No DR	MildNPDR	ModerateNPDR	SevereNPDR	PDR	Blindness
No DR	0.9658	0.0342	0	0	0	0
MildNPDR	0	0.9479	0.0315	0.0206	0	0
ModerateNPDR	0	0	0.8422	0.0853	0.0725	0
SevereNPDR	0	0	0	0.8307	0.1591	0.0101
PDR	0	0	0	0	0.9685	0.03145
Blindness	0	0	0	0	0	1