CRYSTALSIGHT: "Cohort 1.5" Clinical investigation study with OCCUTRACK and Tan Tock Seng Eye Clinic to further develop remote monitoring of maculopathy at home using artificial intelligence for eye tracking.

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Background:

Maculopathies such as age-related macular degeneration (AMD) is a prevalent, chronic, and progressive retinal degenerative disease of the macula [1-2]. One of the major clinical consequences of maculopathy is loss of central vision, which impacts daily living activities such as reading, driving and recognizing faces.

Age-related macular degeneration accounts for 8-7% of all blindness worldwide and is the most common cause of blindness in developed countries, especially in people over 60 years of age. Its prevalence is likely to increase as a result of exponential population aging [3 -5]. The global pool prevalence of AMD (based on an age range of 45-85 years) for early, late, and any age-related macular degeneration is 8.01% (95% CI: 3.98-15.49), 0.37% (0.18-0.77), and 8.69% (4.26-17.40), respectively [6].

The projected number of people with age-related macular degeneration was 196 million worldwide in 2020 (95% CI: 140-261) and is expected to increase to 288 million by 2040 [3]. Previous studies have shown that the age-standardized prevalence of early and late AMD in Singapore was 5.1% and 0.5%, respectively [6]. It is interesting to note that there are no major racial differences in the prevalence of AMD in Singapore [6].

In addition, AMD in Singapore is expected to increase over time due to the aging population and longer life expectancy.

This CRYSTALSIGHT system is a proposed home-based precision monitoring telemedicine device that utilizes advanced eye tracking algorithms that enable comprehensive and intelligent assessment of a person's visual performance non-invasively and from the comfort of their home, without the need for manual or expert intervention. CRYSTALSIGHT is an automated method and system for vision assessment of a subject. The method includes the following: determining a set of test patterns for the subject based on a preliminary assessment of an eye of the subject; displaying the set of test patterns sequentially to the subject; collecting data on the subject's gaze in response to each test pattern displayed; and correlating central vision function of the subjects to the collected gaze data.

The underlying cause of AMD

Age-related macular degeneration (AMD) is the most common cause of irreversible blindness in adults ≥ 60 years old [7]. The underlying defect appears to be premature dysfunction of the retinal pigment epithelium (RPE), a monolayer responsible for most of the maintenance functions of the neurosensory retina.

The etiology of AMD is multifactorial, with both genetic and other modifiable risk factors contributing to personal risk. The phenotypic risk factors such as drusen and pigment abnormalities become more important to predict disease progression during the course of the disease. Demographic and environmental risk factors such as age and smoking are consistently found to be significantly associated with disease progression, while other risk factors such as sex, body mass index (BMI) and education are less commonly associated [8].

In addition, molecular mechanisms involving the lipid-cholesterol pathway, angiogenic factors, inflammation and immune processes play a critical role in the pathophysiology of disease development and progression [9-10].

Disease progression, immediate and late complications of AMD

AMD can be classified as early, intermediate, or late stage [11]. Minimal visual disturbances may occur in a large proportion of patients with early and intermediate stages of AMD and eventually progress to advanced AMD. The development of these advanced subtypes of geographic atrophy (GA) and neovascular disease (NV) is commonly associated with visual impairment and blindness, which may affect quality of life and lead to loss of independence [12-14].

Progression to Wet AMD (or) neovascular AMD (nAMD) is characterised by the formation of new fragile vessels originating from the choriocapillaris [8]. These new vessels grow into the retina with subsequent leakage and/or hemorrhage that can lead to serous RPE detachment accompanied by a rapid loss of vision and eventually causing a vision-threatening scar in the macula [15]. There are several risk factors that may influence the progression of disease, and the rate at which it progresses may vary among individuals [8].

Imaging techniques that can detect the conversion of an early stage of AMD to late-stage Wet AMD include colour fundus photography (CFP), optical coherence tomography (OCT), fluorescein angiography (FAG), indocyanine green angiography (ICGA), and OCT angiography (OCTA). Whereas CFP, OCT, and FAG can detect exudative nAMD by fluid leakage and haemorrhage [8,16].

Treatment of Maculopathies

Maculopathy is more prevalent with ageing and can result in blurred or distorted vision, often accompanied by a dark patch blocking the center of the visual field. In the management of age-related macular degeneration (AMD), patients are required to attend regular check-ups at the specialist eye clinic by the clinician to monitor if their disease. The eye examinations that patients undergo during these clinic visits which may include fundoscopy and optical coherence tomography. A preventive treatment for exudative or wet AMD is the administration of an intravitreal injection of an anti-vascular endothelial growth factor (anti-VEGF) at these regular clinic sessions.

Although anti-vascular endothelial growth factor (VEGF) injections are an effective treatment for many patients with NV [10, 17], some patients do not respond, there is a large treatment burden, and visual loss continues over time.

There is no treatment for GA. Thus, prevention of advanced disease and finding new and effective treatments remains a significant challenge. Identifying individuals with early and intermediate disease at high risk of progression to advanced stages would lead to earlier intervention and reduced burden of visual loss due to AMD [10].

There are many anti-VEGF treatment strategies aimed at minimizing intravitreal injections without compromising visual outcomes as well as to reduce the need for repeated treatments with the associated cumulative risk of endophthalmitis and other adverse events [18-19].

Currently available anti-VEGF treatment schedules include the “as-needed” (PRN) and the “treat-and-extend” regimens. In an “treat -as-needed” regimen, the patient is examined monthly but not always treated, and treatment can be given only if intraretinal or subretinal fluid is present [19-20]. In a “treat-and-extend” regimen, the patient is always treated, but the intervals between examinations are varied [19-20].

Significance of the project and unmet clinical needs

Although anti-vascular endothelial growth factor (VEGF) injections are an effective treatment for many patients with Wet-AMD [17], there are several unmet needs in treatment of AMD and none of them cures the disease or reverses its course [17, 21 – 23]. Some patients do not respond to VEGF injections. There are no standardized treatment schedules, there is a large treatment burden, and visual loss continues over time. Additionally, the main drawback of anti-VEGF therapy is its high cost, which suppose a significant burden on health systems, and often makes such a regimen unaffordable in clinical practice [24] There is no treatment for GA. Therefore, the prevention of advanced disease like Wet-AMD and finding new and effective treatments remain a significant challenge.

Advances in imaging and genetics and molecular technologies have led to the identification of new risk factors for disease progression, but not all have been evaluated in comprehensive prediction models [8]. Perhaps, comprehensive prediction models could lead to the development of tailored, individualized therapy and improve the personalised healthcare.

The management of AMD is diagnosed and monitored today using clinic-based Optical Coherence Tomography (OCT), however this requires burdensome visits. This CRYSTALSIGHT system is a proposed home-based precision monitoring telemedicine device that utilizes advanced eye tracking algorithms that enable comprehensive and intelligent

assessment of a person's visual performance non-invasively and from the comfort of their home, without the need for manual or expert intervention.

As such, the application of this next-generation OCCUTRACK Technology to develop a comprehensive risk score algorithm and to estimate the risk scores to identify individuals at high risk for disease progression to advanced stages would result in earlier intervention and reduced burden of visual loss due to maculopathy. This approach could enable the tailored individualized Anti-VEGF Therapy to promote personalized medicine and improve the quality of life for these patients.

As such, the application of this next-generation OCCUTRACK Technology to develop a comprehensive risk score algorithm and to estimate the risk scores to identify individuals at high risk for disease progression to advanced stages would result in earlier intervention and reduced burden of visual loss due to AMD. This approach could enable the tailored individualized Anti-VEGF Therapy to promote personalized medicine and improve the quality of life of patients with Wet-AMD.

A Proof-of-Concept (POC) was completed by TTSH clinician (Augustinus Laude) and AStar-I^{2}R scientist to co-develop and patent a software, Automated Vision Assessment and Impairment Detection through Gaze Analysis (AVIGA). AVIGA is now referred to as "CRYSTALSIGHT" as part of the commercialization branding. A local medical incubator, Trendlines Medical Singapore, has licensed it from the research party. This led to the spin-off of a new company-OCCUTRACK Pte Ltd to continue the collaboration with TTSH, focusing on the commercialization of the CRYSTALSIGHT.

AVIGA previously used a costly commercial tobii gaze tracker that could potentially limit consumer adoption, the CRYSTALSIGHT system was designed to mitigate costs by incorporating an AI-augmented video camera with gaze tracking algorithms designed to provide a comprehensive assessment of a patient's vision. With this noninvasive technology, retinal specialists can monitor the real time progression and prognosis of patients with AMD while they are in the comfort of their own home without the need for manual or skilled intervention and expensive equipment.

2. STUDY DESIGN

The development of a next-generation 'CRYSTALSIGHT' solution using combinations of a novel and cost-effective eye-tracking system with artificial intelligence-based eye-tracking algorithms that detect macular abnormalities and enable clinicians to review and monitor the prognosis of patients via a web platform through the following deliverables.

a. Evaluate and improve a home-monitoring regimen involving the self-tests of the CRYSTALSIGHT gaze-tracking system.
b. To demonstrate that CRYSTALSIGHT has the same or superior gaze-tracking capacities as Tobii.
c. Evaluate the CRYSTALSIGHT device for its functionality and ease of use as a qualitative measurement tool for patients.
d. Develop the Design History File (DHF) for regulatory filing requirements.

2. This study will improve on the existing gaze-based scoring methodology for disease activity monitoring over time (delta-change) by quantitatively measuring saccadic speed, pursuit and micro-saccades.

Validation of the machine learning algorithm has been completed with an accuracy of xxx > 85% against gold standard test. The Gold Standard Tests used in this validation of the machine learning algorithm are standard visual acuity (VA) and central visual field (VF) test, which are currently used in standard routine clinical practice.

Using fixation data, the accuracy is 0.91, the sensitivity and specificity are 0.76 and 0.95, respectively. Using smooth pursuit, the accuracy is 0.92, the sensitivity and specificity are 0.82 and 0.95, respectively.

TABLE I

THE RESULT OF IMPAIRED VISION DETECTION.

	Fixation	Pursuit
accuracy	0.91	0.92
sensitivity	0.76	0.82
specificity	0.95	0.95

The hypothesis of this study is to show that a person's visual performance can be assessed non-invasively and from the comfort of their home, without the need for manual or expert intervention, by utilizing the newly developed 'CRYSTALSIGHT' device. A previous study

utilized a commercial gaze-tracker "Tobii ET5L", the hypothesis of this study establishes that the CRYSTALSIGHT eye tracking device has comparable non-inferior performance to the commercial camera and generates an objective score while minimizing patients' need to interact with the machine. Tobii ET5L is an infrared gaze-tracking camera, whilst CRYSTALSIGHT is a video-based camera. The quantitative outcome of the study may enable the clinical trial team to determine that the CRYSTALSIGHT device performs with acceptable or similar performance metrics to the commercial device, which provides an indicative score for disease activity in patients with maculopathies. The findings of this study could also potentially show that the CRYSTALSIGHT device may be used in a home-based setting to determine macular disease activity over time.

Previous studies have shown the potential of gaze tracking to provide an objective score with relevant diagnostic assistance information while minimizing patients' need to interact with the machine.

Study Design:

Study population: Consecutive patients with vision problems who have been diagnosed with Wet-AMD attending SOC eye clinics will be recruited in the study after meeting the inclusion and exclusion criteria.

Inclusion Criteria:

1. Participants between ages 21 and 100
2. Both genders
3. Subjects with maculopathies
4. Ability to comply with the study protocol, in the investigator's judgment
5. Subjects must have the cognitive capacity to provide personal consent (i.e. no cognitively impaired persons will be recruited).

Exclusion Criteria:

1. Uncontrolled blood pressure, defined as systolic blood pressure >180 millimeters of mercury (mmHg) and/or diastolic blood pressure >100 mmHg while a patient is at rest.
2. Any concurrent intraocular condition in the study eye that, in the opinion of the investigator, could either reduce the potential for visual improvement or require medical or surgical intervention during the study.
3. History of idiopathic or autoimmune-associated uveitis in either eye.

4. Active ocular inflammation or suspected or active ocular or periocular infection in either eye.
5. Other protocol-specified exclusion criteria may apply.
6. Individuals with indications of cognitive impairment and unable to make decisions for themselves to provide informed consent will be excluded from the study.

Study Procedure:
This cohort study will involve 1 study visit.

Pre-specified clinical outcome: The prespecified adverse clinical outcome used in this study will be the **maculopathy** which will be identified by an increase in central retinal thickness (CRT) of at least 100 microns or a loss of best-corrected VA of 5 letters or more.

Clinical Validation will be a cohort study design to evaluate the diagnostic accuracy of the CRYSTALSIGHT device compared to the Tobii gaze-tracker in patients with macular diseases recruited from the medical retina specialty clinic.

This study will be conducted in accordance with the tenets of the Declaration of Helsinki.

The goal is to recruit a minimum number of 20 patients with diagnosed indication of maculopathies who fit the inclusion and exclusion criteria. Adult individuals will be voluntarily recruited from Tan Tock Seng Hospital (TTSH) Ophthalmology SOC clinics after they had been assessed for eligibility based on established clinical diagnosis from the case notes through TTSHs NGEMR. Informed consent for participation in this study will be obtained. Eye gaze tracking test will be automated, and patients will only need to follow through the stimulus/image shown without physical contact with the eye gaze tracker using CRYSTALSIGHT and Tobii. A series of stimulus dots in the form of a pursuit (moving stimulus) or saccade (fixed stimulus and fixed speed) will be presented on the screen and the user under test (UAT) will need to look at the targets presented. The test is similar to Microperimetry and Humphrey's visual field test. A score will be generated at the end of the test.

A research collaboration agreement was established between TAN TOCK SENG HOSPITAL PTE. LTD. and OCCUTRACK MEDICAL SOLUTIONS PTE LTD on the research project titled: CRYSTALSIGHT: “Cohort 1.5” clinical investigation study with OCCUTRACK and Tan Tock

Seng Eye Clinic to further develop remote monitoring of age-related macular degeneration at home using artificial intelligence for eye tracking.

Research Procedures:

1) CRYSTALSIGHT

2) Tobii

Subjects perform the CRYSTALSIGHT test monocularly and pursue a pre-determined target moving in a customized waveform across the computer screen. The trail of the gaze points generated by the subject following the target is simultaneously recorded and stored. Eye dilation will not be required for the purpose of this research study as fundoscopy nor OCT imaging will not be performed.

As part of the clinical evaluation of subjects during the analysis phase, access and extraction of data will be limited to TTSH's NGEMR and Heidelberg Eye Explorer platform. Clinical information collected for the purposes of this study would include current diagnosis, co-mormid information e.g DM, hyperlipidemia, and hypertension histories along with prior visual assessments documented by optometrists as well as recent OCT imaging.

In addition, this is also to note that NEHR cannot and will not be used for research. Assess of medical records for the purpose of data collection will also be limited to the period dated from 1 March 2025 to 28 February 2026. Clinical information/data collected will be done once off during, or retrospectively after the study visit.

Measurements at Baseline (Day – 1)

The following variables will be collected at initial baseline visit.

- Demographic data (age, gender)
- Phenotypic risk factors such as drusen and pigment abnormalities
- Smoking status
- Co-morbidity status such as diabetes, Cancers, CVD, strokes, kidney diseases
- Drugs history (Eye related)
- Drugs history (Co-morbidity status)
- Eye measurements:
    - CRYSTALSIGHT

- AVIGA
- BCVA (Best Corrected visual acuity)

Sample size calculation

The sample size calculation is based on the intraclass correlation between CRYSTALSIGHT and Tobbi. Our minimum acceptable intraclass correlation coefficient (ICC) is 76% between CRYSTALSIGHT and Tobbi, and the expected ICC is 93%, basing on two- sided significance level of 0.05 and power 0.8, a total of 20 subjects are required. Statistical analysis to assess the eye-tracking performance of CRYSTALSIGHT, will be applied through the following methods:

- The Bland and Altman plot will be used to assess the agreement between CRYSTALSIGNT and Tobbi. The difference between CRYSTALSIGHT and Tobbi of each subject will be plotted on the vertical axis, again, the mean of the two readings of each subject on the horizontal axis. Limits of agreement will be presented in the plot.

- Intraclass correlation Coefficient will be computed using a random effect model, including device type (CRYSTALSIGHT vs. Tobbi) as a fixed factor and subject as a random effect. This model accounts for variability between subjects while assessing agreement between the two devices.

In literature, gaze-tracking accuracy measures such as K-means clustering and Euclidean distances were used and will be evaluated for suitability [35, 36]

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