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The Study Design and Methodology of the Malta Eye Study (TMES), an Ophthalmic Epidemiology Study

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KEYWORDS

Visual Impairment; Prevalence; Malta; Glaucoma; ARMD; Cataract; Diabetic retinopathy

ABSTRACT:

Purpose: The Malta Eye Study (TMES) is a cross-sectional study of the adult Maltese population to determine the prevalence of visual impairment and the respective causative pathologies. The study's design and methods are discussed in this paper.

Methods: A random sample of 5000 Maltese individuals aged 50–80 years, stratified by age, sex, and locality, are being invited for an ophthalmic assessment between September 2021 and May 2024. The validated tools of measurement include the National Eye Institute Visual Function Questionnaire, the EQ-5D-5L, the Ocular Surface Disease Index, and the Quick Mild Cognitive Impairment Score for assessments of visual function, quality of life, dry eye symptoms, and cognitive impairment, respectively. Other tools of measurement involve anthropometrics, visual acuity, autorefraction, keratometry, air-puff tonometry, Goldmann tonometry, slit lamp examination, fundus photography, swept-source optical coherence tomography (SSOCT) scanning of the macula and disc, as well as SSOCT angiography. A saliva sample is also collected for genetic analysis.

Results: The data collection has assessed 1600 individuals up until the end of November 2023. Data from the first year of data collection has shown that the sample was representative in terms of age and gender.

Conclusions: TMES uses up-to-date technology and tools to provide epidemiologic data on visual impairment, eye conditions, risk factors, and genetic associations. Knowledge of the local situation will help determine policymaking in terms of screening and primary and tertiary health care planning. TMES is also compiling a SSOCT angiography portfolio for the assessed participants.

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1. Introduction

Amidst dynamic global population shifts, ophthalmic epidemiology data, as exemplified by the Global Vision Database (1), guides strategy planning targeting visual impairment (VI). Despite reductions in age standardised VI prevalence between 2010 and 2019, the targets set to reduce avoidable blindness (2) remain unmet (3).

Malta, a Mediterranean small-island archipelago state has a current population of 542,051 (4), marking a significant increase from 1985 (5). Currently, there are no local electronic ophthalmic health care records in the state hospital and no recent robust ophthalmic epidemiological data. A 1989 national glaucoma study reported a 0.9% prevalence of blindness and a 9.3% prevalence of low vision in individuals aged 40 and above (6). For open-angle glaucoma, Malta exhibited a prevalence (3.29%, 95% CI 2.56%, 4.023%) comparable to contemporaneous data from predominantly white populations (7, 8).

The Malta Eye Study (TMES) is a population-based, cross-sectional ophthalmic epidemiology study focusing on the adult Maltese population aged 50 to 80 years.

2. Aim and Objectives

Aim

To estimate the prevalence of common eye pathologies and VI in the adult population of Malta aged 50 to 80 years.

Objectives

i. To determine modifiable and non-modifiable risk factors associated with VI and blindness in the population of Malta.
ii. To determine the impact of VI on quality of life.
iii. To establish a repository of salivary DNA to enable future genetic studies of ocular and systemic disease.

3. Methods

Study Population

Given that 65% of VI occurs in the 50+ age group (9) and Malta's population has an average life expectancy of 82.6 years (10), a random sample of subjects aged 50 to 80, stratified by age, sex, and locality region, was obtained from the Malta Electoral Register. The Electoral Register, a 13-volume publicly available document, lists eligible voters in Malta by name, surname, identity card number, and addresses (11).

The Pilot Study

In January 2020, a sample of 50 individuals was invited over five days via postal letters to pre-test the recruitment method, data entry, ophthalmic assessments logistics, and statistical analysis. The turnout was 30%. The pilot revealed issues with manually downloading data from the Optical Coherence Tomography (OCT) machine and autorefractor as initially planned. Following pre-testing, manufacturers were contacted, and automated data collection software was obtained.

Sample Size Determination

Sample sizes for each condition's expected prevalence (Table 1) were calculated using

the confidence interval formula for one proportion in a SCALAX calculator. The calculations involved knowledge of the expected prevalence rates, that were obtained from literature, and the desired level of precision. Following recommendations by the calculator's author, the levels of precision have been chosen as 0.25-0.30P when P<10% and 2-3% when P>10% (12). The known formula (13) for confidence interval for one proportion is given as:

$$n = \frac{Z^2 P(1-P)}{d^2}$$

n is sample size

Z is Z statistic for a level of confidence, 1.96 for 95% confidence level

P is the expected prevalence

d is the precision.

The study's main aim necessitates a sample size of 1800, determined by the highest feasible size within the list (1871, related to myopia estimation). Initially, planning for a c. 60% response rate (14), and accounting for deceased or untraceable individuals, around 3000 invitations were intended. However, after a lower turnout of about 30% in the pilot study, 5000 invitations were randomly drawn.

Table 1 A table that shows the calculated sample size, n, required to assess the prevalence of each eye condition with an anticipated 95% accuracy interval, based on the expected prevalence of the respective eye disorders, P, as obtained from literature, and the desired level of precision, d.

Condition	Expected Prevalence, P (from global data)	95% CI of P	Reference of P	Sample size required, n	Level of Precision, d	Anticipated 95% CI
Visual Impairment (any stage)	20.80%	Not available (added up Mild, MSVI and blindness)	(1)	1583	2.00%	18.8%, 22.8%
Mild Visual Impairment	7.73%	6.62%, 8.82%	(1)	759	1.90%	5.83%, 9.63%
MSVI	11.20%	9.9%, 12.6%	(1)	956	2.00%	9.20%, 13.20%
Blindness**	1.85%	1.57%, 2.11%	(1)	1938	0.60%	1.25%, 2.45%
Myopia	26.50%	23.40%, 29.60%	(15)	1871	2.00%	24.50%,28.50%
Hyperopia	30.90%	26.20%, 35.60%	(15)	1621	2.25%	28.65%,33.15%
Astigmatism	40.40%	34.30%, 46.60%	(15)	1828	2.25%	38.15%, 42.65%
Cataract	17.2%	13.39%, 21.01%	(16)	1368	2.0%	15.2%, 19.2%
Cataract blindness	0.84%	0.70%, 1.0%	(3)	2000	0.40%	0.44%, 1.24%
Cataract MSVI	4.34%	3.71%, 5.02%	(1)	1319	1.10%	3.24%, 5.44%
ARMD (any stage)	8.69%	4.26%, 17.4%	(17)	763	2.00%	6.69%, 10.69%
Early ARMD	8.01%	3.95%, 15.49%	(17)	1812	1.25%	6.76%, 9.26%
Late ARMD*	0.37%	0.18%, 0.77%	(17)	14161	0.10%	0.27%-0.47%
Primary glaucoma	3.54%	2.09%, 5.82%	(18)	1816	0.85%	2.69%, 4.39%
POAG	2.40%	2.0%, 2.8%	(19)	1837	0.70%	1.70%, 3.10%
Diabetic retinopathy	2.30% (22.27% of 10.31%)	Not available as extrapolated from 2 studies	(20,21)	1762	0.70%	1.60%, 3.00%

MSVI: Moderate Severe Visual Impairment, POAG: Primary Open Angle Glaucoma, *sample size not feasible, **Local rates are known to be lower

Ethical and Legal Considerations and Permissions

The study adheres to ethical principles outlined in the Declaration of Helsinki (22) and GDPR (23). Approvals were secured from Mater Dei Hospital (MDH) CEO, Department of Ophthalmology Chairman (Appendix 1), MDH's data protection officer (Appendix 2), and the University of Malta's Faculty Research Ethics Committee (FREC) with approval number FRECMDS_1819_94 (Appendix 3).

Permissions were granted for validated tools' use (Table 2). The research, involving human participants and potential physical intervention, secures informed consent prior to the Ophthalmic Assessment (OA). Collected data is pseudonymized and stored with participant codes. The Lead Researcher (LR) maintains a separate database linking codes to participant details. Despite minimal risk, researchers are trained in Good Code of Practice and GDPR for confidentiality. Genetic analysis will be conducted on anonymized, untraceable samples.

Recruitment

In view of COVID-19 pandemic, the study's main data collection was postponed from March 2020 to Sept 2021. Each potential participant receives a unique eight-character identifier code (e.g., TMES0001). Invitations with date and time details are sent to randomly selected individuals from the electoral register, with 15 invitations per session, 2-4 weeks before the appointment.

Table 2 List of Validated Tools in the Malta Eye Study's Questionnaire

Tool	Variables assessed	Original language/s	Permission/ Licensing organisation /person	Date license/ permission granted
EuroQOL (24)	Health-related Quality of Life: Mobility Self-care Usual activities Pain Discomfort Anxiety/Depression	English and Maltese	Ms Anita Dwarkasing ID29994	3/5/2019
The National Eye Institute Visual Function Questionnaire – 25 (NEIVFQ-25) (25)	Visual function, disability, vision related quality of life: General Health General Vision Ocular Pain Near Activities Distance Activities Social Functioning Mental Health Role Difficulties Dependency Driving Color Vision Peripheral Vision VFQ-25 Composite	English	N/A Tool is available in public domain.	N/A
Ocular Surface Disease Index (OSDI) (26)	Dry eye history: • Vision related function • Ocular symptoms • Environmental triggers	English	Ms Ellie Julian (Allergan®)	06/05/2020
Quick Mild Cognitive Impairment (QMCI) Score (27)	Cognitive impairment	English	Prof DW Molloy	22/11/2019

The National Eye Survey of Trinidad and Tobago Questionnaire (28). Adapted from INTER-HEART (29) and RAAB (30)	Medical history (including ophthalmic and cardiovascular histories) and drug history	English	Dr Tasanee Braithwaite	6/2/2020

Hospital intermediaries use the main hospital's database for contact details of the corresponding invitees for phone reminders, attendance confirmation, encouragement, and rescheduling if needed. Unanswered calls prompt SMS reminders. The invitation letters are in Maltese and English, contain contact details, advise against driving and recommend bringing glasses and medical history (Appendix 4).

The Ophthalmic Assessment (OA)

At any given time two participants have tests performed in a station format (Table 3). Stations 2 and 3 can be performed at any point in time after consent.

Table 3 The Ophthalmic Assessment Stations

Station Number	Station Description	Estimated duration (mins)
1	Greeting, handing information sheet, Consent taking	5
2	Questionnaire	30-40
3	Anthropometrics	5
4	Visual Acuity/focimetry	5
5	Autorefraction, keratometry, pachymetry and tonometry station	5
6	OCT	5
7	Slit lamp anterior segment exam	5
8	Slit lamp dilated fundus examination	5
9	Saliva sample collection	5
	Total	80

Team members and their roles in the OA

The team consists of the project supervisor (FC), co-supervisor (JM), the LR (DA) and a group of trained assistants. DA is the ophthalmologist responsible for conducting all eye assessments (stations 4-8). The assistants are responsible for the recruitment calls, taking signed informed consent, questionnaires, and anthropometrics.

Logistical setup of the OA

Five participants are assessed every day from Monday to Thursday from 2PM till 5PM. One assistant and the LR are available for any given session, starting with the consent and then different stations run in parallel until all the participants complete all.

Equipment, Consumables and Location

TMES makes use of the apparatus and consumables (Appendices 5 and 6) at Mater Dei Hospital Ophthalmology Outpatients to perform the OAs.

The Ophthalmic Assessment Stations

1. Consent for participation.

Participants sign the informed consent form (Appendix 7) after agreeing to the explanation of benefits, potential side effects, confidentiality adherence, pseudonymization of stored data, the option to opt out at any time, and the choice of receiving test results (excluding genetics).

2. Questionnaire

The interviewer performs validated, cross-culturally adapted, and back-translated scoring questionnaires (Table 2) and records responses electronically on LimeSurvey™ (31).

3. Anthropometric measurements

Established standards are used for weight (kg) and height measurements (cm) (32), capillary blood glucose (mmol/L) (33) and blood pressure readings (mmHg) (34).

4. Visual acuity testing

Monocular presenting visual acuity (MPVA) testing is performed with distance vision glasses, if available. Recording is performed using an electronic ETDRS chart with a LogMAR scale(35). Pinhole testing is performed if MVPA was > 0.3 logMAR. If improvement is noted, a best corrected visual acuity is taken following autorefraction and subjective refraction.

5. Autorefraction, keratometry, pachymetry and tonometry station

A validated Visionix® VX120™ device is used (36) for autorefraction, keratometry, pachymetry, iridocorneal angle measurement, air-puff tonometry (average of three readings).

6. Gross and Slit Lamp exam.

Before using the slit lamp, a thorough inspection for face, adnexal, globe, and orbital abnormalities is conducted. Pupils are assessed for size, shape, reactivity, and afferent pupil defect using an indirect ophthalmoscope. Routine slit lamp examination methods include diffuse and parallelepiped illumination, cross-sectional technique, van Herick's method for angle depth estimation, indirect illumination, specular reflection, retro-illumination, fluorescein application for tear break-up time estimation, and the Oxford Grading Scheme for corneal/conjunctival staining (37). Goldmann tonometry is performed with topical Oxybuprocaine.

7. Dilated Fundus Examination

Following the anterior segment exam, Tropicamide 1% dilating drops are administered, and participants wait at least 10 minutes. Binocular indirect non-contact slit lamp dilated fundoscopy is then conducted using a Volk® 90D lens.

8. Swept Source Optical Coherence Tomography (SSOCT) Imaging and Angiography, Fundus Photography.

SSOCT scans are taken using the Rescan wide and Angio12mmx12mm modalities on the Topcon DRI OCT Triton™ to provide macular thickness mapping, optic nerve and retinal nerve fibre layer thickness, SSOCT Angiography images and posterior pole fundus photographs.

9. Saliva Sample Collection for DNA extraction

The participants submit a fresh saliva sample using the provided Oragene® kit, after fasting for one hour. DNA will be subsequently extracted for future analysis from around 1600 subjects from this cohort.

Tests for selected participants

Central Visual Field Testing

Humphrey 24-2 testing is performed on subjects with the following criteria: vertical cup:disc ratio (VCDR) >0.4 or asymmetry between both discs >0.2, IOP greater than 21.0 mmHg, abnormal disc features suggestive of glaucoma, abnormal anterior segment features that could put participant at risk of secondary glaucoma (e.g. angle closure, pseudoexfoliation and pigment dispersion) and history of diagnosed glaucoma/ ocular hypertension.

Criteria used in the clinical diagnosis/staging of common eye disorders.

Definitions of Visual impairment

The participants' MPVAs are tested and participants scoring a logMAR of 0.3 or better in each eye are considered as having no VI. The LR classifies each case of VI

into "VI in the better eye" in cases which have a visual acuity of >0.3 logMAR in both eyes, or "unilateral VI" in cases when one eye has visual acuity >0.3 logMAR and the other has a vision of 0.3 logMAR or better (38,39). For each case of VI, the severity of unilateral VI or of the VI in the better eye is denoted as mild VI (worse than 0.3 logMAR up to and including 0.5 logMAR), moderate to severe VI (MSVI) (worse than 0.5 logMAR up to and including 1.3 logMAR) and blindness (worse than 1.3 logMAR) according to the ICD-11 criteria (40).

Assignment of Causes of Visual Impairment

The LR identifies the primary cause of VI in each eye with visual acuity >0.3. If multiple causes are present in one or both eyes, preventing the determination of a singular primary cause, the label "More than one cause of VI" is assigned.

Uncorrected/undercorrected refractive error (URE) is identified as a cause of VI if pinhole acuity testing improves the participant's vision to at least 0.3 logMAR. Amblyopia is designated as a cause of VI based on clinical findings and participant history, with confirmation required that the VI had been present since childhood.

Grading of Lens Opacities

The LOCSIII criteria (41) are employed to grade cataracts. Retro illumination assesses the cortical and posterior subcapsular zones, while the lens nucleus is examined with a slit beam tilted at 45 degrees. Grading includes nuclear opalescence (out of 6), nuclear colour (out of 6), cortical opacities (out of 5), and posterior subcapsular opacities (out of 5), referencing LOCSIII standard images adjacent to the slit lamp. Cutoff points for cataract types are adapted from a recent meta-analysis (16), where nuclear colour and opalescence grade 4 defined a nuclear sclerosis cataract, cortical opacity grade 2 defined a cortical cataract, and posterior subcapsular grade 2 defined a posterior subcapsular cataract.

Definitions of Grades of Myopia, Hyperopia and Astigmatism

The American Optometric Association (42) definitions for refractive error are used. Refractive error is measured in Dioptres (D). Spherical Equivalent (SE) is defined as Sphere (D) + ½ astigmatic requirement (D). Emmetropia is considered as any spherical equivalent (SE) value ≥-0.50D and ≤+0.50D. Myopia is considered as any SE <-0.50D. Low myopia is any SE <–0.50D to > –3.00D, moderate myopia is any SE ≤-3.00D to ≥ –6.00D and high myopia is any SE <-6.00D. Hyperopia is any SE of >+0.50D. Low Hyperopia is any SE >+0.50D and ≤+2.00D, moderate hyperopia is any SE >+2.00D and ≤+5.00D, high hyperopia is any SE>+5.00D. Astigmatism is any negative cylinder power ≤-0.75(15,43).

Diagnostic Criteria for Glaucoma

The current International Council of Ophthalmology and European Glaucoma Society guidelines (44,45) are used to define glaucoma. Open angle glaucoma definition requires both open angle and glaucomatous optic nerve damage and may or may not include elevated IOPs and visual field damage. Closed angle glaucoma requires closed angles and may or may not require high IOPs, glaucomatous optic nerve damage, and visual field defects. Glaucoma suspects are defined when any criteria for central visual field testing are met. These cases are then reviewed with a visual field test by a glaucoma specialist (FC) to determine whether they were definite glaucoma, glaucoma suspects, physiological cupping, or no glaucoma.

Staging of Diabetic Retinopathy

The International Clinical Diabetic Retinopathy (46) grades diabetic retinopathy (DR) based on slit lamp examination and fundus photography. Since these scales do not have a grade for

anyone with panretinal photocoagulation and stable DR as the British system (47), any individual with signs of panretinal photocoagulation and a stable retina are marked as proliferative DR.

Age Related Macular Degeneration (ARMD) Grading

ARMD is graded according to the Age-Related Eye Disease Study (48) based on slit lamp examination and fundus photography.

OCT-based diagnosis of Vitreomacular disorders

The identification of vitreo-macular conditions is based on the descriptive guidance provided by the European Eye Epidemiology consortium (49).

Data Analysis

Descriptive summaries and inferential statistics shall be conducted from the collected data using SPSS® statistics software (50).

An analysis of recruitment participation, turnout numbers, and response rates shall be conducted using the recruitment data control list. This list includes details on how eligible participants respond (phone, email, SMS), whether they answer the call, accept, or refuse participation, and attend the OA.

The response group's age, gender, and locality will be compared to the 50-80 age group population figures in Malta from the 2021 census to evaluate sample representativeness (51).

On a weekly basis, ophthalmic examination, and questionnaire data from LimeSurvey® are transferred to SPSS® sheets, while OCT and Visionix® data are imported by means of the "OCT data collector" software, and a Visionix® XML file Excel® importer. A dedicated SPSS® database integrates LimeSurvey® files, Visionix®, and OCT data. Another SPSS® database for potential glaucoma participants includes diagnosis details and glaucoma type.

Databases shall be merged using candidate codes for analysis. Detailed clinical data allows computation of variables for analysing prevalence of common eye disorders and visual impairment. For instance, variables indicating the presence of bilateral MSVI, blindness, ARMD and DR shall be created. Prevalence data will be determined using the "descriptive statistics" function, and confidence intervals for each proportion will be calculated using the non-parametric one-sample Clopper Pearson method (52) in SPSS®.

Quality Control Measures

Inter-rater reliability testing

Following assistant training sessions, an inter class correlation (ICC) test was chosen to compare the raters' scorings of the same participants in their questionnaires. A sample size of 6 observations per rater was chosen, since, amongst the five raters, one would have expected a reliability ICC of 0.95 with a minimum acceptable value of 0.70. This sample size was calculated with an online calculator based on Walter et al.'s formula (53). The results were deemed to be satisfactory, as all values were above the acceptable value 0.7.

Intra-rater reliability resting

The ophthalmologist (DA) was assessed for intra-rater reliability. This checked for consistency in how ophthalmic findings (categorical data) were recorded. 27 repeated observations were required for an expected kappa of 0.75 with a precision of 0.25 (+/- expected kappa) when assessing for an outcome with a proportion of 50%. This sample size was calculated with an online calculator (54) based on Shoukri et al.'s formula (55). An ICC test was used for measurements that pertained to Goldmann tonometry, tear film break-up time and van Herick's estimation of the iridocorneal angle. The same sample size sufficed for this reason, given the same

expected ICC and precision (56). The kappa and ICC values for each presence/absence observation and measurement, respectively, were above the expected 0.75.

4. Results

In the initial year of data collection (September 2021 to September 2022), 2234 invitations were sent out, resulting in 31.6% attendance (705 individuals). Of the 1382 contactable participants 759 confirmed attendance, out of which 612 attended, while 623 declined. Additionally, 93 individuals who could not be contacted prior to the appointment, attended. The sample, though representative by age and gender, was under-representative of the Gozo population (Table 4).

5. Discussion

In such a large-scale epidemiology study, despite all efforts to minimise sources of error, bias is inevitable.

Selection bias

The study aims for an optimal response rate and a representative sample of the adult population aged 50-80 in Malta (57,58). Beyond postal invitations, active measures include a Facebook Page with a chat function, a contact phone number, recruitment calls, SMS reminders, and plans for a second round of phone recruitment. Hospital transport and free parking are offered, and media campaigns on social platforms and TV programs are employed for public engagement.

The electoral register excludes certain minorities, such as prisoners or some foreigners, and includes Maltese citizens residing abroad.

The postal invitation for the OA may exclude or limit the participation of illiterate or VI individuals. Additionally, scheduling the assessment from 2-5 pm might hinder attendance for some working-age individuals.

Healthcare access bias exists as data collection is clinic-based and does not include domiciliary visits, potentially excluding bed-bound or disabled participants (including those with visual impairment) lacking access to caregivers for transportation. COVID-19 and the fear of contracting a communicable disease has led to reduced attendance in healthcare settings. People from the sister island Gozo face the additional challenge of ferry crossing to reach the data collection clinic. Some data collection sessions will be held in Gozo, if by the end of the study the representation remains poor.

Non-attendance may stem from individuals who recently checked their eyes, are aware of their eye conditions, or lack ocular symptoms at the time of the invitation. These biases exist in all such studies.

Table 4 Descriptive statistics of sample from the first year of data collection by age, gender and locality and analysis for representativeness

		Census population of Malta aged 50-80(51)	Sample population	p value
Age	Number	168,759	705	
	Mean age	63	64.5	
	Median age	64	64	0.889
	Standard Deviation		8	
	Minimum	50	50	
	Maximum	80	80	
	Range	30	30	
	Skewness		0.017	
	Kurtosis		-1.009	

Gender		**n**	**%**	**n**	**% (95% CI)**	
	Male	84,370	50.0	358	50.8 (47.0, 54.5)	0.706
	Female	84,389	50.0	347	49.2 (45.5, 53.0)	
	Total	168,759	100	708	100	
Locality District		**n**	**%**	**n**	**% (95% CI)**	
	Southern Harbour	30,152	17.9	150	21.3 (18.3, 24.5)	
	Northern Harbour	48,190	28.6	196	27.8 (24.5, 31.3)	
	Southeastern	24,737	14.7	120	17.0 (14.3, 20.0)	
	Western	22,624	13.4	100	14.2 (11.7, 17.0)	
	Northern	28,037	16.6	112	15.9 (13.3, 18.8)	
	Gozo and Comino	15,019	8.9	27	3.8 (2.5, 5.5)	
	Total	168,759	100.0	705	100.0	

Information Bias

Efforts are made to reduce inter-observer bias by training and minimising the number of observers, having the same ophthalmologist examining all participants and by using the same apparatus for all participants. The use of a package of fully validated tools (Table 2) and the use of the same apparatus on all participants (Appendix 5) further helps remove other forms of information bias.

Confounding Bias

The effect of known confounders (age, gender, social class) shall be excluded in the analysis. The effects of further unknown confounders cannot be excluded.

6. Conclusion

TMES is an observational population based ophthalmic epidemiology study that is currently aiming to produce epidemiological data relating to prevalence of VI and common eye conditions, risk factors and genetic associations from a representative random sample of individuals aged 50-80 years of age living in Malta. The study is compiling data obtained from validated questionnaires, visual acuity, slit lamp examination, autorefraction and anterior segment analysis (by Visionix®), SSOCT, coupled with angiography, and saliva DNA samples.

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