HELLENIC JOURNAL OF CARDIOLOGY VOL. ■, 2025: ■-■

OPINION PAPER

NAXCARE: a clinical outcome registry for Naxos disease and related cardiocutaneous syndromes

Adalena Tsatsopoulou,[1,32] Dominic JR. Abrams,[2] Aris Anastasakis,[3] Loizos Antoniades,[4] Elena Arbelo,[5,33,34,35] Eloisa Arbustini,[6] Euan A. Ashley,[7] Angeliki Asimaki,[8] Cristina Basso,[9] Eduardo Bossone,[10] Julia Cadrin-Turigny,[11] Hugh Calkins,[12] Andreina Carbone,[10] Perry M. Elliott,[13] Georgios Efthimiadis,[14] Monica Franzese,[10] Alexandra Frogoudaki,[15] Juan Ramon Gimeno,[16] John McGrath,[17] Jodie Ingles,[18] Juan Pablo Kaski,[13] Andre Keren,[19] George Kohiadakis,[20] Emilia Lazarou,[21] George Lazaros,[21] Stamatios Lerakis,[22] Giuseppe Limongelli,[23] Soultana Meditskou,[24] Luisa Mestroni,[25] Ioanna Metaxa,[26] Emanuele Monda,[23] Eustathios Papatheodorou,[3] Despoina Parharidou,[14] Alexandros Patrianakos,[20] Kalliopi Pilichou,[9] Alexandros Protonotarios,[13] Ioannis Protonotarios,[27] Salvatore Rega,[10] Angelos Rigopoulos,[28] Jeffrey Saffitz,[29] Petros Syrris,[13] Matt Taylor,[30] Johannes Peter van Tintelen,[31] Charalambos Vlachopoulos,[21] Zafeirenia Xylouri,[27] William J. McKenna[13]

[1]Precision Medicine Network in Cardiology Onassis Cardiac Surgery Centre, Athens, Greece
[2]Boston Children's Hospital, Boston, USA
[3]Onassis Cardiac Surgery Centre, Athens, Greece
[4]University of Cyprus Medical School, Nicosia, Cyprus
[5]Arrhythmia Section, Cardiology Department, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain
[6]Fondazione IRCCS Policlinico San Matteo, Pavia, Italy
[7]Stanford University, Stanford, CA, USA
[8]Cardiovascular and Genomics Research Institute, St George's University of London, UK
[9]University of Padua, Medical School, Padua, Italy
[10]IRCCS SYNLAB SDN, Naples, Italy
[11]Cardiovascular Genetics Center, Montréal Heart Institute, Faculty of Medicine, University of Montréal, Montréal, Québec, Canada
[12]Johns Hopkins Medical Institution, Baltimore, USA
[13]Centre for Heart Muscle Disease, UCL Institute of Cardiovascular Science, London, UK
[14]Department of Cardiology, AHEPA University Hospital, Thessaloniki, Greece
[15]Cardiology, Attikon University Hospital, Athens University, Athens, Greece
[16]Inherited Cardiac Disease Department (CSUR/ ERN Guard Heart), Virgen de la Arrixaca University Hospital, Murcia, Spain
[17]Dermatology, King's College London, UK
[18]Garvan Institute of Medical Research, Darlinghurst, New South Wales, Australia
[19]Hadassah-Hebrew University Medical Center, Jerusalem, Israel
[20]Cardiology Department, University Hospital of Heraklion, Heraklion, Greece
[21]First Cardiology Department, School of Medicine, Hippokration General Hospital, National and Kapodistrian University of Athens, Athens, Greece
[22]Department of Cardiology, Mount Sinai Fuster Heart Hospital, Icahn School of Medicine at Mount Sinai, New York, NY, USA
[23]Department of Translational Sciences, University of Campania'Luigi Vanvitelli', Naples, Italy
[24]AHEPA University Hospital, Thessaloniki, Greece
[25]University of Colorado Cardiovascular Institute, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[26]Hellenic Society of Cardiology, Athens, Greece
[27]Acute Medicine, Southampton General Hospital, Southampton, UK
[28]Mitera Hospital, Marousi, Athens, Greece
[29]Harvard Medical School, Department of Pathology, Beth Israel Deaconess Medical Center, Boston, USA
[30]Adult Medical Genetics Program, University of Colorado Anschutz Medical Campus, Aurora, CO, USA
[31]Universitair Medisch Centrum Utrecht, Utrecht, Netherlands
[32]Paediatric Clinic, Hora Naxos, Greece
[33]Institut d'Investigació August Pi i Sunyer (IDIBAPS), Barcelona, Spain
[34]Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain
[35]European Reference Network for Rare, Low Prevalence and Complex Diseases of the Heart - ERN GUARD-Heart, Amsterdam, The Netherlands
Peer review under responsibility of Hellenic Society of Cardiology.

Manuscript received April 10, 2025; accepted April 24, 2025. Available online xxx

ISSN 1109-9666 https://doi.org/10.1016/j.hjc.2025.04.004

ABSTRACT

The NAXCARE (**NAX**os disease and **C**ardiocutaneous **A**ssessment and **R**egistry for **E**valuation) is a global initiative designed to collect, store, and analyze clinical outcomes data on patients with Naxos disease and related cardiocutaneous syndromes (CCS). This registry aims to fill the gaps in clinical knowledge, enhance treatment approaches, and improve patient outcomes by systematically documenting disease progression, genetic profiles, and patient care pathways. The following methodology outlines the registry's design, data collection protocols, management, security measures, and anticipated contributions to research and clinical practice. (Hellenic Journal of Cardiology 2025;■:■-■) © 2025 Hellenic Society of Cardiology. Publishing services by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

1. INTRODUCTION

- **Background**: Naxos disease, a rare genetic condition marked by arrhythmogenic right ventricular cardiomyopathy (ARVC), woolly hair (WH), and palmoplantar keratoderma (PPK), was first identified in Greece in 1986.[1,2] Genetic variants in plakoglobin (JUP), desmoplakin (DSP), and desmocollin2 (DSC2) genes are implicated.[3-6]
- **Naxos disease** is traditionally associated with woolly hair (WH) and palmoplantar keratoderma (PPK); however, cases presenting with sparse hair, alopecia, and bullous lesions early in life have been reported. These dermatologic markers are key indicators preceding cardiomyopathy, emphasizing the need for early detection.[3,7] (Fig. 1)
- **Need for a registry**: The group of disorders within the Naxos disease phenotypic spectrum may remain insufficiently characterized due to their rarity, as they often go unobserved or are inadequately evaluated. Rare diseases pose unique challenges to study, including limited patient populations, geographic dispersion, variability in clinical presentation, and a lack of centralized data. A structured clinical registry can address these challenges by enabling centralized data collection and facilitating international collaboration, ultimately improving diagnostic and therapeutic approaches.
- **Aims and objectives**: The primary goals are to evaluate the natural history, identify clinical and genetic correlations, and assess treatment outcomes. Secondary goals include tracking adverse events, providing a database for future studies, and developing genotype-specific insights.

2. REGISTRY DESIGN

The registry adopts a global, multicenter approach, including 30 centers internationally. It supports both retrospective and prospective data entry, encompassing cases previously documented as well as new patient records (Fig. 2).

Eligible Participants:

- All individuals (>12 months) to adulthood with skin and hair phenotypes consisting of woolly hair or sparse hair or alopecia and palmoplantar keratoderma and/or bullous lesions and cardiomyopathy phenotypes of ARVC, NDLVC, and DCM. Borderline cases, which will be included, might present additional dental anomalies and ventricular arrhythmias not fulfilling the criteria for ARVC, NDLVC, and DCM.
- Infants (0-12 m) with WH, alopecia, PPK, bullous lesions, or erythrodermia of the palms and soles, and any or no features of cardiomyopathy phenotypes of ARVC, NDLVC, or DCM, since the skin phenotypes may present as initial signs of the disease.[2]

3. PATIENT RECRUITMENT AND ENROLLMENT

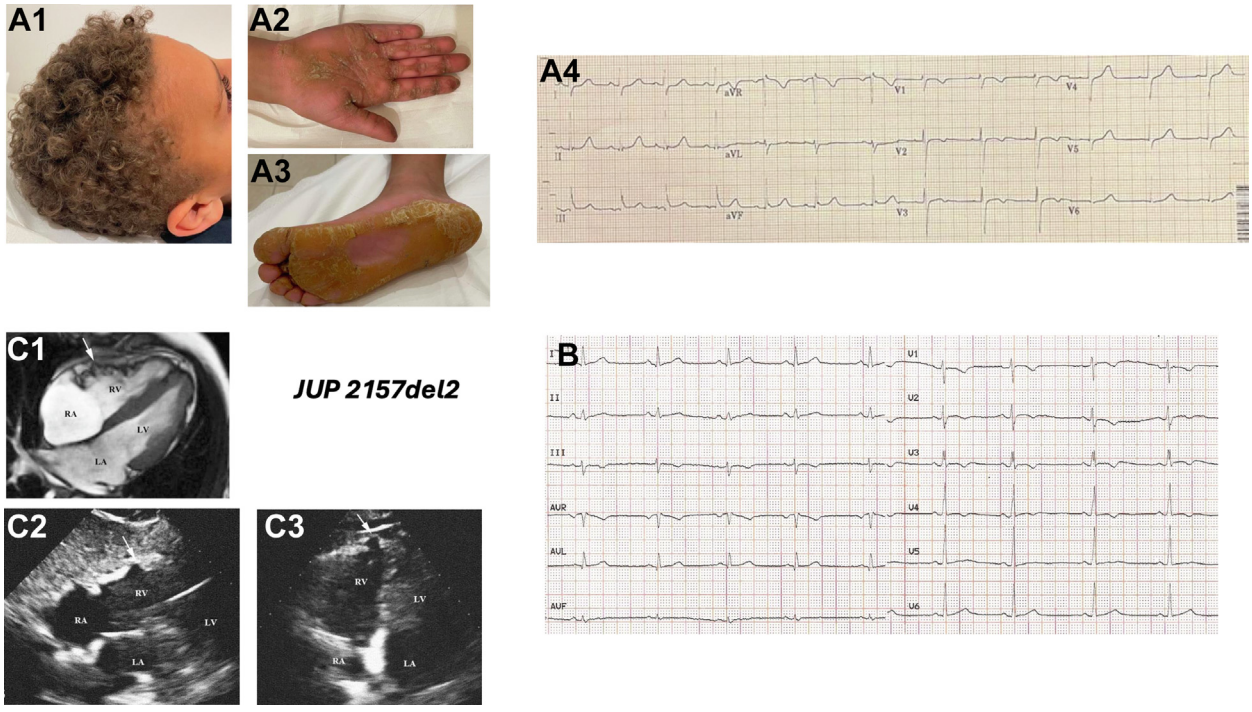
3.1. IDENTIFICATION. Potential participants are identified through collaborating centers and clinics. Ethical protocols ensuring informed consent for data collection and research participation will be applied.

3.2. ENROLLMENT. Both retrospective (previously documented cases) and prospective (new cases) recruitment is ongoing, with a targeted inclusion of cases worldwide to capture a representative sample of disease phenotypes.

4. DATA COLLECTION METHODS

4.1. CLINICAL PRESENTATION (PRESENTING SYMPTOMS AND PHYSICAL EXAMINATION). Clinical presentation in Naxos disease is characterized by distinct cardiac and dermatological manifestations. The variables to be included in the registry will be categorized as follows:

FIGURE 1 **A. A 6-year-old boy with Naxos disease, homozygous for *JUP*2157del, screened as a toddler due to characteristic cutaneous features**



Woolly hair (**A1**) and keratoderma on the palms (**A2**) and soles (**A3**) are evident. His resting 12-lead ECG at the age of 6 years shows no abnormalities, considering that T-wave inversion in V1–V3 is not considered abnormal at this age. No abnormalities were observed on two-dimensional echocardiography. **B.** A 12-lead ECG recording from a boy with Naxos disease at the age of 14 years, following an episode of chest pain and troponin elevation. During a 13-year uneventful follow-up, T-wave inversion beyond V1 was first recorded, coinciding with positive CMR-LGE findings.[8] **C.** Dyskinesia recorded on imaging in patients with Naxos disease homozygous for *JUP*2157del2. On CMR, on the right ventricular posterior (arrow) (**C1**). On two-dimensional echocardiography, on the right ventricular posterior wall (**C2**), and on the right ventricular apex (**C3**).

4.2. DEMOGRAPHIC AND FAMILY HISTORY. Demographic and family history, including proband status, consanguinity details, family history of cardiomyopathy and sudden cardiac death, age at referral, and gender.

4.3. COMORBIDITIES. Comorbidities will be systematically recorded alongside cardiac and dermatological manifestations to refine the clinical profile of affected individuals. Other cardiac and non-cardiac conditions, including coronary artery disease, metabolic and autoimmune disorders, cancer, and thromboembolic events, will be documented for potential links to disease progression.

4.4. CARDIAC VARIABLES. Cardiac variables including presence of cardiovascular symptoms (i.e., New York Heart Association [NYHA] class, unexplained syncope, and palpitations), age at onset of cardiovascular symptoms, reason for clinical presentation (i.e., aborted sudden cardiac death, sustained ventricular tachycardia, symptoms, occasional [abnormal ECG or echocardiogram], and familial screening).

4.5. CUTANEOUS VARIABLES. Cutaneous variables including the presence of cutaneous manifestations (i.e., PPK, WH, sparse hair, alopecia, skin erosions, bullous lesions, and dental abnormalities) and age at onset of the first dermatological feature observed.

5. DIAGNOSTIC TESTING

5.1. ELECTROCARDIOGRAPHY (12-LEAD ECG, HOLTER), ARRHYTHMIAS. Electrocardiogram (ECG) abnormalities are often early markers of cardiomyopathy in Naxos disease and related cardiocutaneous syndromes, sometimes preceding structural changes. Resting 12-lead ECG and 24-h Holter monitoring are essential tools for diagnosis, risk stratification, and management.[3] In a cohort of Naxos disease patients, over 90% exhibited ECG abnormalities as symptoms emerged, with a broad spectrum of

FIGURE 2 **NAXCARE: the registry flow chart**

repolarization, depolarization/conduction abnormalities, and arrhythmias.[9]

5.1.1. Repolarization abnormalities. T-wave inversion is a hallmark ECG feature, with variations depending on disease stage and phenotype:

- In ARVC, the revised diagnostic criteria define major repolarization abnormalities as T-wave inversion in leads V1-V3 and beyond in individuals over 14 years old without complete right bundle branch block (RBBB), present in at least 50% of cases.[10,11]
- Adolescents may experience T-wave reinversion in V2 and V3.[3]
- In Naxos disease, inverted T waves are frequently seen in leads V1 to V3 or across the precordial leads, with low voltage and flat T waves in left precordial leads observed in severe biventricular disease.[3]
- DSP-related cardiocutaneous disease with a dilated cardiomyopathy (DCM) phenotype often exhibits T-wave inversion in inferolateral leads, low QRS voltages, and abnormal Q waves.[12]

5.1.2. Depolarization and conduction abnormalities. Epsilon waves, indicative of delayed conduction due to fibro-fatty replacement of the myocardium, are a major diagnostic criterion in ARVC and have been reported in approximately 30% of cases. In Naxos disease, epsilon waves were detected in 34% of patients and were associated with right ventricular (RV) wall motion abnormalities and increased RV diameter.[13] Other conduction abnormalities include:

- QRS complex prolongation in V1-V3
- Complete or incomplete RBBB
- Low QRS voltage in left precordial leads in severe disease

5.1.3. Arrhythmias and risk stratification. Arrhythmic manifestations are frequent and crucial for risk assessment:

- Over 90% of Naxos disease patients experience frequent ventricular extrasystoles and/or ventricular tachycardia.[3]
- Non-sustained ventricular tachycardia (NSVT) with a left bundle branch block (LBBB) morphology and superior axis is a major diagnostic criterion for ARVC.[10]
- NSVT of other configurations (LBBB with an inferior axis) and the presence of more than 500 premature ventricular complexes on Holter monitoring are considered minor criteria.[10]
- Right bundle branch block (RBBB) ventricular extrasystoles are less common in Naxos disease.[3]

5.1.4. Clinical implications. Given the high prevalence of ECG abnormalities and their prognostic significance, annual ambulatory ECG monitoring is recommended for ARVC patients, Class IC recommendation in the most recent guidelines.[12] In Naxos disease and related cardiocutaneous syndromes, regular ECG and Holter evaluations are critical for early detection and management of electrical instability, which carries a high incidence of ventricular arrhythmias and potential progression to severe cardiomyopathy.

5.2. IMAGING (2-D -ECHO, CMR-LGE). 5.2.1. Non-invasive cardiovascular imaging. Non-invasive cardiovascular imaging techniques play a crucial role in identifying structural and functional cardiac anomalies. In patients with Naxos disease and related cardiocutaneous syndromes, classic features of arrhythmogenic right ventricular cardiomyopathy (ARVC) are mostly observed.[3] However, biventricular involvement has also been described, with phenotypic features resembling dilated cardiomyopathy (DCM) or non-dilated left-ventricular cardiomyopathy (NDLVC). Consequently, a comprehensive evaluation of both right and left heart chambers using transthoracic echocardiography (TTE) and cardiac magnetic resonance imaging (MRI) is essential at the time of diagnosis and during follow-up. To ensure accurate diagnosis and appropriate therapeutic interventions, imaging studies are reviewed by a multidisciplinary team at each center. Specific measurements are performed by an expert non-invasive cardiologist in accordance with current guidelines. Any discrepancies in imaging interpretation and related specific measurements are going to be resolved through consensus discussion.

5.2.2. Two-dimensional (2D) transthoracic echocardiography (2D-TTE). Comprehensive standardized 2D-TTE is performed with commercially available equipment, according to international adult and pediatric guidelines (**Table 1**).[14-16] A dedicated TTE case report form (CRF) will be filled out by all laboratories. Of note, cardiac measurements will be indexed to body area surface (BSA) in adults,[14] while echocardiographic Z scores will be used in the pediatric population.[16]

Due to the complex anatomy of the right ventricle, advanced transthoracic echocardiography (TTE) techniques, such as Doppler strain imaging and 3-D echocardiography (3-DE) (**Table 1**), may also be utilized. However, it is important to note that non-

TABLE 1 Standard and advanced echocardiographic measurements

Echocardiographic view	Measurement (*Standard TTE*)
Parasternal long axes (PLAX)	• LV end-diastolic diameter, mm • LV end-systolic diameter, mm • Interventricular septum thickness (end-diastole), mm • Inferolateral wall thickness (end-diastole), mm • LVOT diameter (zoom), mm • $RVOT_{PLAX}$ diameter, mm • Wall motion abnormalities • RV akinesia, dyskinesia, or aneurysm • Aortic and mitral function • Pericardial effusion (yes/no), mm (end-diastole)
Parasternal short axes (PSAX)	• $RVOT_{PSAX}$ diameter, mm • Pulmonary artery diameter, mm • RVOT acceleration time, ms • RVOT TVI notch (yes/no) • PR early diastolic velocity, m/s • Peak tricuspid velocity, m/s • Wall motion abnormalities • RV akinesia, dyskinesia, or aneurysm • Aortic, mitral, tricuspid, and pulmonary valve function • Pericardial effusion (yes/no), mm (end-diastole)
Apical 4 chamber	• LV end-diastolic volume, ml • LV end-systolic volume, ml • LV end-diastolic volume indexed to BSA, ml/m^2 • LV end-systolic volume indexed to BSA, ml/m^2 • Wall motion abnormalities • LV ejection fraction (%) • RV and LV akinesia, dyskinesia, or aneurysm • LA volume, ml • LA volume indexed to BSA, ml/m^2 • Peak E and A-wave velocity, cm/s, • MV deceleration time (ms) • Pulsed-wave TDI e' velocity lateral, cm/s • Pulsed-wave TDI e' velocity septal, cm/s • Pulsed-wave systolic TDI S', cm/s • Mitral and tricuspid function • Pericardial effusion (yes/no), mm (end-diastole) • Identify thickened moderator band (yes/no). • Basal RV:LV ratio at end-diastole.
Apical 5-chamber	• Peak aortic velocity, m/s • LVOT TVI, cm • Aortic valve function • Identify thickened moderator band (yes/no).
Apical 2-chamber	• LV end-diastolic volume, ml • LV end-systolic volume, ml • LV end-diastolic volume indexed to BSA, ml/m^2 • LV end-systolic volume indexed to BSA, ml/m^2 • Wall motion abnormalities • LV ejection fraction (%) • RV and LV akinesia, dyskinesia, or aneurysm • LA volume, ml • LA volume indexed to BSA, ml/m^2 • Mitral valve function • Pericardial effusion (yes/no), mm (end diastole)
Focused apical on the RV	• RV dimension 1, mm • RV dimension 2, mm • RV end-diastolic area (RVEDA), cm^2 • RV systolic area (RVESA), cm^2 • FAC (RVEDA-RVESA)/RVEDA*100, % • RA area, cm^2 • TAPSE, mm • Peak tricuspid velocity, m/s • Peak E and A-wave velocity, cm/s, • Pulsed-wave TDI e' and a' velocity, cm/s • Pulsed-wave systolic TDI S', cm/s • Tricuspid valve function • Pericardial effusion (yes/no), mm (end-diastole)

Continued on the next page

TABLE 1 Continued

Echocardiographic view	Measurement (*Standard TTE*)
Subcostal	• IVC diameter, mm • IVC collapse, % • RV-free wall thickness, mm • RV and LV akinesia, dyskinesia, or aneurysm • Pericardial effusion (yes/no), mm (end-diastole)
	Measurement (Advanced TTE)
Speckle tracking	• RV longitudinal strain of lateral RV free wall, % • RV mechanical dispersion (SD of time-to-peak strain) (ms) • LV GLS, %
3D-TTE	• 3D RV-EF, % • 3D LV-EF, %

Abbreviations: TTE = transthoracic echocardiography; PLAX = parasternal long axes; PSAX = parasternal short axes; LV = left ventricular; LVOT = left ventricular outflow tract; PR = pulmonary regurgitation; RA = right atrial; RVOT = RV outflow tract; A = mitral inflow A velocity as measured by PW Doppler; E = mitral inflow E velocity as measured by PW Doppler; e' = early diastolic velocity of the mitral annulus as measured by tissue Doppler; MV = mitral valve; TAPSE = tricuspid annular plane systolic excursion; IVC = inferior vena cava; LA = left atrial; S' = pulsed tissue Doppler velocity of lateral tricuspid annulus; TDI = tissue Doppler imaging; TVI = time-velocity integral; FAC = fractional area change; GLS = global longitudinal; EF = ejection fraction.

conventional echocardiographic Doppler indices are not fully validated for the diagnosis or risk stratification of ARVC.[15]

5.2.3. Cardiac magnetic resonance (CMR). CMR is the gold standard in cardiomyopathy assessment, especially for non-invasive RV structure and function

TABLE 2 Cardiac magnetic resonance protocol and measurements

Protocol	Measurement
1. Anatomy 2. LV function 3. RV function (transaxial and RVOT) 4. T1 mapping 5. Oedema 6. LGE 7. LV and RV myocardial tagging	• LV end-diastolic volume, ml • LV end-systolic volume, ml • LV ejection fraction, % • LV regional wall motion anomalies. • LV stroke volume, ml • LV stroke volume indexed to BSA, ml/m^2 • LV mass, g • LV mass indexed to BSA, g/m^2 • Cardiac output, ml/min • RV end-diastolic volume, ml • RV end-diastolic volume indexed to BSA, ml/m^2 • RV end-systolic volume, ml • RV end-systolic volume indexed to BSA, ml/m^2 • RV ejection fraction, % • RV regional wall motion anomalies. • RV stroke volume, ml • RV stroke volume indexed to BSA, ml/m^2 • RV mass, g • RV mass indexed to BSA, g/m^2 • LA area, cm^2 • RA area, cm^2 • Native T1 of remote myocardium, ms • ECV of remote myocardium, % • Native T1 of pathological myocardium, ms • LGE (yes, no) • LGE evaluated with the six SD method • LGE, % • LGE type (1. Subendocardial; 2. intramyocardial; 3. subepicardial; 4. transmural; 5. aspecific). • LA reservoir function, % • LA conduit function, % • LA booster function, % • LV GLS, % • LV GCS, % • LV GRS, % • RV free wall strain, % • Aortic, mitral, tricuspid, and pulmonary valve function

Abbreviations: LV = left ventricular; RV = right ventricular; RA = right atrium; LA = left atrium; BSA = body surface area; ECV = extracellular volume; LGE = late gadolinium enhancement; GLS = global longitudinal strain; GCS = global circumferential strain; GRS = global radial strain.

evaluation.[12,17] All patients undergo a comprehensive CMR at the time of diagnosis and during follow-up (Table 2). A complete LV and RV study is obtained with a slice thickness of 5-6 mm to increase the precision of the assessment.[15] LGE imaging may also be considered, even though the presence of myocardial fibrosis is not currently included as a diagnostic criterion for ARVC.[15] However, cardiac magnetic resonance with LGE remains the foremost imaging modality in non-dilated left-ventricular cardiomyopathy (NDLVC), as it provides confirmation of non-ischemic myocardial fibrosis, which is crucial for diagnosis in most cases.[12] This finding may represent a step in the progression of the cardiac phenotype in Naxos disease and related syndromes.[3]

5.2.4. Other imaging techniques. Cardiac multidetector computed tomography (MDCT) may be an option for patients with non-optimal echocardiographic images and absolute contraindications to CMR (i.e., claustrophobia and non-MR-conditional metallic implants, devices, defibrillators, or pacemakers).[15] Relevant cardiac MDCT parameters include RV and LV measurements, RV-EF, segmental dilatation, regional hypokinesis, and myocardial extracellular volume (ECV) quantification (Table 3). Moreover, radionuclide angiography could provide measurements of RV volumes, RV ejection fraction, and the standard deviation of regional times of end systole when there is an absolute contraindication to both CMR and cardiac MDCT.[15]

5.3. GENETIC TESTING AND VARIANT INTERPRETATION. Genetic testing plays a crucial role in the NAXCARE registry, particularly when using approved detection methods such as whole-genome sequencing (WGS) and panel sequencing (PS). Whole-exome sequencing (WES) covers all genes but has limitations, including inconsistent sequence coverage, gaps, and a lack of information on non-coding regions. These methods help identify disease-associated variants in genes like desmoplakin, desmocollin-2, and plakoglobin, which are known to underlie Naxos disease and related syndromes.[3,18-20] However, challenges remain in detecting new genes and interpreting variants.

The NAXCARE registry will record genetic variants and report them based on their current interpretation, highlighting the importance of accurate genetic analysis. Proper variant interpretation is essential, as pathogenic and likely pathogenic variants are considered clinically significant. Bioinformatics tools and family data will further refine the understanding of these variants. Variants will be reported according to the **HGVS (Human Genome Variation Society) Nomenclature** and classified according to the **ACMG Classification**[21,22] (Supplementary file).

5.4. LABORATORY TESTS. 5.4.1. Clinical biomarkers. Currently, there are no validated circulating biomarkers for the onset of ARVC or NDLVC, but several candidates may help monitor disease progression.[12]

C-reactive protein (CRP) levels are higher in ARVC patients than in those with idiopathic ventricular tachycardia and rise significantly within 24 hours of a ventricular arrhythmia event.[23] **Brain natriuretic**

TABLE 3 Cardiac multidetector computed tomography (MDCT) parameters

Protocol	Measurements
1. Anatomy 2. LV and RV function 3. Myocardial composition (presence of intramyocardial fat). 4. ECV quantification	• LV end-diastolic volume, ml • LV end-systolic volume, ml • LV ejection fraction, % • LV regional wall motion anomalies. • LV stroke volume, ml • LV stroke volume indexed to BSA, ml/m^2 • LV mass, g • LV mass indexed to BSA, g/m^2 • Cardiac output, ml/min • RV end-diastolic volume, ml • RV end-diastolic volume indexed to BSA, ml/m^2 • RV end-systolic volume, ml • RV end-systolic volume indexed to BSA, ml/m^2 • RV ejection fraction, % • RV regional wall motion anomalies. • RV stroke volume, ml • RV stroke volume indexed to BSA, ml/m^2 • RV mass, g • RV mass indexed to BSA, g/m^2 • LA area, cm^2 • RA area, cm^2 • Aortic, mitral, tricuspid, and pulmonary valve function

Abbreviations: LV = left ventricular; RV = right ventricular; RA = right atrium; LA = left atrium; BSA = body surface area; ECV = extracellular volume.

peptide (BNP) levels are elevated in ARVC patients and correlate with RV ejection fraction and severity of RV dysfunction and arrhythmogenic substrate.[24] **High-sensitivity cardiac troponin T (hs-cTNT)** levels are higher in ARVC patients with biventricular involvement, helping identify those at risk of developing biventricular disease.[25] Naxos disease has been reported to start as an episode of myocarditis with troponin elevation, highlighting the importance of hs-cTNT in early detection.[12] **Liver and renal function tests** aid in differential diagnosis and are useful for drug dose adjustment, with liver function paralleling BNP changes and predicting heart failure prognosis.[12]

These biomarkers are becoming integrated into clinical practice for monitoring disease progression and will be included in the NAXCARE registry records to aid in the comprehensive management of patients.

6. MANAGEMENT

The treatment of Naxos disease aims to manage cardiac and cutaneous manifestation, prevent disease progression, and reduce the risk of adverse events. Variables to be included in the registry will be those related to the use of antiarrhythmic medications (e.g., beta-blockers and amiodarone), implantation of implantable cardioverter-defibrillators (ICDs), catheter ablation for ventricular arrhythmias, and heart failure therapies (i.e., beta-blockers, aldosterone antagonists, angiotensin-converting enzyme inhibitors [ACEi], angiotensin receptor blockers [ARBs], sodium-glucose cotransporter 2 inhibitors, and angiotensin receptor neprilysin inhibitors [ARNIs]).[3]

7. FOLLOW-UP AND OUTCOMES

Data collected during the baseline evaluation will also be gathered during follow-up to monitor changes in clinical status, ECG findings, imaging results, and treatment. Follow-up assessments are typically scheduled every 6-18 months, but the treating physician at each center may adjust the frequency based on the patient's individual needs and routine follow-up practices. Adverse outcomes, including death, hospitalizations, heart failure, and arrhythmic events (e.g., non-sustained and sustained ventricular tachycardia, sudden cardiac death, or cardiac arrest), will be evaluated. Additionally, dermatologic outcomes, adverse treatment reactions, and quality-of-life indicators will be monitored to assess the broader impact of the disease and its treatment strategies.

8. VIRTUAL BIOBANK

In addition to collecting genetic and clinical data (including ECG, imaging, and other diagnostic modalities), we aim to integrate a virtual biobank into the NAXCARE registry. A virtual biobank is an electronic repository of biological specimens and associated data within a centralized digital platform (i.e., the NAXCARE registry), independent of the physical storage locations of the specimens.[26]

Registries that incorporate biobanks provide a unique, practical, cost-effective, and impactful solution for rare disease research. They have the potential to improve patient outcomes and alleviate the significant burden associated with rare diseases.[27]

The virtual NAXCARE biobank will systematically document the availability (Yes/No) and storage locations of the following biological materials:

- DNA and/or RNA samples
- Serum and/or plasma samples
- Skin biopsies (fibroblasts)
- Cardiac tissue samples (obtained post-transplantation or via biopsies)
- Induced pluripotent stem cells (iPSCs)
- Hair samples
- Other pertinent biospecimens (buccal swabs)[28,29]

This initiative will consolidate a diverse collection of biological samples, each linked to detailed clinical and genetic information, facilitating efficient identification of specific biosamples. By providing a centralized repository, the virtual biobank will enable researchers to connect with relevant laboratories and assess the feasibility of potential studies, including ethical and legal considerations. Additionally, it may streamline research efforts that would otherwise be challenging or require coordination across multiple biobanks. Importantly, this resource could play a crucial role in developing variant-specific, personalized treatment strategies.

9. QUALITY OF LIFE

9.1. HEALTH-RELATED QUALITY OF LIFE (HR-QoL) AND WORK ABILITY.

HR-QoL describes physical, social, and psychological aspects of well-being and functioning related to health status.[30] In this regard it should be highlighted there is no specific score to evaluate HR-QoL in patients with Naxos disease. Thus, the most used and widely validated questionnaires, such as the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) for adults and the Pediatric Quality of Life Inventory (PedsQL™) in

children and adolescents[31–33] are going to be implemented.

In addition, the Work Ability Index (WAI),[34] is going to be implemented as well.

10. QUALITY CONTROL AND DATA EVALUATION

To ensure robust and reliable data evaluation, the NAXCARE registry employs a multidisciplinary intra-center and inter-center approach. This includes standardized protocols across all participating centers to systematically ensure consistency and comparability across all contributing sites.

Additionally, tailored machine learning (ML) models are being developed, trained, and implemented within the NAXCARE framework. These models will enhance preventive strategies, diagnosis, prognosis, and therapeutic interventions by integrating and analyzing complex datasets. The combination of stringent quality control measures and advanced ML methodologies ensures the generation of high-quality, reproducible data, fostering improved patient outcomes in Naxos disease and related cardiocutaneous syndromes (Fig. 3).

11. DATA MANAGEMENT AND SECURITY

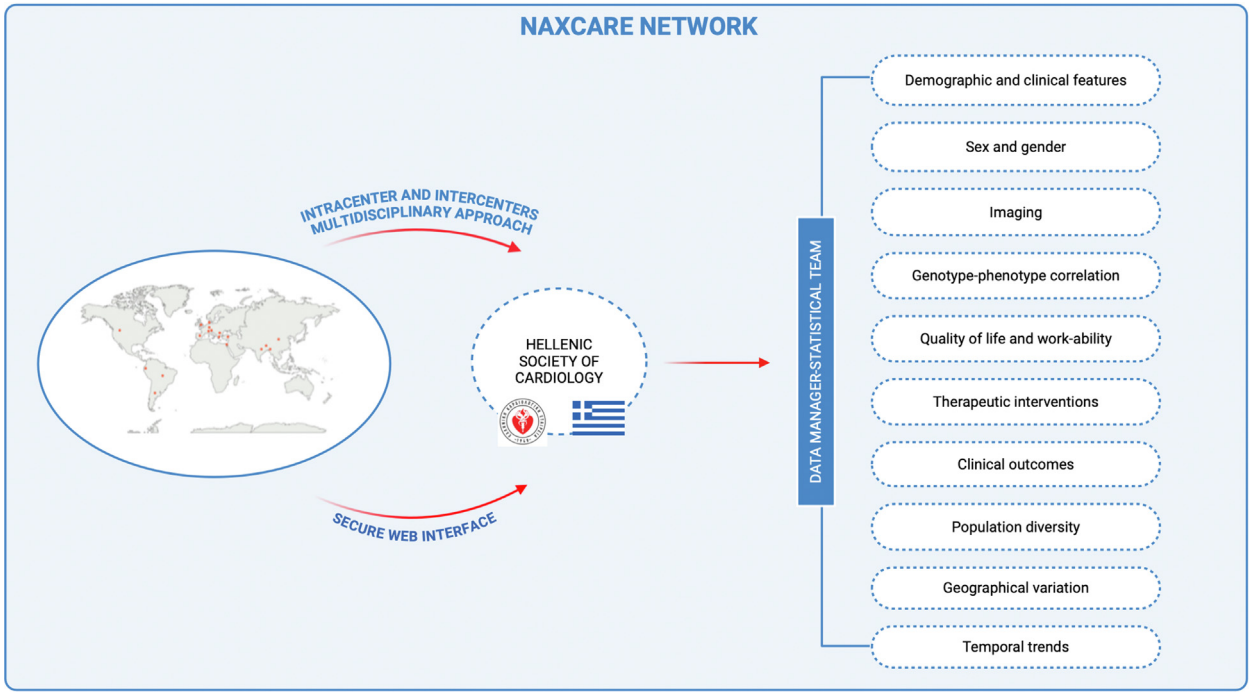
11.1. GOVERNANCE AND OVERSIGHT. The registry's management structure includes a Steering Committee, an International Leaders Committee, and a Data Manager and statistical team. The Steering Committee oversees protocol adherence and data integrity (Fig. 3).

11.2. PLATFORM. Data is systematically recorded on a centralized platform managed by the Hellenic Society of Cardiology, accessible to verified contributors through a secure web interface (https://members.hcs.gr/), ensuring consistency and ease of access across multiple centers (Supplementary file).

11.3. DATA SECURITY. Patient data is pseudonymized for confidentiality, with each patient assigned a unique code in place of identifiable information. Data storage follows strict GDPR-compliant security protocols, with daily encrypted backups hosted in a secure data center in Germany.

11.4. DATA ACCESS LEVELS. Access permissions are tiered; the registry chair has full data access, while other committee members access data only during formal sessions with authorized supervision.

FIGURE 3 **NAXCARE: the registry management structure**



12. STATISTICAL ANALYSIS

12.1. STATISTICAL ANALYSIS PLAN.

12.1.1. Descriptive statistics. Baseline demographics (e.g., age, sex, and ethnicity) and disease characteristics (e.g., genetic variants, clinical presentation, and comorbidities) are summarized to provide an overview of the patient population. Continuous variables are reported as means with standard deviations or medians with interquartile ranges, depending on their distribution. Categorical variables are reported as absolute frequencies and percentages to provide a comprehensive overview of the patient population. Statistical comparisons between subgroups are performed using parametric (*t*-test) or nonparametric (Wilcoxon rank-sum test) approaches for continuous variables and chi-square or Fisher's exact tests for categorical variables, as appropriate.

12.1.2. Survival and event analysis. Time-to-event data, such as arrhythmic events, disease progression, and all-cause mortality, are analyzed using survival analysis techniques, including Kaplan-Meier estimators to estimate event-free survival probabilities, providing a graphical representation of disease progression patterns and event occurrence rates. Cox proportional hazards models are used to identify potential predictors of clinical outcomes. Hazard ratios (HR) with 95% confidence intervals (CI) are reported to quantify the relative risk associated with specific predictors. These methods provide valuable insights into the temporal patterns of disease progression and the factors influencing clinical events.

12.1.3. Genotype-phenotype correlation. Statistical modeling, including regression analyses, is employed to explore associations between specific genetic mutations and clinical presentations. For continuous phenotypic traits, multivariable linear regression is used to assess the effect of specific genetic mutations while adjusting for potential confounders. For binary outcomes (e.g., presence or absence of a clinical feature), logistic regression models are applied to estimate odds ratios (OR) with 95% confidence intervals (CI).

To enhance data reliability and model validation analyses, missing data are assessed and handled appropriately based on predefined criteria.

13. LEGAL AND ETHICAL CONSIDERATIONS

The study will be performed in accordance with the Declaration of Helsinki in its current version (2024). Participants of the prospective cohort will be informed, both verbally and with a specific written document, of the nature and scope of the proposed study, possible benefits for their health, and potential risks. Their consent will be documented by signing the consent form. Participation of subjects in the study is voluntary; the potential participant must be informed of the right to refuse to participate in the research or to withdraw consent to participate at any time without reprisal. The protocol will be submitted for consideration, comment, guidance, and approval to the concerned local ethics committee of each participating and cooperating center before starting the research. Every precaution will be taken to protect the privacy of research participants and the confidentiality of their personal information, according to the European Union directive on General Data Protection Regulation (GDPR). Data transfer for analysis will be performed with anonymous-coded data. Personal data that may lead to identification of the subject will not be transferred.

14. ANTICIPATED IMPACT AND APPLICATIONS

14.1. PATIENT CARE.

The registry provides real-world insights into disease progression, facilitating personalized treatment and better disease management strategies.

14.2. RESEARCH.

The centralized database enables multi-institutional research, supporting publications and aiding in clinical trial recruitment for new therapies tailored to Naxos disease and related CCS.

15. LIMITATIONS AND CHALLENGES

15.1. CHALLENGES. Key challenges include inconsistent follow-up due to the geographic dispersion of patients and variability in data reporting across centers.

15.2. MITIGATIONS. To address these challenges, the registry employs standardized data entry formats and protocols to ensure consistency and streamline the data collection process across all participating centers.

16. CONCLUSION

The NAXCARE registry represents a crucial advancement in the understanding and management of Naxos disease and related cardiocutaneous syndromes

(CCS). By consolidating data from multiple centers around the world, it provides a comprehensive and diverse dataset that will be invaluable for identifying patterns, outcomes, and therapeutic needs. This global collaboration facilitates the development of more personalized and targeted treatment strategies, improving patient care and outcomes. Additionally, the registry contributes to the growing body of clinical knowledge, supporting further research into disease progression, risk factors, and optimal management approaches. Ultimately, NAXCARE plays a pivotal role in advancing both clinical practice and scientific discovery in the field of rare cardiomyopathies and related syndromes.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT and Copilot to improve clarity and enhance the use of the English language. After employing these tools, the authors thoroughly reviewed and edited the content as necessary and take full responsibility for the final content of the publication.

CORRESPONDING AUTHOR. Paediatric Clinic, Hora, Naxos 84300, Greece. E-mail: adalenatsatsop@gmail.com.

REFERENCES

1. Protonotarios N, Tsatsopoulou A, Patsourakos P, et al. Cardiac abnormalities in familial palmoplantar keratosis. *Br Heart J*. 1986;56:321–326. https://doi.org/10.1136/hrt.56.4.321

2. Protonotarios I, Asimaki A, Xylouri Z, Protonotarios A, Tsatsopoulou A. Clinical and molecular aspects of Naxos disease. *Heart Fail Clin*. 2022;18:89–99. https://doi.org/10.1016/j.hfc.2021.07.010

3. Protonotarios A, Asimaki A, Basso C, et al. Naxos disease and related cardio-cutaneous syndromes. *JACC Adv*. 2025;4:101547. https://doi.org/10.1016/j.jacadv.2024.101547

4. McKoy G, Protonotarios N, Crosby A, et al. Identification of a deletion in plakoglobin in arrhythmogenic right ventricular cardiomyopathy with palmoplantar keratoderma and woolly hair (Naxos disease). *Lancet*. 2000;355:2119–2124. https://doi.org/10.1016/S0140-6736(00)02379-5

5. Norgett EE, Hatsell SJ, Carvajal-Huerta L, et al. Recessive mutation in desmoplakin disrupts desmoplakin-intermediate filament interactions and causes dilated cardiomyopathy, woolly hair and keratoderma. *Hum Mol Genet*. 2000;9:2761–2766. https://doi.org/10.1093/hmin/9.18.2761

6. Gerull B, Kirchner F, Chong JX, et al. Homozygous founder mutation in desmocollin-2 (DSC2) causes arrhythmogenic cardiomyopathy in the Hutterite population. *Circ Cardiovasc Genet*. 2013;6:327–336. https://doi.org/10.1161/CIRCGENETICS.113.000097

7. Protonotarios N, Tsatsopoulou A. Naxos disease: cardiocutaneous syndrome due to cell adhesion defect. *Orphanet J Rare Dis*. 2006;1:4. https://doi.org/10.1186/1750-1172-1-4

8. Mavrogeni S, Protonotarios N, Tsatsopoulou A, Papachristou P, Sfendouraki E, Papadopoulos G. Naxos disease evolution mimicking acute myocarditis: the role of cardiovascular magnetic resonance imaging. *Int J Cardiol*. 2013;166:e14–e15. https://doi.org/10.1016/j.ijcard.2012.12.078

9. Protonotarios N, Tsatsopoulou A, Anastasakis A, et al. Genotype-phenotype assessment in autosomal recessive arrhythmogenic right ventricular cardiomyopathy (Naxos disease) caused by a deletion in plakoglobin. *J Am Coll Cardiol*. 2001;38:1477–1484. https://doi.org/10.1016/s0735-1097(01)01568-6

10. Marcus FI, McKenna WJ, Sherrill D, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia: proposed modification of the Task Force Criteria. *Eur Heart J*. 2010;31:806–814. https://doi.org/10.1093/eurheartj/ehq025

11. Tsatsopoulou A, Protonotarios I, Xylouri Z, et al. Cardiomyopathies in children: an overview. *Hellenic J Cardiol*. 2023;72:43–56. https://doi.org/10.1016/j.hjc.2023.02.007

12. Arbelo E, Protonotarios A, Gimeno JR, et al. 2023 ESC Guidelines for the management of cardiomyopathies. *Eur Heart J*. 2023;44:3503–3626. https://doi.org/10.1093/eurheartj/ehad194

13. Protonotarios A, Anastasakis A, Tsatsopoulou A, et al. Clinical significance of epsilon waves in arrhythmogenic cardiomyopathy. *J Cardiovasc Electrophysiol*. 2015;26:1204–1210. https://doi.org/10.1111/jce.12755

14. Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713. https://doi.org/10.1016/j.echo.2010.05.010. quiz 786–788.

15. Haugaa KH, Basso C, Badano LP, et al. Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy-an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2017;18:237–253. https://doi.org/10.1093/ehjci/jew229

16. Lopez L, Saurers DL, Barker PCA, et al. Guidelines for performing a comprehensive pediatric transthoracic echocardiogram: recommendations from the American society of echocardiography. *J Am Soc Echocardiogr*. 2024;37:119–170. https://doi.org/10.1016/j.echo.2023.11.015

17. Cipriani A, Mattesi G, Bariani R, et al. Cardiac magnetic resonance imaging of arrhythmogenic cardiomyopathy: evolving diagnostic perspectives. *Eur Radiol*. 2023;33:270–282. https://doi.org/10.1007/s00330-022-08958-2

18. Patel V, Asatryan B, Siripanthong B, et al. State of the art review on genetics and precision medicine in arrhythmogenic cardiomyopathy. *Int J Mol Sci*. 2020;21:6615. https://doi.org/10.3390/ijms21186615

19. Protonotarios N, Tsatsopoulou A. Naxos disease and Carvajal syndrome: cardiocutaneous disorders that highlight the pathogenesis and broaden the spectrum of arrhythmogenic right ventricular cardiomyopathy. *Cardiovasc Pathol*. 2004;13:185–194. https://doi.org/10.1016/j.carpath.2004.03.609

20. Simpson MA, Mansour S, Ahnood D, et al. Homozygous mutation of desmocollin-2 in arrhythmogenic right ventricular cardiomyopathy with mild palmoplantar keratoderma and woolly hair. *Cardiology*. 2009;113:28–34. https://doi.org/10.1159/000165696

21. Hart RK, Fokkema IFAC, DiStefano M, et al. HGVS Nomenclature 2024: improvements to community engagement, usability, and computability. *Genome Med*. 2024;16:149. https://doi.org/10.1186/s13073-024-01421-5

22. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American college of medical genetics and genomics and the association for molecular pathology. *Genet Med*. 2015;17:405–424. https://doi.org/10.1038/gim.2015.30

23. Stadiotti I, Pompilio G, Maione AS, Pilato CA, D'Alessandra Y, Sommariva E. Arrhythmogenic cardiomyopathy: what blood can reveal? *Heart Rhythm*. 2019;16:470–477. https://doi.org/10.1016/j.hrthm.2018.09.023

24. Matsuo K, Nishikimi T, Yutani C, et al. Diagnostic value of plasma levels of brain natriuretic

peptide in arrhythmogenic right ventricular dysplasia. *Circulation*. 1998;98:2433-2440. https://doi.org/10.1161/01.cir.98.22.2433

25. Akdis D, Saguner AM, Burri H, et al. Clinical predictors of left ventricular involvement in arrhythmogenic right ventricular cardiomyopathy. *Am Heart J*. 2020;223:34-43. https://doi.org/10.1016/j.ahj.2020.01.019

26. De Souza YG, Greenspan JS. Biobanking past, present and future: responsibilities and benefits. *AIDS*. 2013;27:303-312. https://doi.org/10.1097/QAD.0b013e32835c1244

27. Garcia M, Downs J, Russell A, Wang W. Impact of biobanks on research outcomes in rare diseases: a systematic review. *Orphanet J Rare Dis*. 2018;13:202. https://doi.org/10.1186/s13023-018-0942-z

28. Bueno-Beti C, Field E, Tsatsopoulou A, et al. Analysis of buccal mucosa as a prognostic tool in children with arrhythmogenic cardiomyopathy. *Prog Pediatr Cardiol*. 2022;64. https://doi.org/10.1016/j.ppedcard.2021.101458. None.

29. Asimaki A, Protonotarios A, James CA, et al. Characterizing the molecular pathology of arrhythmogenic cardiomyopathy in patient buccal mucosa cells. *Circ Arrhythm Electrophysiol*. 2016;9:e003688. https://doi.org/10.1161/CIRCEP.115.003688

30. Yin S, Njai R, Barker L, Siegel PZ, Liao Y. Summarizing health-related quality of life (HRQOL): development and testing of a one-factor model. *Popul Health Metr*. 2016;14:22. https://doi.org/10.1186/s12963-016-0091-3

31. Carbone A, Palladino R, Franzese M, et al. Health-related quality of life in patients with aortic dissection: an unmet need. *Curr Probl Cardiol*. 2024;49:102138. https://doi.org/10.1016/j.cpcardiol.2023.102138

32. Edouard T, Picot M-C, Bajanca F, et al. Health-related quality of life in children and adolescents with Marfan syndrome or related disorders: a controlled cross-sectional study. *Orphanet J Rare Dis*. 2024;19:180. https://doi.org/10.1186/s13023-024-03191-0

33. Goldfinger JZ, Preiss LR, Devereux RB, et al, GenTAC Registry Consortium. Marfan syndrome and quality of life in the GenTAC registry. *J Am Coll Cardiol*. 2017;69:2821-2830. https://doi.org/10.1016/j.jacc.2017.04.026

34. Magnavita N, Meraglia I, Viti G, Borghese L. The work ability Index (WAI) in the healthcare sector: a cross-sectional/retrospective assessment of the questionnaire. *Int J Environ Res Public Health*. 2024;21:349. https://doi.org/10.3390/ijerph21030349

KEYWORDS Naxos disease, Carvajal syndrome, Arrhythmogenic right ventricular cardiomyopathy, Plakoglobin, Desmoplakin, Palmoplantar keratoderma

APPENDIX A. SUPPLEMENTARY DATA Supplementary data related to this article can be found at https://doi.org/10.1016/j.hjc.2025.04.004.