Draft v.2

National reGistry of hypeRtrophic cArDIomyopathy: regional fEatures, geNeTics and course (GRADIENT)

Russian Multicenter Open-label Observational Clinical Trial

(Project of the Central State Medical Academy of the Department of Presidential Affairs, Almazov National Medical Research Center, and the ESC Working Group on Myocardial and Pericardial Diseases)

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ABBREVIATIONS

CAD	–	Coronary artery disease
CMR	–	Cardiovascular magnetic resonance
CRF	–	Case report form
ECG	–	Electrocardiogram
ECHO	–	Echocardiogram
HCM	–	Hypertrophic cardiomyopathy
HF	–	Heart failure
ICD	–	Implantable cardioverter-defibrillator
IVS		Interventricular septum
LV	–	Left ventricular
SCD	–	Sudden cardiac death
SRT	–	Septal reduction therapy

1. INTRODUCTION

Hypertrophic cardiomyopathy (HCM) is defined as a primary cardiac muscle disorder characterized by the development of left ventricular hypertrophy in the absence of obvious causes for the observed magnitude of hypertrophy [1]. The morphological expression of HCM is confined solely to the heart. Despite the success in reducing HCM mortality rates - achieved mostly through the application of sudden cardiac death (SCD) risk stratification strategies and interventions for SCD prevention [2] - HCM is still associated with: 1) an increased risk of SCD, especially in young adults, 2) the progression of heart failure (HF), 3) atrial fibrillation (AF), and 4) thromboembolic stroke [3]. All-cause mortality in all age cohorts of patients with HCM is still at least twice as high as in same-aged controls [4, 5].

HCM is the most common inherited cardiac disease. The overall prevalence of phenotypically apparent HCM is approximately 1:500 [6], and among those who come to medical attention, it is 1:3200 [7]. Significant progress in cardiac imaging and increasing availability of genetic analysis suggest a greater number of patients with HCM, estimated at 1:200, according to some authors [8]. This means that in Russia, with a population of about 140 million people, the number of patients with HCM and carriers of pathogenic variants in sarcomere genes is around 700 000, of which 280 000 have LV hypertrophy, and 44 000 have a “clinical HCM.”

The understanding of the genetic architecture of HCM has undergone substantial changes over the past 30 years. Initial studies identified sarcomere genes containing mutations that explain the Mendelian (monogenic) inheritance of HCM [9]. In large segregation studies over the past decade, a few additional non-sarcomere genes have demonstrated a strong involvement in the development of HCM [10, 11]. However, pathogenic mutations associated with HCM genes are found in only 60% of patients. Moreover, significant clinical heterogeneity is observed among carriers of the same mutation and within members of the same family [12], including monozygotic twins [13].

In recent years, the concept of a more complex genetic architecture of HCM has been developed. This includes not only the genes responsible for the primary genetic effect but also modifier genes, which contribute to the oligogenic nature of inheritance and phenotype formation in genotype-positive patients [14, 15].

The current understanding of the pathogenesis of HCM in patients who do not have convincing evidence of a causative genetic defect includes a polygenic trait of inherence and phenotype formation under the influence of concomitant diseases, such as diastolic arterial hypertension and obesity [15-17]. However, obtaining evidence for the modifying role of common genetic variants or environmental factors appears even more challenging than identifying new genes. Clearly, large case-control GWAS trials in cohorts of patients who meet the clinical criteria for HCM are required [18].

HCM has been the subject of intensive investigation for over 60 years. However, only in the last decade have studies become multicenter, involving large numbers of patients and providing the best source of real-world data. Currently, there are epidemiological, clinical, and genetic data on patients with HCM from North America and Europe, but not from the Russian Federation[2, 4, 5, 19].

All of the above, along with the recent development of pathogenetic treatment for HCM [20], which is likely to improve not only the quality but also the prognosis of life, underscores the need for an observational registry of patients with HCM in Russian Federation. This registry will help increase knowledge of the epidemiology and prevalence of HCM, ultimately improving diagnosis and management. To assess the feasibility of new interventions, understanding the epidemiological profile of patients with HCM is essential. Clinical characteristics, imaging patterns, and outcomes may vary across different geographic regions. Completing this registry will enhance our understanding of the disease in Russia, and promote measures that modify the natural history of HCM.

2. OBJECTIVE

This study is envisioned as the very first of its kind in the Russian Federation, aiming to provide a comprehensive characterization of the clinical spectrum and disease burden, focusing on the epidemiology and progression of HCM in the largest cohort of adult and pediatric patients from this region. The objectives include understanding the epidemiological profile of Russian population, clarifying the origins of clinical heterogeneity in HCM, and analyzing natural history. The study seeks to elucidate disease progression, identify contributing clinical factors, and explore new as well as previously established associations between genetic and acquired determinants and clinical features of HCM, all based on from a prospective observational study in the Russian population.

2.1 The Additional Objectives of the Study are:

- To evaluate the natural progression of HCM in non-operated patients who have indications for myectomy and in high-risk patients for SCD, who have not been implanted with an ICD.
- To clarify the relationship between pediatric and adult HCM by constructing large pedigrees, including clinically and genetically examined relatives.
- To evaluate real-world clinical practices, both surgical and therapeutic, in the management of LV obstruction.
- To investigate the impact of comorbidities on phenotypic expression of HCM.
- To establish a group of national HCM experts and centers of excellence.

3. STUDY DESIGN AND SELECTION CRITERIA

3.1 Study Type

This is a multicenter observational study (Registry)

3.2 Inclusion Criteria

- Any age
- Signed informed consent form (ICF) for participation in the study, including genetic testing
- Meets the criteria for HCM

3.2.1 HCM Criteria for Probands ≥ 18 Years Based on ECHO or CMR

- End-diastolic LV wall thickness ≥ 15mm in any segment of the LV

3.2.2 HCM Criteria for Probands ≥ 18 Years with Arterial Hypertension

- 1st degree of AH: The same ECHO/CMR criteria as patients without AH
- 2nd and 3rd degrees of AH:
  - Asymmetric LV hypertrophy: the ratio of septum / LV PW ≥ 1.5 or apical HCM
  - If asymmetry < 1.5, the wall thickness must be ≥ 20mm
- For all patients with arterial hypertension, the presence of at least one of the following ECG changes is obligatory:
  - Pathological “dagger” Q wave
  - T-wave inversion ≥ 3mm in ≥ 2 adjacent leads
  - Poor R progression / QS / RV1 > RV2 < RV3 in V1-V4

3.2.3 HCM Criteria for First-degree Relatives ≥ 18 Years Based on ECHO or CMR and ECG [21]:

- End-diastolic LV wall thickness ≥ 13mm in any segment and/or ECG changes in the absence of CAD, such as (at least one of the following):

    - Quantitative signs of LV hypertrophy* + repolarization changes
    - T wave inversions in at least 2 adjacent leads: ≥ 3mm in V3-V6, I, aVL or ≥ 5mm in II, III, aVF
    - Pathological Q waves (> 25% of R) in at least 2 adjacent leads: II, III, aVF (in the absence of left anterior hemiblock) or V1-V4, or I, aVL, V5-V6

*Presence at least one of the following:

- Sokolow-Lyon index (S in V1 + R in V5 or V6) > 35mm
- R or S in limb leads ≥ 20mm
- S in V1 or V2 ≥ 30mm
- R in V5 or V6 ≥ 30mm

3.2.4 HCM Criteria for Children and Adolescents < 18 Years

- End-diastolic LV wall thickness in any segment > 2.5 standard deviations (> 2.5 z-score) above the norms for the index gender, age and weight (or body surface area) in asymptomatic children/adolescents without a family history of HCM
- End-diastolic LV wall thickness in any segment > 2.0 standard deviations (> 2.0 z-score) above the norms for the index gender, age and weight (or body surface area) in children/adolescents with a family history of HCM or a positive genetic test

3.3 Exclusion Criteria

- Uncontrolled arterial hypertension of 2nd – 3rd degree with mild/moderate (< 20mm) or symmetric LV hypertrophy or a “normal” ECG
- Hemodynamically significant congenital or acquired valve heart disease

- Established diagnosis of metabolic, infiltrative, endocrine, or other diseases known as “phenocopies of HCM”

3.4 Target Number of Patients

The size of a representative group of patients with HCM, aimed at assessing the demographic and clinical characteristics of the disease in the Russian population - including the proportion of high-risk patients - was based on the estimated prevalence of HCM in the general population as 1:500 [22] and the population of the Russian Federation (140 million people). Type I error was set at 5%, and Type II error at 20%. The required sample size was 384 patients. To achieve a Type I error of 1%, the sample size would need to be 662 patients.

When planning a prospective observation to assess all-cause mortality, the estimated total mortality rate among adults in the Russian Federation was used, set at 13.2 per 1000 (averaged data for 2010-2019 from the Federal State Statistics Service https://rosstat.gov.ru/folder/12781). The annual mortality rate for patients with HCM was estimated at 45.6 per 1000 (data from the Sarcomeric Human Cardiomyopathy Registry (SHaRe)). The enrollment period was planned for 3 years, with a follow-up period of 1 year. Type I error was set at 5%, Type II error at 20%. The required number of patients for the analysis of all-cause mortality was 912 [808-1006]. To achieve a Type I error of 1%, the required number of patients for the analysis was 1346 [1200-1492].

The group size calculation was performed using the NCSS statistical software package (PASS 2021).

3.5 Sources of HCM Patients

- Consecutive patients who meet the HCM criteria within enrollment period
- Patients who have been examined at the participating centers in the past and may be invited for enrollment
- Patients who have been examined at the participanting centers within the last year, with all enrolment procedures completed

3.6 Stages of Study

3.6.1 Selection Period

- Start Date of Enrolment: October 01, 2023
- End Date of Enrolment: October 01, 2026
- Definition of Enrollment Date: The date of enrollment will be considered the date of the first comprehensive examination at the center.

3.6.2 Follow-up

- Duration of Follow-up: Each patient will be followed for a minimum of one year or until one of the following events occurs:

    - Death
    - Heart transplantation

- Start Date of Follow-up: The start date for each patient's follow-up period will be the date of their enrollment visit.
- End Date of Follow-up: The end date will be defined as one of the following:

    - The date of the last contact during the study completion
    - The date of death
    - The date of heart transplantation

The estimated end date of the follow-up period in the study is October 01, 2027. If investigational staff and technical resources are available, the follow-up period will be extended as long as possible.

During the follow-up period, all deaths, as well as non-fatal HCM-related events and other cardiovascular events, will be recorded. Additionally, information about diagnostic procedures and treatment interventions will also be collected during the follow-up period.

Patients lost to follow up will be assessed until the date of their last contact.

3.6.3 Statistics and Publications

The dates for statistical analysis and the preparation of publications are estimated to be from October 01, 2027 to October 01, 2029.

3.7 Requirements for Investigational Site

- Availability of staff experienced in the management of patients with HCM
- Ability to examine the patients with suspected HCM referred from the other clinics
- Capacity to recruit at least 20 patients
- Availability of a state-of-the-art echocardiograph and specialists with experience in the diagnosis of HCM and differential diagnostics of other causes of LV hypertrophy
- Ability to perform 12-lead ECGs
- Capability to collect, store (in a freezer), and ship blood samples to the Almazov National Medical Research Center for further genetic testing
- The study protocol and informed consent form must be approved by the local Ethics Committee

4. STUDY PROCEDURES

4.1 ENROLLMENT OF PATIENTS

To enroll patients in the study, the following procedures must be followed:

- Obtain Inform Consent
- Collect Personal and Family History
- 2D Transthoracic Echocardiogram with Provocation
- 12-lead ECG at Rest
- 24-Hour Holter Monitoring
- Blood Sample Collection

4.1.1 Obtaining of Informed Consent

- Each patient ≥ 18 years is required to personally sign an informed consent form (ICF) to participate in the observational study, including genetic testing component
- For patients < 18 years, the ICF must be signed by an official representative, which may be one of the parents or a legal guardian. In addition, individuals aged between 14 and 18 years must personally sign the ICF, along with their parent or guardian
- An example of the ICF is available in *Appendix 2* for reference
- Each investigational site has the rights to use its own version of the ICF, approved by the local Ethics Committee.

4.1.2 Obtaining of the Clinical Data

The process for obtaining clinical data is as follows:

♦ Data Collection:
- Clinical data will be gathered during the patient's interview and recorded initially in a paper version of a case report form (CRF) titled "Visit of Enrollment".
- Afterward, the data will be transferred from the paper CRF to an electronic version of the CRF.

♦ Responsibilities of the Center:
- The responsibility for accurately completing both the paper and electronic versions of the CRF lies with the study center conducting the enrollment.

♦ Quality Control:
- Members of the study working group will oversee the quality control of the collecting data.
- They may communicate with investigators to clarify and issues or discrepancies in the CRF.

♦ CRF Completion Guidelines:
- Detailed guidelines for completing the CRF are provided in *Appendix 5* for reference.

♦ CRF "Visit of Enrollment" Sections:

The Visit of Enrollment CRF (*Appendix 6*) will include the following sections:

- Demographic and epidemiological data
- Personal and family history of HCM
- Diagnostic procedures
- Comorbidities
- Pharmacological treatment at enrollment
- Outcomes / follow up visits

4.1.3 Instrumental Examination

The following instrumental examinations will be conducted for all enrolled patients:

4.1.3.1 Echocardiography

All patients will undergo an ECHO investigation at the time of enrollment. The specific parameters to be evaluated during the ECHO are detailed in the CRF "Echocardiogram" (see *Appendix 7*).

4.1.3.2 Electrocardiogram

A 12-lead ECG will be recorded for all patients while at rest during enrollment. The recorded ECG data will be documented in the CRF "Electrocardiogram" (see *Appendix 8*). The scanned or digital version of the ECG must be uploaded to the electronic database of the study to ensure proper storage and accessibility.

4.1.3.3 24-hour ECG Holter Monitoring

- Procedure: All patients must provide data from a 24-hour ECG Holter monitoring, which can be performed either at the enrolling site or at another medical facility, as long as conducted within ± 12 months from the enrollment date.
- Data Recording: the results from the 24-hour ECG monitoring will be documented in the CRF titled "24-hour ECG monitoring" (see *Appendix 9*).

4.1.4 Blood Samples Collection

- Procedure: The procedures for collecting and storing blood samples, as well as coding patients and biosamples, are detailed in *Appendix 2* and *Appendix 3*.

4.1.5 Shipment of Blood Samples for Genetic Study

- Shipment Deadline: Blood samples must be shipped to the Almazov National Medical Research Center no later than 12 months after collection.
- Courier Service: The shipment must be handled by a courier service that is licensed to transport biological material.
- Shipping Conditions: On the day of shipment, blood samples should be removed from the freezer and shipped at room temperature. The samples should not be re-frozen after thawing, and cooling is not required during transportation.
- Enrollment Confirmation: Once the blood samples are received at the central genetic laboratory, the patient is officially considered enrolled in the study.

4.2 FOLLOW-UP

- During follow-up period, patients or their relatives will be contacted by phone at least once every 12 months
- At follow-up visits, information regarding the study endpoints, ant medical examinations, and interventions that have occurred since the time of enrollment will be collected. Investigators are encouraged to make every effort to obtain official medical records that document these endpoints and any interventions that have taken place.
- All follow-up data will be recorded in the CRF titled “Follow up” (see *Appendix 10*).

4.3 GENETIC STUDY

The genetic study aims to identify the causative genetic variants associated with HCM in enrolled patients (probands). The key procedures and stages of the genetic analysis are as follows:

- The genetic testing will be conducted using new-generation sequencing (NGS) with target gene panels.
- **First initial stage** of testing will focus on **39 genes** (listed in *Appendix 11*) that are most frequently associated with the development of HCM in both adults and children. The aim is to identify **pathogenic, likely pathogenic, or variants of unknown significance (VUS)** in genes which could be potentially causative for HCM.
- If no significant genetic variants are found in the initial panel, the gene list will be expanded to an **extensive cardio panel of 172 genes** (and potentially more) that are linked to a variety of inherited cardiovascular diseases (see *Appendix 12*).
- In cases where the extensive panel does not reveal any causative variants, **whole exome sequencing (WES)** may be performed. Additionally, WES may be conducted immediately after receiving a negative result from the 39-gene panel, depending on the clinical features of the disease.
- If pathogenic, likely pathogenic variants, or high-probability VUSs are identified, **cascade family screening** will be offered. This involved testing family members to assess genetic risk and provide further clinical interpretation of the results. Patients will receive genetic counseling both before and after the genetic study. Counseling will cover the aim and significance of the genetic test, the expected results and their potential interpretations, the implications of the genetic findings for disease prognosis and management.

5. ENDPOINTS

5.1 Primary endpoint

The primary endpoint of the study is all-cause mortality (death from any cause).

5.2 Secondary Endpoints

The study will collect and analyze information regarding the following **nonfatal events** during the follow-up period. These events will be assessed both individually and in combination:

1. Appropriate and non-appropriate ICD shocks
2. Successful resuscitation
3. Progression of dyspnea to class III/IV according by NYHA
4. A reduction in LV EF to less than 50%
5. Hospitalization due to HF requiring parenteral diuretics and/or inotropic therapy
6. LVAD implantation
7. Heart transplantation or being on the waiting list
8. Septal reduction therapy
9. Non-fatal ischemic strokes
10. New onset AF
11. New onset non-sustained VT
12. New onset Sustained VT
13. New onset syncope (highly likely arrhythmogenic)
14. Other non-fatal CV events, including but not limited to MI and pulmonary embolism.

6. STATISTICS

6.1 Data Collection

All collected data will be entered into a single, study-specific electronic database. Given the large number of patients expected to enroll in the study, data should be entered after each patient visit – whether the visit is on-site or conducted via phone.

6.2 Statistical Methods

For all variables the normality of distribution will be checked by Shapiro-Wilks. Continuous variables will be expressed as mean ± standard deviation (if normally distributed) or as median and interquartile range (IQR) (P25-P75) for non-normally distributed data. Student's t-test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data) will be used for comparisons of continuous variables, and Chi-square or Fisher tests for categorical variables. Categorical variables will be given as total number and percentages. Correlations were assessed by Pearson's and Spearman's correlation analysis. Survival curves

will be constructed according to the Kaplan-Meier method and comparison will be performed using log-rank test. Survival will be assessed by Cox proportional hazard regression for time depended variables and by binary logistical regression for time independent variables. All p-values will be two-sided, and considered significant when < 0,05.

6.3 Prognosis

- The prognosis for all-cause mortality will be assessed for the entire cohort of patients from the moment of their enrollment.
- The annual incidence of HCM-related events will be analyzed in subgroups of patients who were free from HCM-related events at the time of their enrollment.
- The following covariates will be considered when assessing prognosis: assessment: age at diagnosis, age at enrollment, sex, comorbidities, other clinical factors
- The study will compare mortality rates and disease progression between the following sarcomere gene variant groups:

    - Sarcomere positive group: patients with ≥ 1 pathogenic or likely pathogenic variant linked with HCM.
    - Sarcomere VUS group
    - Sarcomere negative group

- If data on a specific endpoint (e.g., new onset AF) are unavailable, the patient will be excluded from the analysis of that particular endpoint (e.g., “AF and stroke”). However, the patient will still be included in analyses for other applicable endpoints.

6.4 Genome-Wide Association Study (GWAS)

In the study cohort of patients, an analysis of the effect of common genetic variants, identified based on the literature or GWAS, on the course of HCM will be conducted. In the study cohort (partially or entirely), genome-wide sequencing might be performed to replicate the significance of existing variants and to identify new genetic determinants that define the development of the HCM phenotype.

6.5 Comparison Analysis

A comparative analysis of different parameters will be performed across various subgroups, categorized by the following characteristics (but not limited to them):

- Sex
- Age at first diagnosis
- Proband or relative status
- Presence of LV obstruction
- Morphological type of HCM
- Presence of comorbidities
- Presence of mutations or VUSs in sarcomere genes

6.6 Assessment of Examinations and Treatments

In addition to the clinical and genetic spectrum and endpoints, the rate and type of diagnostic and treatment procedures related to HCM will be assessed.

6.7 Registration of Patients with Transformed Diagnosis during Follow-up

In cases where the diagnosis of HCM was reconsidered or declined based on the results of additional investigations after enrollment, such patients will not be included in the prognosis analysis. However, they will be described in the clinical and genetic profile of the study population.

7. ETHICAL ASPECTS

7.1 Informed Consent Form

Patients meeting all inclusion criteria will be considered eligible for the study. Before enrollment, the patient must sign the ICF. The study details should be explained to the patient, either orally or in writing. Patients should be informed that a blood sample will be collected for genetic testing during the study.

7.2 Confidentiality

The data collected during the study and stored in the computer should be protected in accordance with the regulations for the protection of personal information. Investigators will handle all personal information in compliance with medical confidentiality standards and relevant data protection laws.

The confidentiality of data entered into the database will be ensured by assigning a unique identification number to each patient. Simultaneously, all personal information and identification lists will be stored at each center in accordance with procedures established by relevant personal data protection laws.

8. OWNERSHIP AND FUNDING

Each investigational group has the right to publish its own data obtained during the study.

The publication or use of data from the other centers may only occur with the agreement of the principal investigators from those centers.

Given the initiative-based nature of this project, each participant is encouraged to secure their own funding. Grant applications are encouraged, both individually by each center or jointly. Each center may use only its own data for project implementation, or by mutual agreement, data from other study participants. When using data from other centers, the respective participants must be involved as co-executors. In these cases, the grant leader will be the head of the center that receives the funding.

The results of the first Russian register of HCM are intended to be published in both Russian and international journals. Participation in the project implies agreement to follow this protocol and the conditions outlined in section 8.

REFERENCES

1. Elliott PM AA, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, McKenna WJ, Mogensen J, Nihoyannopoulos P, Nistri S, Pieper PG, Pieske B, Rapezzi C, Rutten FH, Tillmanns C, Watkins H.: **2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy.** *EHJ* 2014.

2. Maron BJ RE, Casey SA, Link MS, Lesser JR, Chan RH, Garberich RF, Udelson JE, Maron MS.: **Hypertrophic Cardiomyopathy in Adulthood Associated With Low Cardiovascular Mortality With Contemporary Management Strategies.** *J Am Coll Cardiol* 2015, **65**(18):1915-1928.

3. Maron BJ RE, Casey SA, Maron MS.: **How Hypertrophic Cardiomyopathy Became a Contemporary Treatable Genetic Disease With Low Mortality. Shaped by 50 Years of Clinical Research and Practice**. *JAMA Cardiol* 2016, **1**(1):98-105.

4. Lorenzini M AZ, O'Mahony C, Guttman OP, Gimeno JR, Monserrat L, Anastasakis A, Rapezzi C, Biagini E, Garcia-Pavia P, Limongelli G, Pavlou M, Elliott PM.: **Mortality Among Referral Patients With Hypertrophic Cardiomyopathy vs the General European Population.** *JAMA Cardiol* 2019.

5. Ho CY, Day SM, Ashley EA, Michels M, Pereira AC, Jacoby D, Cirino AL, Fox JC, Lakdawala NK, Ware JS *et al*: **Genotype and Lifetime Burden of Disease in Hypertrophic Cardiomyopathy: Insights from the Sarcomeric Human Cardiomyopathy Registry (SHaRe)**. *Circulation* 2018, **138**(14):1387-1398.

6. Maron BJ, Gardin JM, Flack JM, Gidding SS, Kurosaki TT, Bild DE: **Prevalence of hypertrophic cardiomyopathy in a general population of young adults. Echocardiographic analysis of 4111 subjects in the CARDIA Study. Coronary Artery Risk Development in (Young) Adults**. *Circulation* 1995, **92**(4):785-789.

7. Maron MS HJ, Lucove JC, et al. : **Occurrence of clinically diagnosed hypertrophic cardiomyopathy in the United States.** *Am J Cardiol* 2016, **15**(11710):1651-1654. .

8. Semsarian C, Ingles J, Maron MS, Maron BJ: **New perspectives on the prevalence of hypertrophic cardiomyopathy**. *J Am Coll Cardiol* 2015, **65**(12):1249-1254.

9. Geisterfer-Lowrance AAT KS, Tanigawa G, Vosberg HP, McKenna W, Christine E. Seidman CE, Seidman JG.: **A Molecular Basis for Familial Hypertrophic Cardiomyopathy: A beta Cardiac Myosin Heavy Chain Gene Missense Mutation.** *Cell* 1990, **62**:999-1006.

10. Ochoa JP, Sabater-Molina M, García-Pinilla JM, Mogensen J, Restrepo-Córdoba A, Palomino-Doza J, Villacorta E, Martinez-Moreno M, Ramos-Maqueda J, Zorio E *et al*:

Formin Homology 2 Domain Containing 3 (FHOD3) Is a Genetic Basis for Hypertrophic Cardiomyopathy. *Journal of the American College of Cardiology* 2018, **72**(20):2457-2467.

11. Lopes LR, Garcia-Hernandez S, Lorenzini M, Futema M, Chumakova O, Zateyshchikov D, Isidoro-Garcia M, Villacorta E, Escobar-Lopez L, Garcia-Pavia P *et al*: **Alpha-protein kinase 3 (ALPK3) truncating variants are a cause of autosomal dominant hypertrophic cardiomyopathy**. *Eur Heart J* 2021, **42**(32):3063-3073.

12. Oliva-Sandoval MJ, Ruiz-Espejo F, Monserrat L, Hermida-Prieto M, Sabater M, Garcia-Molina E, Ortiz M, Rodriguez-Garcia MI, Nunez L, Gimeno JR *et al*: **Insights into genotype-phenotype correlation in hypertrophic cardiomyopathy. Findings from 18 Spanish families with a single mutation in MYBPC3**. *Heart* 2010, **96**(24):1980-1984.

13. Jansweijer JA vS-ZK, Tanck MWT, van Tintelen JP, Christiaans I, van der Smagt J, Vermeer A, Bos JM, Moss AJ, Swan H, Priori S, Rydberg A, Tfelt-Hansen J, Ackerman M, Olivotto I, Charron P, Gimeno JR, van den Berg M, Wilde A, Pinto YM.: **Heritability in genetic heart disease: the role of genetic background.** *Open Heart* 2019, **6**(1):e000929.

14. Burns C, Bagnall RD, Lam L, Semsarian C, Ingles J: **Multiple Gene Variants in Hypertrophic Cardiomyopathy in the Era of Next-Generation Sequencing**. *Circ Cardiovasc Genet* 2017, **10**(4):e001666.

15. Harper AR GA, Grace C, et al.: **Common genetic variants and modifiable risk factors underpin hypertrophic cardiomyopathy susceptibility and expressivity.** *NAt Genet* 2021, **53**(2):135-142.

16. Tadros R, Francis C, Xu X, Vermeer AMC, Harper AR, Huurman R, Kelu Bisabu K, Walsh R, Hoorntje ET, Te Rijdt WP *et al*: **Shared genetic pathways contribute to risk of hypertrophic and dilated cardiomyopathies with opposite directions of effect**. *Nat Genet* 2021, **53**(2):128-134.

17. Nollet EE, Westenbrink BD, de Boer RA, Kuster DWD, van der Velden J: **Unraveling the Genotype-Phenotype Relationship in Hypertrophic Cardiomyopathy: Obesity-Related Cardiac Defects as a Major Disease Modifier**. *J Am Heart Assoc* 2020, **9**(22):e018641.

18. McKenna WJ, de la Higuera Romero L, Hernandez SG, Ochoa JP: **Value of clinical and genetic evaluation in inherited cardiomyopathy: insights and challenges**. *The Journal of Cardiovascular Aging* 2021.

19. Charron P, Elliott PM, Gimeno JR, Caforio ALP, Kaski JP, Tavazzi L, Tendera M, Maupain C, Laroche C, Rubis P *et al*: **The Cardiomyopathy Registry of the EURObservational Research Programme of the European Society of Cardiology: baseline data and contemporary management of adult patients with cardiomyopathies**. *Eur Heart J* 2018, **39**(20):1784-1793.

20. Olivotto I OA, Barriales-Villa R, et al.: **Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2020, **396**(10253):759-769.

21. McKenna WJ, Spirito P, Desnos M, Dubourg O, Komajda M: **Experience from clinical genetics in hypertrophic cardiomyopathy: proposal for new diagnostic criteria in adult members of affected families**. *Heart* 1997, **77**(2):130-132.

22. **Гипертрофическая кардиомиопатия**. *https://crminzdravgovru/schema/283_1* 2020.

23. М.Н.Алехин СЮБ-З, Н.Ф.Берестень, А.А.Бощенко, А.В.Врублевский, Л.О.Глазун, В.А.Кузнецов, В.В.Митьков, М.Д.Митькова, Г.П.Нарциссова, Н.Ю.Неласов, В.И.Новиков, Е.Н.Павлюкова, О.Р.Пестовская, М.К.Рыбакова, М.А.Саидова, В.А.Сандриков, В.П.Седов, В.И.Скидан, М.Ю.Чернов: **Стандартизация проведения трансторакальной эхокардиографии у взрослых: консенсус экспертов Российской ассоциации специалистов ультразвуковой диагностики в медицине (РАСУДМ) и Российской ассоциации специалистов функциональной диагностики (РАСФД)**. *Ультразвуковая и функциональная диагностика* 2021, **2**:63-79.

APPENDICES

1. Leaders of the study and members of working group
2. Informed consent form
3. Coding of Patient and genetic tubes
4. Blood collection and storage guidelines
5. Guidelines for CRF completion
6. “Enrollment visit” form
7. “Echocardiogram” form
8. “Electrocardiogram” form
9. “24-hour ECG monitoring” form
10. “Follow-up visit” form
11. Target panel of genes associated with HCM (39 genes)
12. Extensive panel of genes (172 genes and more)

Appendix 1

STEERING COMMITTEE

Chairman: prof. William McKenna, Institute of Cardiovascular Science, University College London, London, UK

1. **Prof. Alexandra Konradi**, MD, DSc, Deputy Director General for Research, Head of Arterial Hypertension Research Department, Almazov National Medical Research Centre, St-Petersburg, Russia
2. **Prof. Michael Arad,** professor, scientific researcher of Seidman Lab, Dept. of Genetics, Harvard Medical School and HHMI, Boston, USA; professor of cardiology at the Institute of Heart Failure and Center for Cardiomyopathy and Hereditary Heart Disease, Sheba Medical Centre; Associate Professor in the Department of Cardiology, Tel Aviv University, Israel
3. **Prof. Iacopo Olivotto,** associate professor of cardiology, Head of Cardiomyopathies Unit, department of experimental and clinical medicine, University of Florence, Italy
4. **Dr. Natalia Sonicheva**, cardiologist, secretary of the National Research League of Cardiogenetics of Russia
5. **Dr. Juan Pablo Ochoa**, cardiologist, Heart Failure and Inherited Cardiac Diseases Unit, Hospital Universitario Puerta de Hierro Majadahonda, Comunidad de Madrid, Spain. Head of the cardiology department at HealthinCode

LEADERS OF THE PROJECT

1. Antonis Pantazis, former President of the ESC Working Group on Myocardial and Pericardial Diseases; cardiologist at the Cardiovascular Research Centre, Royal Brompton and Harefield National Health Service Foundation Trust, London, UK.

2. Dmitry Zateyshchikov, MD, DSc, professor, head of the department of Internal medicine, Cardiology and Functional diagnostics, Central State Medical Academy of the Department of Presidential Affairs; head of the primary vascular center, Moscow City Clinical Hospital #29; scientific researcher, laboratory of genetics, Federal Scientific Clinical Centre of the Federal Medical and Biological Agency of Russia, Moscow.
3. Anna Kostareva, MD, DSc, Director of the Institute of Molecular Biology and Genetics, Almazov National Medical Research Centre, St-Petersburg, Russia
4. Olga Moiseeva, MD, DSc, Director of the Heart and Vascular Institute; senior scientific researcher in noncoronary myocardial diseases, Almazov National Medical Research Centre, St-Petersburg, Russia

WORKING GROUP

1. Olga Chumakova, MD, PhD, cardiologist, certified specialist in echocardiography, assistant professor in the department of Internal medicine, Cardiology and Functional diagnostics, Central State Medical Academy of the Department of Presidential Affairs; scientific researcher in the laboratory of genetics, Federal Scientific Clinical Centre of the Federal Medical and Biological Agency of Russia, Moscow.
2. Sofia Andreeva, MD, cardiologist, Almazov National Medical Research Centre, St-Petersburg, Russia
3. Vadim Zaitsev, MD, cardiologist, Almazov National Medical Research Centre, St-Petersburg, Russia
4. Larisa Minushkina, MD, DSc, cardiologist, professor in the department of Internal medicine, Cardiology, and Functional diagnostics, Central State Medical Academy of the Department of Presidential Affairs, Moscow
5. Michael Alekhin, MD, DSc, professor, head of the functional diagnostics department, Central Clinical Hospital of Department of Presidential Affairs; vice-president of the Russian Association of Specialists in Ultrasound Diagnostics in Medicine (RASUDM), Moscow
6. Tatiana Tipteva, MD, PhD, cardiologist, EACVI certified specialist in echocardiography, K+31 Medical center “Petrovsky vorota”, Moscow