

https://dspace.org/

An assessment of genetic presdisposition in idiopathic dilated cardiomyopathy (IDCM) in Johannesburg

Bailly, Claude Didier

2018

https://hdl.handle.net/10539/27986

Downloaded from a DSpace repository. https://dspace.org/

AN ASSESSMENT OF GENETIC PRESDISPOSITION IN IDIOPATHIC DILATED CARDIOMYOPATHY (IDCM) IN JOHANNESBURG

Student: Dr Claude Didier Bailly

Student number: 1510667

Department: Department of Human Genetics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg; and National Health Laboratory Service, Johannesburg, South Africa

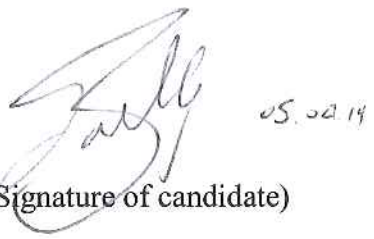
E-mail: claude.bailly@nhls.ac.za

A research report (in the format of a "submissible" paper) submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree Master of Medicine (MMed), Medical Genetics

Johannesburg, 2018

Declaration

I, **Claude Bailly,** declare that this research report (in the format of a "submissible" paper) is my own, unaided work. It is being submitted for the Degree Master of Medicine (MMed), Medical Genetics, at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at any other University.



05.02.19

(Signature of candidate)

Contribution of the candidate to the paper

Declaration: Student's contribution to the article(s) and agreement of co-authors

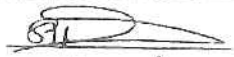
I, Claude Bailly, student number 1510667, declare that this Research Report is my own work and that I contributed significantly towards the research findings presented in the paper intended for the publication below.

Signature of student:  **Date:** 01.04.19

Primary Supervisor: Prof Amanda Krause **Signature:**  **Date:** 05.04.19

Agreement by co-authors: By signing this declaration, the co-authors listed below agree to the use of the article(s) by the student as part of his Research Report.

Article Title: An Assessment of Genetic Predisposition in Idiopathic Dilated Cardiomyopathy (IDCM) in Johannesburg.

Authors	Name	Signature	Date
1st Author	Claude Bailly		01.04.19
2nd Author	Amanda Krause		05.04.19
3rd Author	Sasha Henriques		27/03/19
4th Author	Nqoba Tsabedze		02/04/2019

Presentations arising from this research project

1. SASHG Biennial Congress 2017, 13th – 16th August, Durban, KwaZulu-Natal (poster presentation): Authors: Bailly C, Krause A, Tsabedze N, Henriques S. An Assessment of Genetic Predisposition in Idiopathic Dilated Cardiomyopathy (IDCM) in Johannesburg – Pedigree Interpretation Results.

Abstract (MMed submission)

Familial disease is implicated in 20-50% of cases of idiopathic dilated cardiomyopathy (IDCM) worldwide. The contribution of genetic factors to the frequency of familial dilated cardiomyopathy (DCM) in the Johannesburg area is unknown. The aim of this study was to describe the demographic characteristics of patients with IDCM assessed at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), and to determine if evidence of familial disease is present. Fifty probands were screened by family pedigree analysis. The majority of the probands were male (38/50 probands, 76%) with a mean age of 41.7 years at diagnosis of IDCM. Pedigree analysis identified a combination of positive (defined as having a family member with one of the following: a diagnosis of DCM, peripartum cardiomyopathy, an unexplained cardiac death in an individual less than 50 years old, a family member requiring a pacemaker for a cardiac arrhythmia or cardiac transplant for cardiac failure) and intermediate-risk family pedigrees (defined as having a family member with either a cardiac death over the age of 50 years or a history of unexplained cardiac failure) in 23/50 (46%) pedigrees. From the 50 probands, family members were ascertained from 21 families (55 first-degree relatives and 27 second-degree relatives) and were clinically screened by electrocardiogram (ECG) and echocardiography. No asymptomatic family members were found to have "features of DCM" or "features of pre-symptomatic DCM". Family members with "possible pre-symptomatic DCM" were identified in 11/21 (52.4%) families. This included "possible pre-symptomatic DCM" identified by an abnormality on echocardiogram in 4 individuals from 3 families (14.3%), all first-degree relatives of the proband. "Possible pre-symptomatic DCM" based on findings of a conduction defect identified on electrocardiogram (either a sinus dysfunction or first/second/third degree heart-block) was identified in 8/21 (32.8%) families. This consisted of a total of 11 individuals; 9 individuals were first-degree relatives (81.8%) and 2 of the 11 (18.2%) were second-degree relatives. This study demonstrated that screening by both performing a 3-generation family history and clinical screening (by physical examination, ECG and echocardiogram) of first-degree family members of probands with IDCM is indicated to identify families with familial DCM.

Acknowledgements

I would like to thank my supervisors for their ongoing support and guidance.

Table of Contents

Declaration ii
Contribution of the candidate to the paper iii
Presentations arising from this research project iv
Abstract (MMed submission) v
Acknowledgements vi
List of figures viii
List of tables ix
List of abbreviations x
Title page 1
Introduction 4
Objectives 5
Methods 6
Discussion 13
Conclusion 17
References 19

Appendices

A. Approved research protocol

B. Ethics clearance certificate

C. Turn-it-in report

D. South African Medical Journal author guidelines

List of figures

Figure 1: Flow chart of study population 7

Figure 2: Family pedigree analysis results 11

List of tables

Table 1. Family pedigree analysis – criteria for classification 8
Table 2. Categorization of family members based on ECG and echocardiogram screening. 9
Table 3: Results of screening of asymptomatic family members. 12
Table 4: Results of cardiac conduction abnormalities identified in relatives with "Possible pre-symptomatic DCM with cardiac conduction abnormality" 13

List of abbreviations

ARVCM	Arrhythmogenic right ventricular cardiomyopathy
DCM	Dilated cardiomyopathy
ECG	Electrocardiogram
HCM	Hypertrophic cardiomyopathy
IDCM	Idiopathic dilated cardiomyopathy
LVEF	Left ventricular ejection fraction
LVIDd	Left ventricular internal diameter end diastole
LVNCC	Left ventricular non-compaction cardiomyopathy
PPCM	Peripartum cardiomyopathy

Research article in the format of a 'submissible' paper

Title page

An assessment of genetic predisposition in idiopathic dilated cardiomyopathy (IDCM) in Johannesburg

Authors: Claude Bailly[1], MBChB, Sasha Henriques[1] BSc (Hons) Biological Sciences, MSc Science Communication, MSc Genetic Counselling, Nqoba Tsabedze[2], MBBCh, FCP, Cert. Cardiology, Amanda Krause[1], MBBCh, Ph.D.

Affiliation: [1]Division of Human Genetics, National Health Laboratory Service; and School of Pathology, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg; [2]Department of Internal Medicine, Division of Cardiology, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa.

Corresponding author: C. Bailly (email: claude.bailly@nhls.ac.za; telephone +27 11 489 9227)

Funding: None to declare

Conflicts of interest: None

Acknowledgements: I want to thank Professor Amanda Krause and Professor Nqoba Tsabedze for their support and guidance throughout.

Author contributions: N. Tsabedze, A. Krause and S. Henriques conceived the study topic. C. Bailly developed and wrote the study protocol, was involved in the recruitment and screening of the participants, collected and analysed the pedigree data and wrote the article. N. Tsabedze and A. Krause supervised the study and data collection, revised the article and approved the final version.

Abstract ('submissible' paper)

Background. Familial disease is implicated in 20-50% of cases of idiopathic dilated cardiomyopathy (IDCM) worldwide. The contribution of familial factors to IDCM in the Johannesburg area is unknown.

Objective. To describe the demographic details of patients with IDCM who presented at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), and to determine if any evidence of familial disease exists through family history assessment and clinical screening of relatives.

Method. This is a single centre, cohort study performed at a quaternary care centre at CMJAH, Johannesburg. Fifty unrelated probands diagnosed with IDCM and available first- and second-degree relatives were included in this study. A 3-generation family pedigree was drawn up for all fifty probands. The pedigrees were analysed to identify the presence or absence of familial disease and categorized as positive, intermediate, negative or unreliable according to the family history obtained. From the 50 proband cases, 21 had family members available for screening for features of IDCM. Eighty-two family members (55 first-degree and 27 second-degree relatives) were screened clinically. Screening included a personal history, full physical examination, electrocardiogram (ECG) and echocardiography.

Results. The mean age at diagnosis of IDCM in the probands was 41.7 years (SD 12.4). The majority of probands were males (N= 38, 76%). Of 50 pedigrees analysed 14 (28%) were positive and likely to be indicative of familial DCM, and 9 (18%) were at intermediate-risk for familial disease. Eighty-two asymptomatic family members were screened, with a median age of 33 years (range 11 to 76 years). No asymptomatic family members were identified with either "features of DCM" or "pre-symptomatic DCM". Eleven families out of the 21 families who attended screening had members with "possible pre-symptomatic DCM" identified by abnormality on echocardiogram in 3 families (14.3%) (4 individuals, all first-degree relatives of the index case) or identified on the basis of a conduction defect (an arrhythmia or first/second/third degree heart-block) in 8 families (72.7%) (11 individuals; 9 individuals were first-degree relatives and 2 of the 11 were second-degree relatives).

Conclusion. Screening for IDCM should include performing a 3-generation family history and clinical screening of all first-degree family members. As IDCM has an age-related penetrance, at risk family members should receive follow up for screening to assess for symptoms and signs of IDCM. Genetic testing would potentially identify which family members are at high-risk and would benefit from screening, and may be a less expensive option.

Keywords: idiopathic dilated cardiomyopathy, screening, hereditary, familial

Introduction

Cardiac failure is the commonest cardiovascular manifestation in urban Africa.[1] Dilated cardiomyopathy (DCM), defined as left ventricular dilatation and systolic dysfunction, is a major cause of heart failure in adults between the 3rd and 4th decade of life.[1-3] It is the leading cause for heart transplantation worldwide.[3] Although population-based data on the burden of DCM in sub-Saharan Africa are lacking, it is reported to account for up to 48% of patients hospitalized with cardiac failure. Idiopathic dilated cardiomyopathy (IDCM) is the second most common form of cardiomyopathy after hypertensive cardiomyopathy in the Heart of Soweto Study Cohort.[4-6]

Idiopathic dilated cardiomyopathy (IDCM), a form of DCM without an identifiable cause, can be diagnosed after exclusion of secondary causes and other primary cardiomyopathies. Secondary causes include untreated hypertension, myocarditis triggered by infection, coronary artery disease, valvular heart disease, congenital heart disease, autoimmune disease, metabolic factors, alcohol abuse and nutritional deficiencies.[1,4] The other primary cardiomyopathies, which are classified according to morphofunctional phenotype, include hypertrophic obstructive cardiomyopathy (HCM), restrictive cardiomyopathy (RCM), arrhythmogenic right ventricular cardiomyopathy (ARVC) and left ventricular non-compaction cardiomyopathy (LVNCC).[7] Genetic conditions with dilated cardiomyopathy as a presenting feature include the muscular dystrophies (Duchenne and Becker muscular dystrophy as well as their carrier states, Emery-Dreifuss muscular dystrophy and limb-girdle muscular dystrophy), hereditary haemochromatosis, Friedreich's ataxia, Barth syndrome, mitochondrial myopathies and numerous inborn errors of metabolism.[8,9] Up to half of all cases of IDCM are believed to be hereditary or familial.[1,2,4,10] Timeous referral of patients with DCM for management of cardiac failure, arrhythmias and life-saving interventions such as cardiac transplantation is of utmost importance. This highlights the importance of identifying patients with familial DCM and screening their family members to identify at-risk pre-symptomatic family members.[1]

Patients with DCM most commonly present with decompensated cardiac failure.[10] Other manifestations may include arrhythmias, sudden cardiac death and less commonly, a thromboembolic event.[8,11,12] Most patients with DCM are diagnosed once they become symptomatic, however, pre-symptomatic affected individuals can be detected on routine cardiovascular examination by identifying echocardiographic signs of left ventricular enlargement, a decreased ejection fraction and/or fractional shortening, wall motion abnormalities and atrial enlargement, and electrocardiographic features including a primary, secondary or tertiary

atrioventricular block, a left or right bundle branch block, abnormal QRS patterns (including left or right axis deviation), premature ventricular or atrial contractions, atrial fibrillation or flutter and ventricular arrhythmias/tachycardias.[8] This so-called pre-symptomatic stage may persist for months to years without the onset of symptoms.[8] Identifying pre-symptomatic individuals can provide an opportunity for invoking lifestyle changes and allow for pharmacological therapy to be initiated in the earlier stages of the course of the disease, with the aim of limiting the progression of cardiac failure and controlling arrhythmia.[10,13] Diagnosis of DCM requires specialist investigations such as echocardiography which is mostly limited to tertiary medical centres.[4]

Familial DCM is a monogenic disorder with mutations identified in more than 40 genes. It is mostly inherited in an autosomal dominant manner, although autosomal recessive, X-linked, and mitochondrial patterns of inheritance have been described.[2,14] Autosomal dominant familial DCM is characterized by incomplete and/or variable expressivity with respect to age of onset, severity of symptoms and risk of complications.[14] Advances in genetic testing have changed the approach to the genetic diagnoses of cardiomyopathies. Familial DCM is the most genetically heterogeneous of the cardiomyopathies.[15] A major role-player in familial DCM is the *TTN* gene, encoding the protein titin. Approximately 20-25% of familial DCM patients have a truncating mutation in this gene.[15] Truncating mutations in the *TTN* gene have also been found in patients with peripartum cardiomyopathy, which shares clinical features with IDCM and may be part of the spectrum of familial DCM.[16,17] In some patients with familial DCM, the findings of cardiac conduction defects may point to a mutation in specific genes such as *LMNA* and *SCN5A*. Identifying the genetic mutation may alter specific management. For example it is recommended that individuals with *LMNA* mutations benefit from early implantable cardioverter-defibrillators (ICD).[18,19] Targeted gene panels using next generation sequencing are commonly used in first world countries and have a diagnostic yield of 30 – 35%.[9,19,20] The causative mutations in South African patients have not been investigated or identified to date.

Objectives

To describe the demographic details of patients with IDCM in the Johannesburg area and to determine if any evidence of familial disease exists through family history assessment and clinical screening of relatives.

Methods

Study design and study population

This was a single-centre, study performed at the Cardiology Department, Charlotte Maxeke Johannesburg Academic Hospital (CMJAH). This study was approved by the University of the Witwatersrand Human Research Committee (HREC ref. no. M150467). The study participants were recruited from the co-author's (Dr Nqoba Tsabedze) study entitled, "Genetics of Idiopathic Dilated Cardiomyopathy Study in Johannesburg" and included the first 50 probands diagnosed with IDCM and available family members seen over an 18-month period (from July 2015 to February 2017). A total of 162 participants attended screening, including 50 probands, 55 firs-degree relatives and 27 second-degree relatives. Nine participants were excluded as they were found to not be related to the proband, and a further 21 participants were excluded as they were found to be distant relatives (third-degree relatives or further). See Figure 1 for the included study population. Written informed consent was obtained by the co-authors for the utilisation of any relevant clinical data.

Each proband was diagnosed with IDCM based on fulfilling all of the following criteria: 1) clinical evidence of cardiac failure with left ventricular dilation; 2) left ventricular ejection fraction (LVEF) of <50% on echocardiography; 3) exclusion of common secondary causes of DCM. All probands were offered clinical screening for family members; however, only 21 of the probands had family members available for screening.

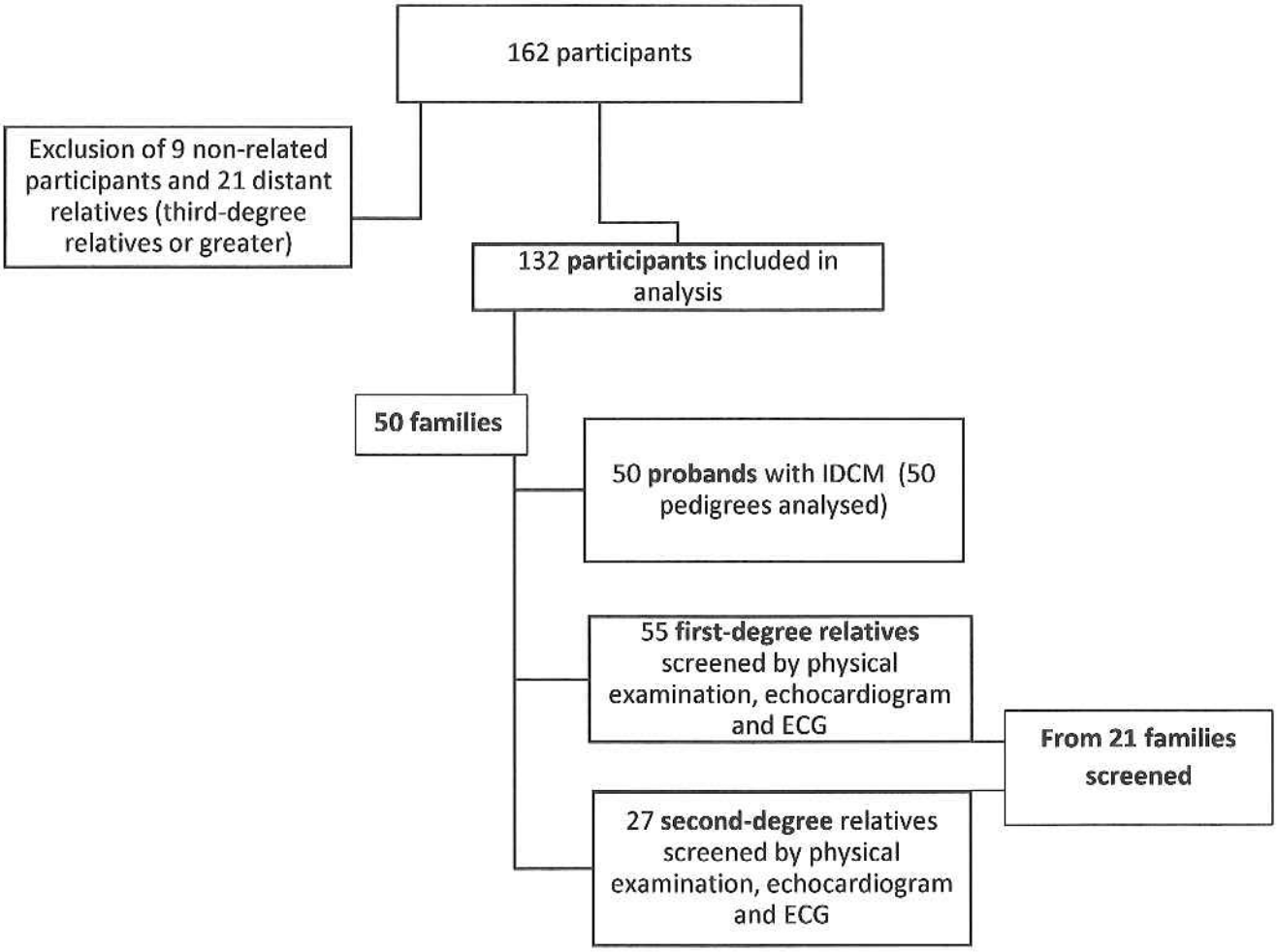


Figure 1: Flow chart of study population

All study participants had a comprehensive clinical assessment including a 3 to 4 generation family pedigree, personal medical history, clinical examination (performed by the co-author Dr N. Tsabedze, a cardiologist), electrocardiogram (ECG), and echocardiogram. Data collected for each study participant included ethnicity, gender, current age, age at which the proband was diagnosed with IDCM, clinical cardiovascular examination detail, electrocardiogram (ECG) and echocardiogram findings. Further relevant family history included ischaemic heart disease, cerebrovascular disease which likely reflected a thromboembolic event, hypertension or other relevant genetic conditions including muscular dystrophies. Based on each family history, a family pedigree was constructed and analysed. A pedigree software programme (PedigreeXP Version 2.1.0.174) was used to electronically draw complicated family pedigrees to assist with visualization of the family pedigrees. Each family was classified as either positive for familial DCM, intermediate-risk family history, negative family history or unknown status (see Table 1 for criteria).

Table 1. Family pedigree analysis – criteria for classification	
Positive for familial DCM	A family member of the index case with at least one of the following findings: 1) a diagnosis of DCM; 2) a history of peripartum cardiomyopathy; 3) a history of an unexplained cardiac death < 50 years; 4) a family member requiring a pacemaker for a cardiac arrhythmia; 5) a family member received a cardiac transplantation for cardiac failure.
Intermediate-risk family history	If a family member had a history of a cardiac death over the age of 50 years, or a history of unexplained cardiac failure.
Negative family history	No history of DCM, unexplained cardiac death, cardiac failure and no history of family members with symptoms of cardiac failure
Unknown status	Those with an unknown or unreliable family history due to lack of information of family history.

Screening of asymptomatic family members included a physical examination, ECG and echocardiography. Echocardiography assessment included left ventricular internal diameter in diastole (LVIDd) and left ventricular ejection fraction (LVEF). An enlarged LVIDd (greater than the 95th centile for sex and age) as well as a LVEF of less than 50% was considered abnormal.[8] ECG findings included screening for cardiac conduction abnormalities including a primary, secondary or tertiary atrioventricular block, a left or right bundle branch block, abnormal QRS patterns (including left or right axis deviation), premature ventricular or atrial contractions, atrial fibrillation or flutter and ventricular arrhythmias/tachycardias. The echocardiogram and ECG findings were interpreted with assistance from Dr N. Tsabedze, a cardiologist and co-author of the study.

Based on the above findings, each asymptomatic family member was categorised into one the following groups: 1) features of DCM; 2) features of pre-symptomatic DCM; 3) possible pre-symptomatic DCM and cardiac conduction abnormality; 4) no features of DCM. See Table 2 for criteria for categorization of family members based on screening.

Table 2. Categorization of family members based on ECG and echocardiogram screening.	
Features of DCM	Family members with a LVEF of <50% and a LVIDd >95th centile for age and sex
Features of pre-symptomatic DCM	Family members with a LVEF <50% and a LVIDd >95th centile for age and sex
Possible pre-symptomatic DCM	Family members with a LVEF >50%, LVIDd <95th centile for age and sex, and/or ECG abnormality (arrhythmia, sinus node dysfunction, first-, second- and/or third-degree heart block, bundle branch block, abnormal QRS pattern)
No features of DCM	Family members who have a LVEF >50%, LVIDd <95th centile for age and sex and a normal ECG

Statistical analysis

Statistical analysis was performed using TIBCO® Statistica Version 13.3 (2018) Software. Descriptive statistics of the study cohort were applied as either means with standard deviations if normally distributed or medians with interquartile ranges if not normally distributed. Frequency analysis was performed for discrete variables and represented as percentages with 95% confidence intervals where appropriate. A t-test was performed to assess for significant age differences between male and female probands. A p-value of <0.05 was considered statistically significant.

Results

Index Case Demographics

Fifty probands were included in the study cohort. Of the probands, 38 (76%) were male. The mean age at diagnosis of IDCM was 41.7 (SD 12.4) years for all probands, 42.5 (SD 11.24) years for males and 39.3 (15.85 SD) years for females, with no statistically significant differences in the ages of men and women (p value 0.5). The racial distribution comprised 43 (86%) black Africans, 3 (6%) white, 3 (6%) with mixed ancestry and 1 (2%) patient of Indian descent.

Pedigree analysis

As per the criteria set out in Table 1, 14 (28.0%) out of the 50 pedigrees analysed had a positive family history for familial DCM, 9 (18%) had an intermediate-risk family history, 12 (24%) had a negative family history and 15 (30%) had an unreliable family history. Positive or intermediate family pedigrees were thus seen in 23 (46%) families. See Figure 2 for a summary of the pedigree analysis.

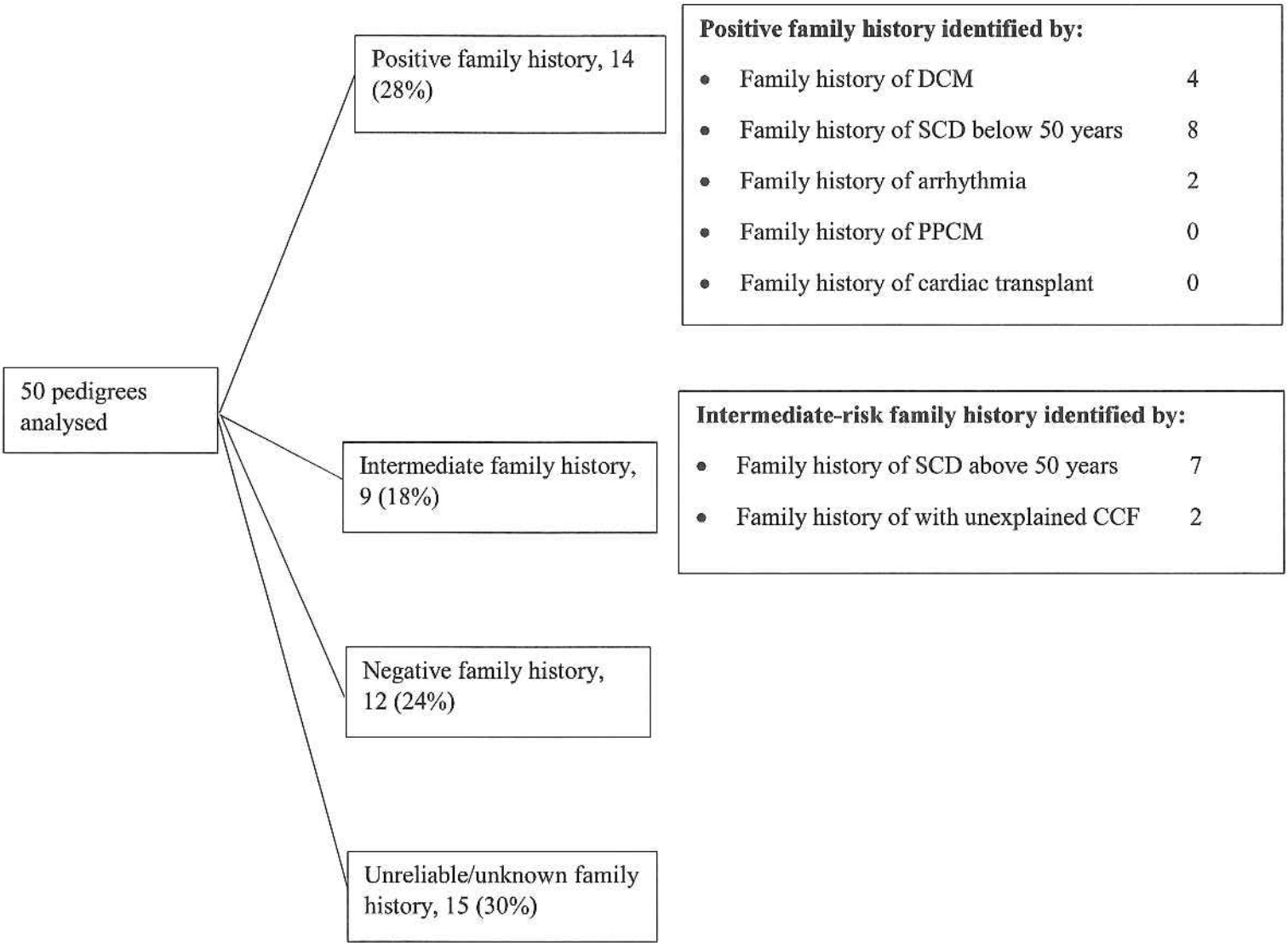


Figure 2: Family pedigree analysis results

DCM, Dilated cardiomyopathy; SCD, sudden cardiac death; PPCM, peripartum cardiomyopathy; CCF, congestive cardiac failure

Family member analysis

Fifty-five first-degree relatives were screened, including 25 males (45.5%) and 30 females (54.5%) with a median age of 38 years (range 11 to 76 years). Twenty-seven second-degree relatives were screened, including 11 males (41%) and 16 females (59%) with a median age of 22 years (range 12 to 72 years).

According to the criteria stated in the methods, none of the 82 asymptomatic family members included in the screening analysis had identifiable "features of DCM". One first-degree family

member who attended screening already had a diagnosis of IDCM and was symptomatic. Further, none of the 82 asymptomatic family members were identified with "pre-symptomatic DCM".

Eleven families were identified with family members with "possible pre-symptomatic DCM". In three families (14%), 4 first degree relatives of the probands, had abnormalities detected on echocardiogram. In eight families (38%), 11 individuals were identified with "possible pre-symptomatic DCM" based on finding a cardiac conduction defect (either a sinus node dysfunction or a first/second/third degree heart-block). Nine of the 11 individuals (81.8%) were first-degree relatives and 2 of the 11 individuals (18.2%) were second-degree relatives. No identifiable features of DCM were detected in 10 (48%) families screened. The results of the screening for the asymptomatic family members are summarised in Table 3.

Table 3: Results of screening of asymptomatic family members.

Total of 21 families attended screening and included 82 asymptomatic family members, 55 first degree and 27 second degree relatives.

	Number of families (n=21)	**Number of 1st degree relatives (n=55)**	**Number of 2nd degree relatives (n=27)**
"Features of DCM"	0	1 (2%) (Diagnosis of IDCM made prior to study)	0
"Features of pre-symptomatic DCM"	0	0	0
"Possible pre-symptomatic DCM with echocardiogram anomaly"	3 (14%)	4 (7%)	0
"Possible pre-symptomatic DCM with cardiac conduction abnormality"	8 (38%)	9 (16%)	2 (7%)
"No features of DCM"	10 (48%)	41 (75%)	25 (93%)

DCM, dilated cardiomyopathy; IDCM, idiopathic dilated cardiomyopathy

Table 4: Results of cardiac conduction abnormalities identified in relatives with "Possible pre-symptomatic DCM with cardiac conduction abnormality"		
Cardiac conduction abnormality identified	No. of 1st degree relatives (n=9)	No. of 2nd degree relatives (n=2)
Intraventricular conduction delay	1	0
Sinus dysfunction	3	0
First-degree heart block	4	2
Second-degree heart block	0	0
Third-degree hear block	1	0

Discussion

Pedigree analysis

IDCM is associated with a high mortality and is an important contributor to the burden of disease in Africa.[1] This study shows that the patients with IDCM seen at CMJAH are diagnosed at a similar age to those reported elsewhere, with an average age of diagnosis of 41 years. Our study also showed that more males appear to be more affected than females, with 76% of index cases being male. This is in accordance with the literature with males are almost twice as likely to be affected.[1,4] The racial distribution of 43 (86%) black Africans reflects the racial profile of the institution and study population. Further studies of people of African ancestry are needed as little data exists on IDCM in this population.

A positive family history was found in 14 (28%) of the 50 family pedigrees analysed, which is similar to the findings reported by Ntusi *et al* where familial disease was found in 26.6% of patients with IDCM by family pedigree analysis in Cape Town.[5] The pedigrees with positive and intermediate family histories appeared most consistent with an autosomal dominant pattern of inheritance: 13 out of the 14 (93%) positive family histories were clearly consistent with an autosomal dominant inheritance pattern having affected individuals in at least 2 generations and only 1 out of 14 (7%) had a possible autosomal recessive or X-linked inheritance pattern, a family with male non-identical twins affected with IDCM. This may also be explained by a germline mutation in a parent, or autosomal dominant disease with reduced penetrance. The interpretation of the family

histories may be further complicated by non-penetrance, age-related penetrance and variable expressivity which may be features of familial DCM and appeared to be evident in the family pedigrees analysed. In only 4 of the 14 (26%) cases with a positive family history did the proband give a history that they had a relative with a known diagnosis of IDCM.

In 2 out of 9 (22%) families with an intermediate-risk family history, a history of unexplained cardiac failure was given, emphasizing the importance of a diagnosis of the cause of cardiac failure and exclusion of secondary causes and other primary cardiomyopathies. The remainder of the intermediate risk families (7 out of 9) (77%) had unexplained deaths believed to be due to a cardiac event in family members over the age of 50 years, further illustrating the possible age-related penetrance and variable expressivity of familial DCM in the individuals who demised. A high index of suspicion is needed if there is a family history of any individuals with symptoms of cardiac failure, arrhythmias or unexplained sudden death.[8] The symptoms of typical cardiac failure are also non-specific, which is a limitation to the validity and accuracy of a family history, further emphasizing the importance of an objective evaluation of left ventricular function, particularly in first-degree relatives of probands with IDCM.

In the 12 (24%) probands classified as having a negative family history, the probands were able to give a detailed family history where there was no history of any relatives with cardiac disease or unexplained cardiac deaths, and the proband appeared to be the first and only case of IDCM in the pedigree. This negative family history appears to be much lower than reported by Ntusi *et al* where 73.4% of their cases of IDCM appeared to be non-familial.[5] This can be explained by our classification of the family pedigrees, which included intermediate-risk family histories and unknown or unreliable family histories, resulting in a lower negative family history in our study.

An unknown or unreliable family history was found in 15 (30%) of cases. This was mostly explained by probands not having recent contact with relatives who resided in different provinces or countries, probands not having knowledge of the cause of death in relatives, difficulty in accessing death certificates in relatives with unexpected or unknown deaths, and a general lack of knowledge of their relatives and family histories. These factors make the use of family pedigree as a primary assessment tool somewhat insensitive. A positive family history is significant and requires follow-up, but a negative family history does not exclude familial DCM.

Screening analysis

In a single family, one individual (a sibling of the index case) who attended screening was symptomatic and was found to have been previously diagnosed with IDCM. No family members screened fulfilled criteria for "features of DCM" or "features of pre-symptomatic DCM". This may be explained by the disease penetrance typically occurring in adult life, and relatively young adults (median age 33 years; range 11 to 76 years) were screened who may not yet have developed detectable cardiac abnormalities.

In 11 out of 21 families (52.4%) criteria for "possible pre-symptomatic DCM" were identified. "Possible pre-symptomatic DCM" was identified by an abnormality on echocardiogram in 3 families (14.3%), all first-degree relatives of the index case. Echocardiography assessment included left ventricular internal diameter in diastole (LVIDd) and left ventricular ejection fraction (LVEF). An enlarged LVIDd (greater than the 95th centile for sex and age) as well as a LVEF of less than 50% was considered abnormal.[8] The echocardiogram abnormalities identified included: an increased LVIDd in 3 individuals; 2 males from the same family with an LVIDd of 63mm (>95th centile) and 56mm (>95th centile), a female with an LVIDd of 57mm (>95th centile) from another family, and a reduced LVEF in a female with an LVEF of 38%. None of the 27 second-degree relatives had abnormalities detected on echocardiogram, showing that screening by echocardiogram appears more beneficial for first-degree relatives, as might be predicted.

Eight out of 21 families (38.1%) with "possible pre-symptomatic DCM" were identified based on a cardiac conduction defect (either a sinus dysfunction or first/second/third degree heart-block) in a family member. Due to the limited specificity of cardiac failure symptoms, we opted to screen all available family members to objectively confirm or exclude DCM. This led to a high number of second-degree relatives being screened. It is recommended that screening is ideally limited to first-degree relatives, and screening of second-degree relatives is usually only performed when there are anxious relatives or in families with a particularly lethal or penetrant phenotype.[8,19]

South African patients suffering from IDCM are often in resource-limited environments where there may be a delay in diagnosis. When a patient is diagnosed with IDCM, there is a good opportunity for screening family members and patient education regarding the possibility of the condition being familial.

An evaluation of patients with IDCM should include investigating whether the disease is familial.[19] A cascade approach to screening of first-degree relatives should be used including:

- Taking a 3-generation family history, keeping in mind the lack of specificity of cardiac failure symptoms and possibility of unknown and unreliable family histories.
- Clinical screening for cardiomyopathy in first-degree relatives through clinical examination, an echocardiogram and an ECG to determine if any relatives are affected.[2,9]

The landscape of genetic testing is changing with the advent of next-generation sequencing (NGS) technology. As whole exome or genome genetic testing becomes more accessible, cardiac clinicians will increasingly request genetic testing for probands and family members. The role of the geneticist will be for pre- and post-test counselling, patient education and interpreting results of genetic testing. Speciality centres will need to be established for these patients in the future. If genetic testing were available, it may be offered to individuals with sporadic IDCM, familial DCM or peripartum and pregnancy associated cardiomyopathy.[9] The rationale for identifying a causal mutation would be to allow mutation-specific cascade screening of family members. This will determine which family members require ongoing surveillance and which do not.[2,15] When a DCM mutation is identified in an asymptomatic individual, screening by physical examination, echocardiogram and ECG has been recommended to commence from childhood annually. When a familial mutation has not been identified or testing has not been performed, first-degree relatives of an individual with IDCM should be screened every 3 to 5 years from childhood.[5,18,19] Limitations to genetic testing would include the high cost and possible low detection rate of pathogenic mutations. Mutations may be population specific and distinguishing clearly pathogenic mutations from benign polymorphisms may be a challenge as the genetics of IDCM has not been fully investigated and established in African and South African patients. These genetic studies need to be done, and once local mutation profiles are established, may provide an effective way to identify pre-symptomatic at-risk family members.

Limitations

Our study has some limitations. Patients are often uncertain of their family histories and uninformed concerning the cause of death in their relatives, which is a major limitation to interpreting a family history. Further, reviewing hospital records of deceased relatives is a challenge when the relatives demised in peripheral hospitals. The small number of first-degree relatives screened is a limitation

as most guidelines advocate for screening of first-degree relatives only in IDCM. In our setting this was difficult as many relatives lived far away, some even in neighbouring countries, and were unable to attend screening. This likely also affected the accuracy of the family histories as many individuals had not had recent and frequent contact with family members. The small number of probands included in the study likely affected the capacity to detect significant findings.

Conclusion

Our research has shown that familial disease is common in patients presenting with IDCM at CMJAH based on family history and screening of relatives. Forty-sixty percent of the probands had a positive or intermediate-risk family history. Family pedigrees were almost exclusively consistent with an autosomal dominant inheritance pattern showing variable expressivity and age-related penetrance, with probands giving family histories of cardiac disease and deaths occurring in individuals both below and above the age of 50 years. Screening for familial disease with history alone is insufficient as an unreliable and unknown family history was found in 30% of the cases.

We have also shown a benefit in screening first-degree family members. Although no asymptomatic family members that were screened by ECG and echocardiogram were found to have "features of DCM" or "features of pre-symptomatic DCM". Family members were identified in 11 families out of the 21 families (52.4%) with "possible pre-symptomatic DCM with cardiac conduction abnormality". Co-ordinating the family screening to include first-degree relatives appears to be appropriate and is best undertaken with the assistance of a professional trained in genetics who can interpret complicated family histories and pedigrees.

These findings have an impact on the clinical evaluation of patients with IDCM at CMJAH. The evaluation of a proband should include a thorough 3-generation family history, genetic counselling for the family, and 3-5 yearly clinical screening by physical examination, echocardiogram and ECG of first-degree relatives. Although the age of commencement of screening is uncertain, guidelines suggest screening from childhood, especially in cases of early onset and aggressive phenotypes. This represents a significant challenge and cost in our current health-care system, particularly if first-degree relatives who live significant distances from centres with cardiology services. Future research would include identifying the causative genetic mutations that contribute significantly to IDCM in South Africa and establishing locally appropriate genetic testing. Patients presenting with IDCM

could then be given accurate genetic counselling and testing, and screening could be rationalized to high-risk family members who are carriers of a predisposing mutation.

Acknowledgements

Our sincere appreciation goes to all of the "Genetics of Idiopathic Dilated Cardiomyopathy in Johannesburg" study investigators. We are grateful to the patients and their family members who participated.

References

1. Ntusi NB, Badri M, Gumedze F, Wonkam A, Mayosi BM. Clinical characteristics and outcomes of familial and idiopathic dilated cardiomyopathy in Cape Town: a comparative study of 120 cases followed up over 14 years. S Afr Med J. 2011;101(6):399-404.
2. Park HY. Hereditary Dilated Cardiomyopathy: Recent Advances in Genetic Diagnostics. Korean Circ J. 2017;47(3):291-298.
3. Tayal U, Prasad S, Cook SA. Genetics and genomics of dilated cardiomyopathy and systolic heart failure. Genome Med. 2017;9(1):20.
4. Sliwa K, Damasceno A, Mayosi BM. Epidemiology and etiology of cardiomyopathy in Africa. Circulation. 2005;112(23):3577-3583.
5. Ntusi NB, Wonkam A, Shaboodien G, Badri M, Mayosi BM. Frequency and clinical genetics of familial dilated cardiomyopathy in Cape Town: implications for the evaluation of patients with unexplained cardiomyopathy. S Afr Med J. 2011;101(6):394-398.
6. Stewart S, Wilkinson D, Hansen C, Vaghela V, Mvungi R, McMurray J, et al. Predominance of heart failure in the Heart of Soweto Study cohort: emerging challenges for urban African communities. Circulation. 2008;118(23):2360-2367.
7. Arbustini E, Narula N, Tavazzi L, Serio A, Grasso M, Favalli V, et al. The MOGE(S) classification of cardiomyopathy for clinicians. J Am Coll Cardiol. 2014;64(3):304-318.
8. Hanson EL, Hershberger RE. Genetic Counseling and Screening Issues in Familial Dilated Cardiomyopathy. J Genet Couns. 2001;10(5):397-415.
9. Hershberger RE, Siegfried JD. Update 2011: clinical and genetic issues in familial dilated cardiomyopathy. J Am Coll Cardiol. 2011;57(16):1641-1649.
10. Broch K, Andreassen AK, Hopp E, Leren TP, Scott H, Muller F, et al. Results of comprehensive diagnostic work-up in 'idiopathic' dilated cardiomyopathy. Open Heart. 2015;2(1):e000271. https://doi: 10.1136/openhrt-2015-000271
11. Mestroni L, Maisch B, McKenna WJ, Schwartz K, Charron P, Rocco C, et al. Guidelines for the study of familial dilated cardiomyopathies. Collaborative Research Group of the European Human and Capital Mobility Project on Familial Dilated Cardiomyopathy. Eur Heart J. 1999;20(2):93-102.
12. Mestroni L, Rocco C, Gregori D, Sinagra G, Di Lenarda A, Miocic S, et al. Familial dilated cardiomyopathy: evidence for genetic and phenotypic heterogeneity. Heart Muscle Disease Study Group. J Am Coll Cardiol. 1999;34(1):181-190.
13. Taylor MR, Carniel E, Mestroni L. Cardiomyopathy, familial dilated. Orphanet J Rare Dis. 2006;1:27. https://doi.org/10.1186/1750-1172-1-27
14. Charron P, Arad M, Arbustini E, Basso C, Bilinska Z, Elliott P, et al. Genetic counselling and testing in cardiomyopathies: a position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2010;31(22):2715-2726.
15. McNally EM, Barefield DY, Puckelwartz MJ. The genetic landscape of cardiomyopathy and its role in heart failure. Cell Metab. 2015;21(2):174-182.
16. Tibazarwa K, Sliwa K, Wonkam A, Mayosi BM. Peripartum cardiomyopathy and familial dilated Cardiomyopathy: a tale of two cases. Cardiovasc J Afr. 2013;24(5):e4-7.
17. Ware JS, Li J, Mazaika E, Yasso CM, DeSouza T, Cappola TP, et al. Shared Genetic Predisposition in Peripartum and Dilated Cardiomyopathies. N Engl J Med. 2016;374(3):233-241.
18. Skrzynia C, Berg JS, Willis MS, Jensen BC. Genetics and heart failure: a concise guide for the clinician. Curr Cardiol Rev. 2015;11(1):10-17.

19. Japp AG, Gulati A, Cook SA, Cowie MR, Prasad SK. The Diagnosis and Evaluation of Dilated Cardiomyopathy. J Am Coll Cardiol. 2016;67(25):2996-3010.
20. Garcia-Pavia P, Cobo-Marcos M, Guzzo-Merello G, Gomez-Bueno M, Bornstein B, Lara-Pezzi E, et al. Genetics in dilated cardiomyopathy. Biomark Med. 2013;7(4):517-533.

NATIONAL HEALTH LABORATORY SERVICE

WITS

13 March 2017

Faculty of Health Sciences Postgraduate Office

RE: Dr C. Bailly revision of the protocol to the Supervisor/Head of the Department

This is to confirm that the student, Dr. Claude Bailly (Student number: 1510667), has made the corrections as suggested at the School of Pathology Assessor Group Meeting on the 22nd of February 2017 (see list of corrections attached).

I, the Supervisor, acknowledge that the student has made the necessary corrections as stipulated by the committee.

Supervisor 1	Supervisor 2	Supervisor 3
Prof A. Krause	Ms S. Henriques	Dr N. Tsabedze
13/3/2017	13/3/2017	
Date	Date	Date

This report is intended solely to record the observations and/or opinion of the writer. It does not constitute a medico-legal report.

1 Muddenontein Road, Sandringham, Johannesburg, South Africa

Prof Ear Such Ms Joyce Magale
Private Bag X8, Sandringham, 2131, South Africa
+27 (0) 11 386 6800 0859 00 NHLS(6457)

5299296

University of the Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
FACULTY OF HEALTH SCIENCES
ASSESSORS MEETING

CANDIDATE: Claude Didier Bailly (1510667)

Date of Assessor Group Meeting: 22nd Feb 2017

School / Department / Division: Pathology

[Yes] [No] Is the research question clearly identified and described?

Comments:

[Yes] [No] [Not entirely]

Is the design of the study and methods the methods used appropriate for the research question being asked?

Comments: (1) Consolidated the objective 2, 3, 4, 5. →
(2) Remove cost effective as an objective.
(3)

Is the study feasible within:

i. the applicant's resources? [Yes] [No]

ii. the departments resources? [Yes] [No]

iii. the time frame? [Yes] [No]

CANDIDATE'S SURNAME: Bailly	FIRST NAME/S: Claude Didier	STUDENT NUMBER: 1510667

CURRENT QUALIFICATIONS: MBChB (UFS)

TEL: 011 489 9227	CELL: 0721921185	E-MAIL: claude.bailly@nhls.ac.za

DEGREE FOR WHICH PROTOCOL IS BEING SUBMITTED: MMed (Medical Genetics)

PART-TIME OR FULL-TIME: Full-time

FIRST REGISTERED FOR THIS DEGREE:	TERM : 1	YEAR: 2015

DEPARTMENT: Division of Human Genetics, NHLS, WITS

TITLE OF PROPOSED RESEARCH:

An assessment of genetic predisposition in idiopathic dilated cardiomyopathy (IDCM) in Johannesburg

CANDIDATE'S SIGNATURE:	DATE: 25.01.2017

SUPERVISOR #1'S NAME: Prof. A. Krause

% OF SUPERVISION TO BE PROVIDED BY SUPERVISOR #1: 40%

SUPERVISOR #1'S QUALIFICATIONS: MBBCh (WITS), Ph.D

SUPERVISOR #1'S DEPARTMENT: Division of Human Genetics

SUPERVISOR #1'S ADDRESS / TEL / E-MAIL: NHLS, Braamfontein (Corner of De Korte and Hospital Street), 011 489 9223,
amanda.krause@nhls.ac.za

SUPERVISOR #2'S NAME: Sasha Henriques

% OF SUPERVISION TO BE PROVIDED BY SUPERVISOR #2: 40%

SUPERVISOR #2'S QUALIFICATIONS: BSc (Hons) Biological Sciences, MSc Science Communication

SUPERVISOR #2'S DEPARTMENT: Division of Human Genetics

SUPERVISOR #2'S ADDRESS / TEL / E-MAIL: NHLS, Braamfontein (Corner of De Korte and Hospital Street), 011 489 9223
sasha.henriques@nhls.ac.za

SUPERVISOR #3's NAME: Dr. Ngoba Tsabedze

% OF SUPERVISION TO BE PROVIDED BY SUPERVISOR #3: 20%

SUPERVISOR #3'S QUALIFICATIONS: MBBCh (WITS), FCP (SA), Cert. Cardiology (SA)

SUPERVISOR #3'S DEPARTMENT: Cardiology Department, WITS

SUPERVISOR #3'S ADDRESS / TEL / E-MAIL: Charlotte Maxeke Johannesburg Academic Hospital, 011 488 3610
Ngoba.Tsabedze@wits.ac.za

SYNOPSIS OF RESEARCH:

Synopsis of Research

Idiopathic dilated cardiomyopathy (IDCM) is a form of dilated cardiomyopathy without an identifiable cause. My study is a retrospective analysis of family pedigrees and clinical screening data (ECG and echocardiography data) of relatives to patients diagnosed with idiopathic dilated cardiomyopathy (IDCM) who were seen at CMJAH. They have enrolled in the "Genetics of Idiopathic Dilated Cardiomyopathy in Johannesburg" study. The index cases have been extensively investigated, without cause for their dilated cardiomyopathy (DCM) being found and have therefore been diagnosed with IDCM.

My study is to determine whether African and South African individuals with IDCM have evidence of familial disease. A diagnosis of familial DCM requires a careful history and clinical screening of relatives, and if available, genetic testing. Identifying pre-symptomatic family members results in improved patient management.

We intend to try to identify any evidence supporting familial disease in these patients, firstly through pedigree analysis, and secondly by clinical screening of relatives through analysing screening data to identify any features suggestive of pre-symptomatic IDCM, further supporting a genetic component.

ETHICS PENDING: ETHICS APPROVED: (circle appropriate symbol)	IF Y SUPPLY ETHICS CLEARANCE No:

SIGNATURE OF SUPERVISOR/S:		

An assessment of genetic predisposition in idiopathic dilated cardiomyopathy (IDCM) in Johannesburg.

Research Proposal

Student:

Dr Claude Didier Beilly

MBChB (UFS), DCH

Student number A0044125

Supervisor 1:

Prof Amanda Krause

MBBCh (WITS), Ph.D

Co-Supervisor 2:

Dr Ngoba Tsabedze

MBBCh (WITS), FCP (SA), Cert. Cardiology (SA)

Co-supervisor 3:

Ms Sasha Henriques

BSc (Hons) Biological Sciences

MSc Science Communication

MSc Genetic Counselling

Literature review

Introduction

Cardiomyopathy is an umbrella term referring to myocardial disease associated with cardiac dysfunction. The cardiomyopathies include dilated cardiomyopathy (DCM), hypertrophic cardiomyopathy (HCM), restrictive cardiomyopathy (RCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC) (Sliwa et al., 2005, McNally et al., 2015). DCM is defined as left ventricular dilatation and systolic dysfunction in the absence of coronary artery disease, hypertension or valvular disease sufficient to cause systolic impairment. Idiopathic dilated cardiomyopathy (IDCM) is a form of DCM without an identifiable cause (Sliwa et al., 2005, Ntusi et al., 2011a, Broch et al., 2015).

DCM affects all age groups; however, the most common age of onset is adults in the 3rd and 4th decades of life. Severity of DCM is increased in men, and they also appear twice as likely to be affected compared to women (Sliwa et al., 2005, Ntusi et al., 2011a). Patients with DCM usually present with decompensated cardiac failure (Broch et al., 2015). Other manifestations include arrhythmias, sudden cardiac death and less commonly, a thromboembolic event (Mestroni et al., 1999a, Mestroni et al., 1999b, Hanson and Hershberger, 2001). Most patients with DCM are diagnosed because they present with symptoms, however, the disease can also be detected on routine cardiovascular examination in patients who report as asymptomatic. A so-called pre-symptomatic stage may persist for months to years without the onset of symptoms (Hanson and Hershberger, 2001). Diagnosis of DCM often requires specialist investigations such as echocardiography which is mostly limited to tertiary medical centres (Sliwa et al., 2005).

Aetiology of DCM

The causes for DCM are many, and the cardiac dilatation likely represents an end-stage phenotype to a compromised myocardium (Broch et al., 2015). Amongst Africans, causative factors include

untreated hypertension, myocarditis (viral, parasitic and bacterial causes), coronary artery disease, valvular heart disease, congenital heart disease, autoimmune disease, metabolic factors, alcohol abuse and nutritional deficiencies (Sliwa et al., 2005, Ntusi et al., 2011a). There are many genetic conditions that have dilated cardiomyopathy as a manifesting feature, including the muscular dystrophies (Duchenne and Becker muscular dystrophy) as well as their carrier states, Emery-Dreifuss and limb-girdle muscular dystrophy, hereditary haemochromatosis, Friedrich's ataxia, Barth syndrome, mitochondrial myopathies as well as inborn errors of metabolism (Hanson and Hershberger, 2001, Hershberger and Siegfried, 2011). Diagnostic testing is usually extensive and includes routine blood tests, electrocardiogram (ECG) echocardiography and coronary angiography as guided by the patient's history, age and risk factors. These diagnostic tests generally have a modest diagnostic yield in identifying the cause of DCM and often fail to identify a cause of the disease (Hanson and Hershberger, 2001, Broch et al., 2015). When no medical cause can be found, and the condition appears to be sporadic and isolated in a single family member, the patient is diagnosed with idiopathic dilated cardiomyopathy (IDCM). It has been recognised that a subset of IDCM is likely genetic in aetiology. Among patients with IDCM, some were found to have first degree relatives affected with IDCM, further implying a genetic aetiology. When the cause of IDCM is believed to be familial, it is termed familial DCM or inherited DCM. When a genetic mutation is found in a family, the IDCM is often referred to as genetic DCM. Therefore, an accurate diagnosis of IDCM is vital for meaningful genetic counselling and the diagnosis should be made at expert centres with reasonable exclusion of other causes (Hanson and Hershberger, 2001, Taylor et al., 2006, Somsen et al., 2011, Japp et al., 2016).

In up to 50% of IDCM cases the disease is believed to be familial, with 20 to 50% of IDCM estimated to be caused by a genetic mutation transmitted through typical modes of Mendelian inheritance (Ntusi et al., 2011a, Skrzynia et al., 2015). Familial disease is identified by accurately analysing the family history of affected individuals and identifying both symptomatic and

asymptomatic family members through clinical examination and screening. Screening of first degree relatives by performing an ECG and echocardiogram is much more sensitive for identifying familial disease than by obtaining a family history alone (Hershberger and Siegfried, 2011). A diagnosis of familial disease is supported if there are at least two related family members meeting standard diagnostic criteria for IDCM (Hershberger and Siegfried, 2011, Skrzynia et al., 2015). Standard diagnostic criteria include establishing the presence of left ventricular enlargement (most commonly assessed by echocardiography) and systolic dysfunction (an ejection fraction of less than 50% is considered as systolic dysfunction, and can be measured by echocardiography, nuclear medicine studies or cardiac MRI studies) and establishing the absence of a medical cause for the DCM. Familial disease is believed to present at a younger age with worse ventricular function and prognosis. In the absence of a relative with a known diagnosis of IDCM, a high index of suspicion is needed if there is a family history of individuals with symptoms of cardiac failure, arrhythmias or unexplained sudden death (Hanson and Hershberger, 2001).

Genetics of familial DCM

Inheritance

In familial DCM, pedigree analysis may reveal autosomal dominant (AD), autosomal recessive (AR), X-linked (XL) or mitochondrial inheritance. The majority of pedigrees are consistent with an autosomal dominant pattern of inheritance. Many features may complicate the presentation of familial disease even in autosomal dominant inheritance pedigrees. These include incomplete penetrance, age-related penetrance where disease causing mutations usually manifest as a disease phenotype in the adult years, and variable expressivity (Hershberger and Siegfried, 2011, McNally and Puckelwartz, 2015, Skrzynia et al., 2015). With regards to variable expressivity, some family members may show only some characteristics of a DCM phenotype, for example mild ventricular enlargement without systolic dysfunction, arrhythmias or conduction system defects with only

borderline DCM features. Within a large family with familial disease, a wide range of clinical findings may therefore be present. Identifying genetic and non-genetic causes for cardiovascular disease and DCM within the same family can also be challenging, as the DCM in the individuals needs to be distinguished from other forms of secondary dilatation and dysfunction of the ventricles, which may be secondary to a cardiac or systemic condition (Taylor et al., 2006, Hershberger and Siegfried, 2011). Although screening of asymptomatic relatives by echocardiography and electrocardiogram was primarily recommended for those cases where an autosomal dominant pattern of inheritance was identified through family history, it is now thought that screening asymptomatic family members by these methods is applicable regardless of the family history, and may assist in establishing the most likely mode of inheritance (Hanson and Hershberger, 2001).

The different forms of cardiomyopathy each have a heritable component. More than one-hundred genes have been linked to the inherited forms of cardiomyopathy, of which DCM is the most genetically heterogeneous (McNally et al., 2015). The same gene may also be implicated in multiple forms of cardiomyopathy. Environmental factors (e.g. diet), exposure to toxins, and comorbidities such as ischaemic heart disease, valvular heart defects, systemic illness as well as the influence of sex can contribute to the particular cardiomyopathy phenotype. Despite this marked heterogeneity, several critical genetic mutations are often present (McNally et al., 2015). Family studies of inherited cardiomyopathies often identify a primary pathogenic variant, but the genome contains many additional variants, called secondary variants which may modify the expression of the primary pathogenic variant. The influence of the entire genome may therefore need to be considered. This concept has challenged "single gene disorder" thought on cardiomyopathy. An improvement in genetic testing will hopefully result in more precise diagnosis and management (McNally et al., 2015, McNally and Puckelwartz, 2015).

Molecular genetics

The genes implicated in familial DCM play a role in coding for components of myocytes, such as the cystoskeleton, nuclear and sarcomere proteins. More than 50 genes have been implicated in DCM, most of which encode sarcomeric proteins. With current genetic testing, even large panels of more than 50 genes have only about a 50% sensitivity to detect mutations (Ntusi et al., 2011b, Skrzynia et al., 2015, Japp et al., 2016).

A major role-player in cardiomyopathy is the *TTN* gene, which encodes the protein titin. Titin is the largest protein in the human body; it plays a role in sarcomere integrity and is critical in left ventricular functioning. *TTN* is most commonly mutated in IDCM, and approximately 20 - 25% of IDCM patients have a truncating variant in this gene. Studies have identified missense mutations in this gene in patients with both IDCM and HCM, as well as control groups with normal cardiac function. These variants are therefore difficult to interpret. Interpretation of variants is also complicated by racial and ethnic backgrounds. This has been demonstrated by the misclassification of variants believed to be causal for HCM. These variants which were believed to be causal for HCM needed to be re-classified as benign variants, due to the variant being common in the general population and significantly more common among black Americas than among white Americans. This highlights the need to use ancestry-matched controls to interpret genetic variants (Manrai et al., 2016). Variants which cause frameshifts, stop mutations and alter splice sites may be easier to classify as being pathogenic (McNally et al., 2015, McNally and Puckelwartz, 2015, Skrzynia et al., 2015). Some individuals with *TTN* truncation have been shown to have a normal cardiac phenotype revealing the role of modifier genes and environmental factors (Japp et al., 2016). In some patients with familial DCM, the findings of cardiac conduction defects may point to a specific gene mutation such as *LMNA* and *SCN5A*. Identifying the genetic mutation may alter management, for example it is recommended that individuals with *LMNA* mutations benefit from early implantable cardioverter-

defibrillator (ICD) implantations (Skrzynia et al., 2015). In most cases, there is no clear genotype-phenotype correlation.

Genetic testing and surveillance

As IDCM may be familial, and therefore possibly genetic, part of evaluation of the proband will be to identify familial DCM. A cascade approach to screening of first-degree relatives should be used including taking a family history, a medical history of the relatives, a thorough clinical examination as well as an echocardiogram and an ECG to determine if any relatives are affected, further supporting familial DCM. (Hershberger and Siegfried, 2011). If genetic testing is available, it may be offered to individuals with IDCM, familial DCM or peripartum and pregnancy associated cardiomyopathy (Hershberger and Siegfried, 2011). Routine genetic testing is only recommended in familial DCM where 2 or more individuals are affected, and has a diagnostic yield of 30 – 35% using multi- gene panel testing (Hershberger et al., 2009, Japp et al., 2016). At present, the principal rationale for identifying a causal mutation is to allow mutation-specific cascade screening of family members. This will determine which family members require ongoing surveillance from those who do not (Japp et al., 2016). Genetic counselling, a process which provides individuals and relatives with information on the nature, inheritance and implications of a genetic disorder, is essential to facilitate informed decision-making. Appropriate genetic counselling will be of importance to create an awareness of the heritability among family members. Pre-test counselling and the interpretation of genetic results will also be a major role for the genetics team when testing becomes available (Hershberger and Siegfried, 2011, Skrzynia et al., 2015). Even if genetic testing is not feasible, the identification of individuals that are pre-symptomatic is of value. Early treatment can retard adverse modelling, prevent symptoms of heart failure and increase life expectancy. As familial DCM can exhibit age-dependant penetrance, repeated clinical screening is recommended to detect late onset disease (Japp et al., 2016). In situations where a causal mutation is known in a family and testing is feasible, individuals who test negative for the genetic mutation can be eliminated from an ongoing

screening protocol. A new diagnosis of IDCM should prompt screening in first degree relatives by not only family history, but by ECG and echocardiography. Family history is often difficult, and familial disease may be underestimated. Family history alone will also not unmask pre-symptomatic relatives (Japp et al., 2016, Hanson and Hershberger, 2001, Skrzynia et al., 2015).

Dilated cardiomyopathy in Africa and South Africa

In Africa DCM is responsible for 10 to 17% of cardiac conditions encountered at autopsy and is responsible for up to 48% of patients hospitalised for heart failure. Along with rheumatic heart disease and hypertension, DCM is one of the leading causes of heart failure in Africa. (Sliwa et al., 2005). The Heart of Soweto study, a contemporary study which examined the burden of cardiovascular disease in urban Africa, identified heart failure as the commonest cardiovascular diagnosis (Ntusi et al., 2011a). Although there are no population based data on the burden of DCM in Africa, DCM is an important cause of heart failure. IDCM, whether it is believed to be familial or non-familial, is associated with a high mortality rate, and evidence shows that these patients are not timeously referred for life-saving interventions such as cardiac transplantation (Ntusi et al., 2011a). Studies done at Groote Schuur Hospital have shown that familial DCM is common in African patients with IDCM, with an autosomal dominant pattern of inheritance being most commonly demonstrated. However very little is known of the frequency and genetics of IDCM in the rest of Africa and South Africa (Ntusi et al., 2011b). South African patients suffering from IDCM are often in resource-limited environments and delay in arriving at a diagnosis is not surprising.

Rationale for study

Distinguishing familial cases of IDCM from the so-called "sporadic" cases can have important implications for the patient and his family. A diagnosis of familial DCM requires a careful family history, clinical screening of relatives and where available, genetic testing. The role of the geneticist will be to explain the heritability, coordinate clinical and genetic screening processes, and with the

landscape of genetics altering rapidly, interpretation and explaining of results. The patients seen at CMJAH are South African and African families who reside in the Johannesburg area. These have enrolled in the "Genetics of idiopathic dilated cardiomyopathy in Johannesburg" study. They have been extensively investigated, without cause for their DCM being found and have been diagnosed with IDCM. We intend to try to identify any evidence supporting familial disease through pedigree analysis, and screening of relatives to identify any features suggestive of pre-symptomatic DCM, further supporting a genetic component. Genetic counselling in this context will create an awareness of the possible familial component of IDCM, and screening of first degree relatives will be strongly encouraged. Identifying a genetic component will give further motivation to the importance of genetic counselling in patients with IDCM in the Johannesburg area, and further evidence of the importance of a cardio-genetics service being a vital component to a tertiary centre such as CMJAH. The study will examine the evidence supporting a familial and therefore a genetic component to IDCM seen in Johannesburg, and assess whether a South African screening protocol is needed for these patients and their families.

Aim of Study

The aim of the study is to assess whether there is evidence for a genetic predisposition to the DCM seen amongst patients diagnosed with IDCM and their relatives who were screened in Johannesburg at CMJAH. If so, a further aim is to develop a screening protocol for these patients and their families, which would include genetic counselling.

Study Objectives

1. To describe the clinical characteristics of IDCM in Johannesburg patients including their ethnicity, gender and age at diagnosis.
2. To identify the frequency of familial disease identified through detailed family history of IDCM as well as through the screening of first and second degree relatives by

echocardiogram and electrocardiogram (ECG), and in doing so, try to identify the likely mode of inheritance through analysis of the family pedigrees.

3. To develop a clinically useful screening tool for familial DCM in the South African context.

Methods

Eligibility criteria

1. South African and African patients with a diagnosis of IDCM who have participated in the Genetics of Idiopathic Dilated Cardiomyopathy Study in Johannesburg will be included.
2. All first and second degree family relatives of the index cases who presented for screening will be included in the analysis.
3. More distant relatives of the index case who presented for screening will be included in the study where first and second degree relatives were not available.

Exclusion criteria

1. Individuals who are not related to the index case who presented for screening will be excluded from the analysis.

Study design

This study will be conducted on a retrospective basis, focussing on clinical and pedigree information obtained from patients who presented to CMJAH over a 2-year period with a working diagnosis of IDCM. Thirty family pedigrees will be analysed.

The index cases have been enrolled in Dr N. Tsabedze's Ph.D. study entitled "Genetics of Idiopathic Dilated Cardiomyopathy Study in Johannesburg". Family members of the index cases were invited for screening to identify if they had any features of DCM. My role as part of the research team included the following: 1) Constructing a 3-4 generation family pedigree for each index case; 2) Genetic counselling of the index cases and family members on the suspected heritability of DCM; 3)

Explaining the planned exome sequencing to the index cases and family members that would be performed through the Genetics of Idiopathic Dilated Cardiomyopathy Study.

Specific information obtained through the 3-4 generation family pedigree included:

- The ethnicity of the family
- The age of diagnosis of the index case
- The sex of the index case
- Any first and second degree relative(s) to the index case known with a confirmed diagnosis of DCM
- Any history of sudden cardiac death or sudden unexplained death in individuals less than 50 years old
- Any history of family members diagnosed with peripartum cardiomyopathy
- Any history of family members requiring pacemakers
- Any history of family members requiring cardiac transplantation
- Any symptoms of cardiac failure, arrhythmias, syncope amongst the family members screened

The pedigrees were hand drawn at the time of consultation and will be converted to an electronic format using a pedigree software drawing programme called PedigreeXP to assist with analysis. Using the pedigree information, families will be categorized into 4 groups:

- Positive for familial IDC: If a relative(s) of the index case has a diagnosis of DCM, if any relative(s) has a history of peripartum cardiomyopathy, if any relative(s) has a history of an unexplained cardiac death below the age of 50 years, if any relative(s) has required a pacemaker for a cardiac arrhythmia, or if any relative(s) has required a cardiac transplantation for cardiac failure, they will be considered as a family positive for familial dilated cardiomyopathy based on history.

- Intermediate family: If a family member has a history of a cardiac death over the age of 50 years, or a history of unexplained cardiac failure, they will be given an intermediate status.
- Negative family: If the family has no history of DCM, unexplained cardiac death, cardiac failure or no history of individuals with symptoms of cardiac failure, the family will be categorized as negative for familial DCM based on history.
- Unknown status: Those who have an unknown or unreliable family history will be given an unknown status.

Each pedigree will also be assessed for individuals with a history of:

- Ischaemic heart disease
- Cerebrovascular disease (likely a thromboembolic event)
- Hypertension
- Other medical conditions such as a history of any genetic conditions including muscular dystrophies.

In terms of the clinical screening, special attention will be given to screening criteria necessary for a diagnosis of DCM. Therefore, the following data will be of interest from the clinical screening of index cases and family members:

- Echocardiogram findings: LVEDD (left ventricular end diastolic diameter) and LVEF (left ventricular ejection fraction)
- ECG findings indicating an underlying arrhythmia

Based on these findings individuals who were screened will be categorized as:

- Features of DCM: Family members with a LVEF of < 50% and a LVEDD > 95th centile for age and sex and who are symptomatic, will be categorized as having features of DCM.

- Features of pre-symptomatic DCM: Family members with a LVEF < 50% and a LVEDD > 95th centile for age and sex who are asymptomatic, will be categorized as having features of pre-symptomatic DCM.
- Cardiac conduction abnormality and possible pre-symptomatic DCM: Family members with a LVEF > 50% and a LVEDD < 95th centile for age and sex and who are identified as having a cardiac arrhythmia on ECG will be classified as having a cardiac conduction abnormality and possible presymptomatic DCM.
- No features of DCM: Family members who have a LVEF >50% and a LVEDD < 95th centile for age and sex with a normal ECG will be categorized as having no features of DCM.

Data analysis

The data analysis will be two-fold:

The pedigree analysis will be tabulated on a Microsoft Excel spreadsheet. Using the pedigree data, families will be categorized as being positive, negative, intermediate or unknown for a diagnosis of familial DCM. Other data including the gender, age and ethnicity of the proband and relatives will also be tabulated on a Microsoft Excel spreadsheet, as well as whether they have a history of DCM, peripartum cardiomyopathy, symptoms of heart failure or arrhythmia. Bar graphs will be used to describe the demographic data. A copy of the data collection sheet is attached (Appendix 1).

The screening clinical data (LVEF and LVEDD) of the index cases and the included screened family member will be presented as means or as a percentage as appropriate and will be tabulated on a Microsoft Excel spreadsheet to assist with the analysis. Screening data will categorize individuals that have been screened as having features of DCM, pre-symptomatic DCM, possible pre-symptomatic DCM (in those with a cardiac conduction abnormality) or negative for features of DCM. Chi-test and Fischers exact test will be used for categorical data. Normal distribution data will be presented as a mean and standard deviation. Non-parametric data will be presented as median and

interquartile ranges. Categorical data will be presented as numbers and percentages. A copy of the data analysis sheets are attached (Appendix 2 and 3).

Limitation

In South Africa, few family members know detailed or accurate information around the cause of death in family members. They may be unaware of the symptoms of cardiac failure, or many family members may not have been formally diagnosed with DCM. The limitations of screening by family history alone are therefore likely to be a potential limitation to this study. This will be partly offset by the clinical data.

Ethics

This retrospective analysis will be done on data collected during Dr N. Tsabedze's Ph.D. titled "The Genetics of Idiopathic Dilated Cardiomyopathy in Johannesburg". I have been part of the research team since 01.04.2016. Ethics approval has been obtained for his study (Ethics Clearance Certificate No. M150467).

Timing

2016		2017						2018
	Oct-Nov	Jan-Mar	Apr	May	June	Jul	Aug-Dec	Jan-June
Ethics application								
Data collection completion								
Data analysis								
Writing research Report								

Funding:

This study will be a retrospective analysis of the family pedigrees and screening data collected as part of Dr N. Tsabedze's Ph.D. study "Genetics of Idiopathic Dilated Cardiomyopathy in Johannesburg". The licence for usage of the pedigree drawing programme, PedigreeXP, has been paid for by the Department of Human Genetics. No further costs are anticipated.

References

BROCH, K., ANDREASSEN, A. K., HOPP, E., LEREN, T. P., SCOTT, H., MULLER, F., AAKHUS, S. & GULLESTAD, L. 2015. Results of comprehensive diagnostic work-up in 'idiopathic' dilated cardiomyopathy. *Open Heart,* 2, e000271.

HANSON, E. L. & HERSHBERGER, R. E. 2001. Genetic Counseling and Screening Issues in Familial Dilated Cardiomyopathy. *J Genet Couns,* 10, 397-415.

HERSHBERGER, R. E., COWAN, J., MORALES, A. & SIEGFRIED, J. D. 2009. Progress with genetic cardiomyopathies: screening, counseling, and testing in dilated, hypertrophic, and arrhythmogenic right ventricular dysplasia/cardiomyopathy. *Circ Heart Fail,* 2, 253-61.

HERSHBERGER, R. E. & SIEGFRIED, J. D. 2011. Update 2011: clinical and genetic issues in familial dilated cardiomyopathy. *J Am Coll Cardiol,* 57, 1641-9.

JAPP, A. G., GULATI, A., COOK, S. A., COWIE, M. R. & PRASAD, S. K. 2016. The Diagnosis and Evaluation of Dilated Cardiomyopathy. *J Am Coll Cardiol,* 67, 2996-3010.

MANRAI, A. K., FUNKE, B. H., REHM, H. L., OLESEN, M. S., MARON, B. A., SZOLOVITS, P., MARGULIES, D. M., LOSCALZO, J. & KOHANE, I. S. 2016. Genetic Misdiagnoses and the Potential for Health Disparities. *N Engl J Med,* 375, 655-65.

MCNALLY, E. M., BAREFIELD, D. Y. & PUCKELWARTZ, M. J. 2015. The genetic landscape of cardiomyopathy and its role in heart failure. *Cell Metab,* 21, 174-82.

MCNALLY, E. M. & PUCKELWARTZ, M. J. 2015. Genetic Variation in Cardiomyopathy and Cardiovascular Disorders. *Circ J,* 79, 1409-15.

MESTRONI, L., MAISCH, B., MCKENNA, W. J., SCHWARTZ, K., CHARRON, P., ROCCO, C., TESSON, F., RICHTER, A., WILKE, A. & KOMAJDA, M. 1999a. Guidelines for the study of familial dilated cardiomyopathies. Collaborative Research Group of the European Human and Capital Mobility Project on Familial Dilated Cardiomyopathy. *Eur Heart J,* 20, 93-102.

MESTRONI, L., ROCCO, C., GREGORI, D., SINAGRA, G., DI LENARDA, A., MIOCIC, S., VATTA, M., PINAMONTI, B., MUNTONI, F., CAFORIO, A. L., MCKENNA, W. J., FALASCHI, A., GIACCA, M. & CAMERINI 1999b. Familial dilated cardiomyopathy: evidence for genetic and phenotypic heterogeneity. Heart Muscle Disease Study Group. *J Am Coll Cardiol,* 34, 181-90.

NTUSI, N. B., BADRI, M., GUMEDZE, F., WONKAM, A. & MAYOSI, B. M. 2011a. Clinical characteristics and outcomes of familial and idiopathic dilated cardiomyopathy in Cape Town: a comparative study of 120 cases followed up over 14 years. *S Afr Med J,* 101, 399-404.

NTUSI, N. B., WONKAM, A., SHABOODIEN, G., BADRI, M. & MAYOSI, B. M. 2011b. Frequency and clinical genetics of familial dilated cardiomyopathy in Cape Town: implications for the evaluation of patients with unexplained cardiomyopathy. *S Afr Med J,* 101, 394-8.

SKRZYNIA, C., BERG, J. S., WILLIS, M. S. & JENSEN, B. C. 2015. Genetics and heart failure: a concise guide for the clinician. *Curr Cardiol Rev,* 11, 10-7.

SLIWA, K., DAMASCENO, A. & MAYOSI, B. M. 2005. Epidemiology and etiology of cardiomyopathy in Africa. *Circulation,* 112, 3577-83.

SOMSEN, G. A., HOVINGH, J., TULEVSKI, I. I. & SEIDMAN, C. E. 2011. Clinical cardiogenetics. *In:* BAARS, H. F., SMAGT, J. J. V. D. & DOEVENDANS, P. A. (eds.). London: Springer.

TAYLOR, M. R., CARNIEL, E. & MESTRONI, L. 2006. Cardiomyopathy, familial dilated. *Orphanet J Rare Dis,* 1, 27.

Appendix 1: Family History Data Capture Sheet

Family	Affected relative (Y/N)	Cardiac Death < 50 (Y/N)	Pacemaker (Y/N)	Cardiac transplant (Y/N)	Cardiac death >50 (Y/N)	Unexplained CCF (Y/N)	PPCM history (Y/N)	Unreliable (Y/N)
Family 1								
Family 2								
Family 3								
Family 4								

Family	Positive Family	Intermediate Family	Negative Family	Unknown Family	If positive: likely mode of inheritance
Family 1					
Family 2					
Family 3					
Family 4					

Appendix 2: Clinical Screening Data Capture Sheet

Family	Ethnicity	Age	Gender	LVEF %	LVEDD (SD)	Cardiac arrhythmia (Y/N)	Features of DCM (Y/N)	Features of pre-symptomatic DCM (Y/N)	Cardiac conduction abnormality/ Possible DCM (Y/N)	No features of DCM
Family1										
Proband 1										
Relative 1.1										
Relative1.2										
Relative1.3										
Relative 1.4										

Appendix 3: Combined Family History and Clinical Screening Data Capture Sheet

	No. of families	No. of relatives screened	No. of relatives with features of DCM	No. of relatives with features of pre-symptomatic DCM	No. of relatives with cardiac conduction abnormality and possible pre-symptomatic DCM	Relatives screened with no features of DCM
Positive family history						
Intermediate family						
Negative family						
Unknown family						

Faculty of Health Sciences, Postgraduate Office
Phillip V Tobias Building, 2nd Floor
Cnr York & Princess of Wales Terrace, Parktown 2193
Tel: (011) 717 2745 | Fax: (011) 717 2119
Email: Methoto.senamela@wits.ac.za

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

RECOMMENDATION FOR APPOINTMENT OF SUPERVISOR(S) OF RESEARCH REPORT, DISSERTATION OR THESIS

Motivation / Reason for Appointment:
Prof. A Krause, Head of Department (Human Genetics) has supervised a large number of Ph.D's. Dr N. Tsabedze as the study is part of the "Genetics of Idiopathic Dilated Cardiomyopathy" Ph.D and for clinical guidance and knowledge of cardiomyopathy. S. Henriques for experience in counselling of patients with cardiomyopathies

Recommendation of Division / Department / School:
Supported.

Student Surname and Full name(s)	Bailly, CD
Student number	1510667
Degree	MMed (Medical Genetics)
Div / Dept / School	Division of Human Genetics, School of Pathology, WITS, NHLS
Title	An assessment of genetic predisposition in idiopathic dilated cardiomyopathy (IDCM) in Johannesburg.

(Supervisor 1): Prof. Amanda Krause
(Name &Surname)

Supervision %: 40%

Supervisor Qualifications: MBBCh (WITS) Ph.D

Supervisor Department: Division of Human Genetics

Supervisor Telephone: 011 489 9223 E-mail: amanda.krause@nhls.ac.za

Supervisor 2: Sasha Henriques
(Name &Surname)

Supervision %: 40%

Supervisor Qualifications: BSc (Hons) Biological Sciences, MSc Science Communication

Supervisor Department: Division of Human Genetics

Supervisor Telephone: 011 489 9902 E-mail: sasha.henriques@nhls.ac.za

Student Signature:

Supervisor 3: Dr. Ngoba Tsabedze
(Name & Surname)

Supervision %: 20%

Supervisor Qualifications: MBBCh (WITS), FCP (SA), Cert. Cardiology (SA)

Supervisor Department: Cardiology

Supervisor Telephone: 011 4883610 E-mail: Ngoba.Tsabedze@wits.ac.za

Student Signature:

Supervisor 1 Signature: Supervisor 2 Signature: Supervisor 3 Signature:

RECOMMENDATION BY HEAD OF DIVISION / DEPARTMENT / SCHOOL:

Prof J Mahlangu
(Full name(s) and Surname).

RECEIVED AND SUPPORTED
(Date)

APPROVAL BY CHAIR OF ASSESSOR GROUP:
(On behalf of the FGSC)

N. H NKALA
(Full name(s) and Surname)

22/02/2017
(Date)

PLEASE NOTE: RECOMMENDATION FOR APPOINTMENT OF SUPERVISOR(S) FOR CIRCULATION TO THE FGSC FOR APPROVAL

R14/49 Dr Claude Didier Bailly

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M1702103

NAME: (Principal Investigator)	Dr Claude Didier Bailly
DEPARTMENT:	Human Genetics National Health Laboratory Services University of the Witwatersrand
PROJECT TITLE:	An Assessment of Genetic Predisposition in Idopathic Dilated Cardiomyopathy (IDCM) in Johannesburg
DATE CONSIDERED:	Adhoc
DECISION:	Approved unconditionally
CONDITIONS:	Sub-Study (M150467)
SUPERVISOR:	Prof Amanda Krause and Dr Nqoba Tsabedze
APPROVED BY:	Professor P. Cleaton-Jones,Chairperson, HREC (Medical)
DATE OF APPROVAL:	31/03/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 10004,10th floor, Senate House/2nd floor, Phillip Tobias Building, Parktown, University of the Witwatersrand. I/We fully understand the the conditions under which I am/we are authorised to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. in this case, the study was initially review in February and will therefore be due in the month of February each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

Date 1.04.17

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

ORIGINALITY REPORT

15%	10%	12%	%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	open.uct.ac.za Internet Source	1%
2	"Cardiovascular Genetics and Genomics", Springer Nature, 2018 Publication	1%
3	www.ncbi.nlm.nih.gov Internet Source	1%
4	"Clinical Cardiogenetics", Springer Nature, 2016 Publication	1%
5	www.blueshieldca.com Internet Source	1%
6	Reed E. Pyeritz. "The Genetics of Cardiac Electrophysiology in Humans", Elsevier BV, 2013 Publication	1%
7	www.onlinejacc.org Internet Source	1%
8	www.ashg.org Internet Source	1%

9	breast-cancer-research.biomedcentral.com Internet Source	<1%
10	issuu.com Internet Source	<1%
11	"Abstracts : Abstracts", European Journal of Heart Failure, 2015. Publication	<1%
12	Jakobs, P.M.. "Novel lamin A/C mutations in two families with dilated cardiomyopathy and conduction system disease", Journal of Cardiac Failure, 200109 Publication	<1%
13	Mehroz Ehsan, He Jiang, Kate L.Thomson, Katja Gehmlich. "When signalling goes wrong: pathogenic variants in structural and signalling proteins causing cardiomyopathies", Journal of Muscle Research and Cell Motility, 2017 Publication	<1%
14	www.hal.inserm.fr Internet Source	<1%
15	www.omicsonline.org Internet Source	<1%
16	Ponder, B.. "RISK ESTIMATION AND SCREENING IN FAMILIES OF PATIENTS WITH MEDULLARY THYROID CARCINOMA", The	<1%

	Lancet, 19880220 Publication	
17	J. -P. Mecklin. "Screening for Colorectal Carcinoma in Cancer Family Syndrome Kindreds", Scandinavian Journal of Gastroenterology, 5/1/1987 Publication	<1%
18	"ASGBI abstracts 2009 Oral presentations", British Journal of Surgery, 05/2009 Publication	<1%
19	www.hta.nhsweb.nhs.uk Internet Source	<1%
20	eurheartj.oxfordjournals.org Internet Source	<1%
21	www.uptodate.com Internet Source	<1%
22	Deirdre Nauman. "The Family History as a Tool to Identify Patients at Risk for Dilated Cardiomyopathy", Progress in Cardiovascular Nursing, 12/2008 Publication	<1%
23	www.samj.org.za Internet Source	<1%
24	pmj.bmj.com Internet Source	<1%

25	docplayer.net Internet Source	<1%
26	pure.uva.nl Internet Source	<1%
27	Portig, I.. "Familial inflammatory dilated cardiomyopathy", European Journal of Heart Failure, 200612 Publication	<1%
28	papyrus.bib.umontreal.ca Internet Source	<1%
29	www.biomedsearch.com Internet Source	<1%
30	link.springer.com Internet Source	<1%
31	A.C. BECKER. "Acute Coronary Syndromes in Treatment-Naïve Black South Africans with Human Immunodeficiency Virus Infection", Journal of Interventional Cardiology, 02/2010 Publication	<1%
32	P Z Szymanski, M Badri, B M Mayosi. "Clinical characteristics and causes of heart failure, adherence to treatment guidelines, and mortality of patients with acute heart failure: Experience at Groote Schuur Hospital, Cape Town, South Africa", South African Medical	<1%

Journal, 2018
Publication

33	Kushner, J.D.. "Clinical Characteristics of 304 Kindreds Evaluated for Familial Dilated Cardiomyopathy", Journal of Cardiac Failure, 200608 Publication	<1%
34	www.geneticsmr.com Internet Source	<1%
35	www.scribd.com Internet Source	<1%
36	www.childrenscardiomyopathy.org Internet Source	<1%
37	Muller, T.. "Dilated cardiomyopathy may be an early sign of the C826A Fukutin-related protein mutation", Neuromuscular Disorders, 200505 Publication	<1%
38	Yoshitatsu Sei, Xilin Zhao, Joanne Forbes, Silke Szymczak et al. "A Hereditary Form of Small Intestinal Carcinoid Associated With a Germline Mutation in Inositol Polyphosphate Multikinase", Gastroenterology, 2015 Publication	<1%
39	www.arquivosonline.com.br Internet Source	<1%

Hyemoon Chung, Makoto Amaki, Seiji

40	Takashio, Hiroyuki Takahama et al. "Effect of Mitral Valve Surgery in Patients With Dilated Cardiomyopathy and Severe Functional Mitral Regurgitation", Circulation Journal, 2018 Publication	<1%
41	jcp.bmj.com Internet Source	<1%
42	spandidos-publications.com Internet Source	<1%
43	Ehst, B.D.. "Cutaneous Manifestations of Internal Malignancy", Current Problems in Surgery, 201005 Publication	<1%
44	d-scholarship.pitt.edu Internet Source	<1%
45	www.pubfacts.com Internet Source	<1%
46	Kathy A. Crispell. "Familial cardiomyopathies: Significant causes of heart failure", Current Cardiology Reports, 05/2003 Publication	<1%
47	www.jcmr-online.com Internet Source	<1%
48	emedicine.medscape.com Internet Source	<1%

49	Ojji, D., J. Atherton, K. Sliwa, J. Alfa, M. Ngabea, and L. Opie. "Left Ventricular Systolic Dysfunction in Asymptomatic Black Hypertensive Subjects", American Journal of Hypertension, 2015. Publication	<1%
50	Refiloe Keketso Mopeli, Debbie White, Daynia Ballot. "An audit of primary medical conditions in children admitted to the paediatric intensive care unit of Charlotte Maxeke Johannesburg Academic Hospital", South African Journal of Child Health, 2016 Publication	<1%
51	Tibazarwa, K.. "Peripartum Cardiomyopathy in Africa: Challenges in Diagnosis, Prognosis, and Therapy", Progress in Cardiovascular Diseases, 201001/02 Publication	<1%
52	Hong, Young Mi. "Cardiomyopathies in children", Korean Journal of Pediatrics, 2013. Publication	<1%
53	Satu Kärkkäinen. "A novel mutation, Arg71Thr, in the δ-sarcoglycan gene is associated with dilated cardiomyopathy", Journal of Molecular Medicine, 12/01/2003 Publication	<1%

Exclude quotes	On	Exclude matches	Off
Exclude bibliography	On		

SAMJ The South African Medical Journal
Leading research impacting clinical care in Africa

Submissions

» Online Submissions
» Author Guidelines
» Copyright Notice
» Privacy Statement

Online Submissions

Already have a Username/Password for South African Medical Journal?
GO TO LOGIN

Need a Username/Password?
GO TO REGISTRATION

Registration and login are required to submit items online and to check the status of current submissions.

Author Guidelines

The *SAMJ* has launched a new submission and tracking system. Authors will be required to register a profile on the Editorial Manager platform in order to submit a manuscript.

To submit a manuscript, please proceed to the *SAMJ* Editorial Manager website: www.editorialmanager.com/samj

To access and submit an article already in production, please see the guidelines here.

Author Guidelines

Please view the Author Tutorial for guidance on how to submit on Editorial Manager.

Please take the time to familiarise yourself with the policies and processes below. If you still have any questions, please do not hesitate to ask our editorial staff (tel.: +27 (0)21 532 1281, email: submissions@hmpg.co.za).

SAMJ policies

- Types of articles considered by the SAMJ
- Article Processing Charges
- Authorship
- Conflict of interest
- Research ethics committee approval
- Clinical trials
- Protection of patient's rights to privacy
- Copyright notice
- Privacy statement
- Ethnic classification
- CPD

Manuscript preparation

- Preparing an article for anonymous review
- General article format/layout
- Preparation notes by article type
- Illustrations
- Tables
- References

From submission to acceptance



click here for eBook version

POPULAR ARTICLES

» Antibiotic use and resistance: Knowledge, attitudes and perceptions among primary care prescribers in South Africa

» Compulsory community service for doctors in South Africa: A 15-year review

» Infant feeding practices in Soweto, South Africa: Implications for healthcare providers

» Mortality analysis of people with severe mental illness transferred from long-stay hospital to alternative care in the Life Esidimeni tragedy

» Alcohol marketing and adolescent alcohol consumption: Results from the International Alcohol Control study (South Africa)

- Submission and peer-review
- Production process
- Changing contact details or authorship

Publication

- Online versus print
- Errata and retractions
- Indexing

SAMJ Policies

Type of articles considered by the SAMJ

The *SAMJ* will no longer limit the articles accepted to those that have 'general medical content', but is intending to capture the spectrum of medical and health sciences, grouped by relevance to the country's burdens of disease. This content will include research in the social sciences and economics that is relevant to the medical issues around our burden of disease. Please see 'A new vision for the *SAMJ* – and a call for papers' for a full discussion of the new directions for the *SAMJ*.

We accept the following types of articles:

- Research
- Reviews
- Clinical trials
- Editorials
- In Practice (Previously Forum incl. Case Reports)
- Correspondence
- Obituaries
- Book reviews
- Ad hoc supplements e.g. guidelines, conference/congress abstracts, Festschrifts*

The following articles are by invitation only:

- Guest editorial
- Continuing Medical Education (CME)

*Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Publication Fees

All articles published in the *South African Medical Journal* are open access and freely available online upon publication. This is made possible by applying a business model to offset the costs of peer review management, copyediting, design and production, by charging a publication fee of R5 250 (ex vat) for each research article published. The charge applies only to **Research** articles submitted after 1 March 2017. The publication fee is standard and does not vary based on length, colour, figures, or other elements.

When submitting a Research article to the *SAMJ*, the submitting author must agree to pay the publication fee should the article be accepted for publication. The publicaiton fee is payable when your manuscript is editorially accepted and before production commences for publication. The submitting author will be notified that payment is due and given details on the available methods of payment. Prompt payment is advised; the article will not enter into production until payment is received.
Queries can be directed to claudian@hmpg.co.za.

Please refer to the section on 'Sponsored Supplements' regarding the publication of supplements, where a charge is applicable. Queries can be directed to dianes@hmpg.co.za or claudian@hmpg.co.za

Authorship

Tweets by @SAMJ_online

SAMJ SA Medical @SAMJ_or

The June 2017 issu the South African M Journal has been published online #openaccess at samj.org.za #SAMJ

May 3

SAMJ SA Medical @SAMJ_or

The November 201 of the South Africar Medical Journal ha: published online #openaccess at samj.org.za #SAMJ

Nov

SAMJ SA Medical @SAMJ_or

The July 2016 issue South African Medi

Embed View

KEYWORDS

AIDS Africa Antibiotic resistance Book review Children Epidemiology Ethics Guidelines HIV HIV/AIDS Influenza Malaria Mental health National Health Insurance South Africa Stroke Trauma Tuberculosis children epidemiology pregnancy

Named authors must consent to publication. Authorship should be based on: (*i*) substantial contribution to conceptualisation, design, analysis and interpretation of data; (*ii*) drafting or critical revision of important scientific content; or (*iii*) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to www.icmje.org)

If authors' names are added or deleted after submission of an article, or the order of the names is changed, all authors must agree to this in writing.

Please note that co-authors will be requested to verify their contribution upon submission. Non-verification may lead to delays in the processing of submissions. Author contributions should be listed/described in the manuscript.

Conflicts of interest

Conflicts of interest can derive from any kind of relationship or association that may influence authors' or reviewers' opinions about the subject matter of a paper. The existence of a conflict – whether actual, perceived or potential – does not preclude publication of an article. However, we aim to ensure that, in such cases, readers have all the information they need to enable them to make an informed assessment about a publication's message and conclusions. We require that both authors and reviewers declare all sources of support for their research, any personal or financial relationships (including honoraria, speaking fees, gifts received, etc) with relevant individuals or organisations connected to the topic of the paper, and any association with a product or subject that may constitute a real, perceived or potential conflict of interest. If you are unsure whether a specific relationship constitutes a conflict, please contact the editorial team for advice. If a conflict remains undisclosed and is later brought to the attention of the editorial team, it will be considered a serious issue prompting an investigation with the possibility of retraction.

Research ethics committee approval

Authors must provide evidence of Research Ethics Committee approval of the research where relevant. Ensure the correct, full ethics committee name and reference number is included in the manuscript.

If the study was carried out using data from provincial healthcare facilities, or required active data collection through facility visits or staff interviews, approval should be sought from the relevant provincial authorities. For South African authors, please refer to the guidelines for submission to the National Health Research Database. Research involving human subjects must be conducted according to the principles outlined in the Declaration of Helsinki. Please refer to the National Department of Health's guideline on Ethics in Health research: principles, processes and structuresto ensure that the appropriate requirements for conducting research have been met, and that the HPCSA's General Ethical Guidelines for Health Researchershave been adhered to.

Clinical trials

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. All clinical trial reports must also contain a data sharing statement as per the recommendations of the ICMJE. Statements are to indicate:

- whether individual deidentified participant data will be shared;
- what data in particular will be shared; whether additional, related documents will be available;
- when the data will become available and for how long; by what access criteria data will be shared.

Please see the ICJME announcement for further details and illustrative examples of data sharing statements: ICMJE Data Sharing Statements for Clinical Trials

Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The SAMJ therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Protection of rights to privacy

Patient

Information that would enable identification of individual patients should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) has given informed written consent for publication and distribution. We further recommend that the published article is disseminated not only to the involved researchers but also to the patients/participants from whom the data was drawn. Refer to Protection of Research Participants. The signed consent form should be submitted with the manuscript to enable verification by the editorial team.

Other individuals

Any individual who is identifiable in an image must provide written agreement that the image may be used in that context in the *SAMJ*.

Copyright notice

Copyright remains in the Author's name. The work is licensed under a Creative Commons Attribution - Noncommercial Works License. Authors are required to complete and sign an Author Agreement form that outlines Author and Publisher rights and terms of publication. The **Author Agreement form** should be uploaded along with other submissions files and any submission will be considered incomplete without it.

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement. The *SAMJ* does not hold itself responsible for statements made by the authors.

Previously published images

If an image/figure has been previously published, permission to reproduce or alter it must be obtained by the authors from the original publisher and the figure legend must give full credit to the original source. This credit should be accompanied by a letter indicating that permission to reproduce the image has been granted to the author/s. This letter should be uploaded as a supplementary file during submission.

Privacy statement

The *SAMJ* is committed to protecting the privacy of its website and submission system users. The names, personal particulars and email addresses entered in the website or submission system will not be made available to third parties without the user's permission or due process. By registering to use the website or submission system, users consent to receive communication from the *SAMJ* or its publisher HMPG on matters relating to the journal or associated publications. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

Ethnic/race classification

Use of racial or ethnicity classifications in research is fraught with problems. If you choose to use a research design that involves classification of participants based on race or ethnicity, or discuss issues with reference to such classifications, please ensure that you include a detailed rationale for doing so, ensure that the categories you describe are carefully defined, and that socioeconomic, cultural and lifestyle variables that may underlie perceived racial disparities are appropriately controlled for. Please also clearly specify whether race or ethnicity is classified as reported by the patient (self-identifying) or as perceived by the investigators. Please note that is not appropriate to use self-reported or investigator-assigned racial or ethnic categories for genetic studies.

Continuing Professional Development (CPD)

SAMJ is an HPCSA-accredited service provider of CPD materials. Principal authors can earn up to 15 CPD continuing education units (CEUs) for publishing an article; co-authors are eligible to earn up to 5 CEUs; and reviewers of articles can earn 3 CEUs. Each month, *SAMJ* also publishes a CPD-accredited questionnaire relating to the academic content of the journal. Successful completion of the questionnaire with a pass rate of 70% will earn the reader 3 CEUs. Administration of our CPD programme is managed by Medical Practice Consulting. To complete questionnaires and obtain certificates, please visit MRP Consulting

Manuscript preparation

Preparing an article for anonymous review

To ensure a fair and unbiased review process, all submissions are to include an anonymised version of the manuscript. The exceptions to this are Correspondence, Book reviews and Obituary submissions.

Submitting a manuscript that needs additional blinding can slow down your review process, so please be sure to follow these simple guidelines as much as possible:

- An anonymous version should not contain any author, affiliation or particular institutional details that will enable identification.
- Please remove title page, acknowledgements, contact details, funding grants to a named person, and any running headers of author names.
- Mask self-citations by referring to your own work in third person.

General article format/layout

Accepted manuscripts that are not in the correct format specified in these guidelines will be returned to the author(s) for correction, which will delay publication.

General:

- Manuscripts must be written in UK English.
- The manuscript must be in Microsoft Word format. Text must be single-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes).
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Include sections on Acknowledgements, Conflict of Interest, Author Contributions and Funding sources. If none is applicable, please state 'none'.
- Scientific measurements must be expressed in SI units except: blood pressure (mmHg) and haemoglobin (g/dL).
- Litres is denoted with an uppercase L e.g. 'mL' for millilitres).

- Units should be preceded by a space (except for % and ºC), e.g. '40 kg' and '20 cm' but '50%' and '19ºC'.
- Please be sure to insert proper symbols e.g. μ not u for micro, a not a for alpha, b not B for beta, etc.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- If you wish material to be in a box, simply indicate this in the text. You may use the table format –this is the *only* exception. Please DO NOT use fill, format lines and so on.

SAMJ is a generalist medical journal, therefore for articles covering genetics, it is the responsibility of authors to apply the following:

- Please ensure that all genes are in italics, and proteins/enzymes/hormones are not.

- Ensure that all genes are presented in the correct case e.g. TP53 not Tp53.

**NB: Copyeditors cannot be expected to pick up and correct errors wrt the above, although they will raise queries where concerned.

- Define all genes, proteins and related shorthand terms at first mention, e.g. '188del11' can be glossed as 'an 11 bp deletion at nucleotide 188.'

- Use the latest approved gene or protein symbol as appropriate:
  - Human Gene Mapping Workshop (HGMW): genetic notations and symbols
  - HUGO Gene Nomenclature Committee: approved gene symbols and nomenclature
  - OMIM: Online Mendelian Inheritance in Man (MIM) nomenclature and instructions
  - Bennet et al. Standardized human pedigree nomenclature: Update and assessment of the recommendations of the National Society of Genetic Counselors. J Genet Counsel 2008;17:424-433: standard human pedigree nomenclature.

Preparation notes by article type

- Research
- Editorials
- CME
- In Practice and Case reports
- Reviews
- Clinical trials
- Correspondence
- Obituaries
- Book reviews
- Guidelines

Research

Guideline word limit: 4 000 words

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: Introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important clinical question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. Describe the study methods in as much detail as possible so that others would be able to replicate the study should they need to. Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section, which should consider primary outcomes first before any secondary or tertiary findings or post-hoc analyses. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

Select figures and tables for your paper carefully and sparingly. Use only those figures that provided added value to the paper, over and above what is written in the text.

Do not replicate data in tables and in text .

Structured abstract

- This should be 250-400 words, with the following recommended headings:
  - **Background:** why the study is being done and how it relates to other published work.
  - **Objectives:** what the study intends to find out
  - **Methods:** must include study design, number of participants, description of the intervention, primary and secondary outcomes, any specific analyses that were done on the data.
  - **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
  - **Conclusion:** must be supported by the data, include recommendations for further study/actions.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors.
- Do not include any references in the abstracts.

Here is an example of a good abstract.

Main article

All articles are to include the following main sections: Introduction/Background, Methods, Results, Discussion, Conclusions.

The following are additional heading or section options that may appear within these:

- Objectives (within Introduction/Background): a clear statement of the main aim of the study and the major hypothesis tested or research question posed
- Design (within Methods): including factors such as prospective, randomisation, blinding, placebo control, case control, crossover, criterion standards for diagnostic tests, etc.
- Setting (within Methods): level of care, e.g. primary, secondary, number of participating centres.
- Participants (instead of patients or subjects; within Methods): numbers entering and completing the study, sex, age and any other biological, behavioural, social or cultural factors (e.g. smoking status, socioeconomic group, educational attainment, co-existing disease indicators, etc)that may have an impact on the study results. Clearly define how participants were enrolled, and describe selection and exclusion criteria.
- Interventions (within Methods): what, how, when and for how long. Typically for randomised controlled trials, crossover trials, and before and after studies.
- Main outcome measures (within Methods): those as planned in the protocol, and those ultimately measured. Explain differences, if any.

Results

- Start with description of the population and sample. Include key characteristics of comparison groups.
- Main results with (for quantitative studies) 95% confidence intervals and, where appropriate, the exact level of statistical significance and the number need to treat/harm. Whenever possible, state absolute rather than relative risks.
- Do not replicate data in tables and in text.
- If presenting mean and standard deviations, specify this clearly. Our house style is to present this as follows:
- E.g.: The mean (SD) birth weight was 2 500 (1 210) g. Do not use the ± symbol for mean (SD).
- Leave interpretation to the Discussion section. The Results section should just report the findings as per the Methods section.

Discussion

Please ensure that the discussion is concise and follows this overall structure – sub-headings are not needed:

- Statement of principal findings
- Strengths and weaknesses of the study
- Contribution to the body of knowledge
- Strengths and weaknesses in relation to other studies
- The meaning of the study – e.g. what this study means to clinicians and policymakers
- Unanswered questions and recommendations for future research

Conclusions

This may be the only section readers look at, therefore write it carefully. Include primary conclusions and their implications, suggesting areas for further research if appropriate. Do not go beyond the data in the article.

Editorials

Guideline word limit: 1 000 words

These opinion or comment articles are usually commissioned but we are happy to consider and peer review unsolicited editorials. Editorials should be accessible and interesting to readers without specialist knowledge of the subject under discussion and should have an element of topicality (why is a comment on this issue relevant now?) There should be a clear message to the piece, supported by evidence.

Please make clear the type of evidence that supports each key statement, e.g.:

- expert opinion
- personal clinical experience
- observational studies
- trials
- systematic reviews.

CME (by invite only)

CME is intended to provide readers with practical, up-to-date information on medical and related matters. It is aimed at those who are not specialists in the field.

From January 2016, all CME articles will be printed in full in the *SAMJ*. Please try to adhere strictly to the guidelines on word count as we have a page limit for the print issue of the *SAMJ*. We reserve the right to place some tables and reference lists online if this is necessary for space.

In practice, this means that each CME topic usually covers two issues of the print issue of the *SAMJ*.

The guest editor, in consultation with the editor, is responsible for convening a team of authors, deciding on the subjects to be covered and for reviewing the manuscripts submitted. The suggestion is for 4 - 5 articles, although there is some room for flexibility contingent on discussions with the editor.

For queries about these guidelines please feel free to contact the CME editor, Dr Bridget Farham, by email (ugqirha@iafrica.com) or telephone (+27 (0)21 789 2331).

Review process

The guest editor reviews the articles and returns them to the CME editor for review and final approval.

Guest editorials

Guideline word limit: 1 000 words

- Include the guest editor's personal details (qualifications, positions, affiliation, e-mail address, and a short personal profile (50words)).
- If possible, include a photograph of the author(s) at high enough resolution for print. It is preferable to provide two guest editorials, one for each issue, so that the content of the articles in each issue is covered.

Articles

Guideline word limit: 2 000 - 3 000 words

- Each article requires an abstract of ±200 words.

- The editor reserves the right to shorten articles but will send a substantially shortened article back for author approval.

Personal details

Please supply: Your qualifications, position and affiliations and MP number (used for CPD points); Address, telephone number and fax number, and your e-mail address; and a short personal profile (50words)and a few words about your current fields of interest.

In Practice

Guideline word limit: 2 000 - 3 000words

This section includes articles that would previously have been accepted into the Forum section, and case reports.

In practice articles are those that draw attention to specific issues of clinical, economic or political interest regarding medicine and healthcare in southern Africa. They are assigned to a topic:

- Case report
- Clinical practice
- Clinical alert
- Issues in medicine
- Issues in public health
- Healthcare delivery
- Consensus/Position statement
- Medicine and the environment
- Medicine and the law
- Cochrane corner

An In Practice article should follow the following format – sub-headings are not necessary, but may be used for clarity:

- Author affiliations and qualifications: to be the same as for Research. Provide all authors' names and initials, qualifications and full affiliations, and corresponding author.
- Short abstract: does not need to be structured, but should capture the essential features of the article
- Introduction: the reason for the article and the issue being addressed
- Recent research, discussion, local policy around the issue – include your own research where appropriate
- All statements should be referenced and, if opinion only, this should be stated
- Discussion: how this article adds to the discussion around a particular topic
- If a clinical practice or policy point is at issue, this needs to be emphasised, using a box with highlights if appropriate.

Essentially In practice is an opportunity for a more discursive approach to topics of clinical, economic or political importance in southern African health systems. It is not an opportunity to put forward unsubstantiated opinions!

Case reports

The *SAMJ* has recently started to accept case reports. The cases must come from Africa, preferably southern Africa unless the condition is common to all African countries, and must be either a completely new description of a clinical condition or result (use Google!) or a case that highlights important practice or management issues.

Please use the following format for case reports:

- Title of case: do not include the words 'a case report' in the title
- Summary/abstract: up to 150 words summarising the case presentation and outcome
- Background: why is this case important and why did you write it up?
- Case presentation: presenting features, medical, social, family history as appropriate
- Case management: should be according to best practice, and if not, please explain why
- Investigations, if relevant: save space by simply saying 'normal' if, for example, renal function was completely normal, rather than listing normal

results, highlight the abnormal – or indeed the normal if this is clinically significant
- Differential diagnosis, if relevant
- Treatment, if relevant
- Outcome and follow-up
- Discussion – a VERY BRIEF review of similar published cases
- Teaching points: 3 - 5 bullet points
- References: as per the *SAMJ* house style
- Tables and figures: keep to a minimum. Use clinical images where relevant – we need hi-res versions for print, and identifiable persons must have a consent form
- Patient consent: please include a statement about patient consent to a written case report. This should be uploaded as a supplementary file.

Clinical trials

Guideline word limit: 4000 words

As per the recommendations published by the International Committee of Medical Journal Editors (ICMJE), clinical trial research is any research that assigns individuals to an intervention, with or without a concurrent comparison/control group to study the cause-and-effect relationship between the intervention and health outcomes. All clinical trials should be registered with the appropriate national clinical trial registry (or any international primary register, if relevant), and the trial registration number should be cited at the end of the abstract. Since 1st December 2005, all clinical trials conducted in South Africa have been required to be registered in the South African National Clinical Trials Register. The *SAMJ* therefore requires that clinical trials be registered in the relevant public trials registry at or before the time of first patient enrollment as a condition for publication. The trial registry name and registration number must be included in the manuscript.

Please refer to the general guidelines for all papers at the top of this article for additional requirements with respect to ethics approval, funding, author contributions, etc. The format of original research articles should be followed for reporting of clinical trial results.

Review articles

Guideline word limit: 4 000 words

These are welcome, but should be either commissioned or discussed with the Editor before submission. A review article should provide a clear, up-to-date account of the topic and be aimed at non-specialist hospital doctors and general practitioners.

Please ensure that your article includes:

- Abstract: unstructured, of about 100-150 words, explaining the review and why it is important
- Methods: Outline the sources and selection methods, including search strategy and keywords used for identifying references from online bibliographic databases. Discuss the quality of evidence.
- When writing: clarify the evidence you used for key statements and the strength of the evidence. Do not present statements or opinions without such evidence, or if you have to, say that there is little or no evidence and that this is opinion. Avoid specialist jargon and abbreviations, and provide advice specific to southern Africa.
- Personal details: Please supply your qualifications, position and affiliations and MP number (used for CPD points); address, telephone number and fax number, and your e-mail address; and a short personal profile (50 words) and a few words about your current fields of interest.

Correspondence (Letters to the Editor)

Guideline word limit: 500 words

Letters to the editor should relate either to a paper or article published by the SAMJ or to a topical issue of particular relevance to the journal's readership

- May include only one illustration or table

- Must include a correspondence address.

Book reviews

Guideline word limit: 400 words

Should be about 400 words and must be accompanied by the publication details of the book. Provide a hi-res image of the cover if possible (with permission from the copyright holder).

Obituaries

Guideline word limit: 400 words

Should be offered within the first year of the practitioner's death, and may be accompanied by a photograph.

Guidelines

Guidelines should always be discussed with the Editor prior to submission.

Because of the intensive review process required to ensure Guidelines are independent, evidence-based and free from commercial bias, they are usually published as a supplement to the *SAMJ*, the costs of which must be covered by sponsorship, advertising or payment by the guideline authors/association. We will provide a quote based on the expected length of the guideline and whether it is to appear online only, or in print, which must be accepted by the body putting the guidelines together before submitting the work to the SAMJ.

The Editor reserves the right to determine the scheduling of supplements. Understandably, a delay in publication must be anticipated dependent upon editorial workflow.

All guidelines should include a clear, transparent statement about all sources of funding and an explicit, clear statement of conflicts of interest of any of the participants in the guidelines about industry funding for lectures, research, conference participation etc.

All guidelines should be structured according to Agree II.

Please access this website before putting the guidelines together, download the Agree 11 instrument and use this to put the guidelines together.

All submitted guidelines will be sent to the local Agree II appraisal committee for review and must be endorsed by an appropriate body prior to consideration and all conflicts of interest expressed.

A structured abstract not exceeding 400 words (recommended sub-headings: *Background, Recommendations, Conclusion*) is required. Sections and sub-sections must be numbered consecutively (e.g. 1. Introduction; 1.1 Definitions; 2.etc.) and summarised in a Table of Contents.

Illustrations/photos/scans

- If illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.
- Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Fig. 1)'.
- Each figure must have a caption/legend: Fig. 1. Description (any abbreviations in full).
- All images must be of high enough resolution/quality for print.
- All illustrations (graphs, diagrams, charts, etc.) must be in PDF or jpeg form.
- Ensure all graph axes are labelled appropriately, with a heading/description and units (as necessary) indicated. Do not include decimal places if not necessary e.g. 0; 1.0; 2.0; 3.0; 4.0 etc.
- Scans/photos showing a specific feature e.g. *Intermediate magnification micrograph of a low malignant potential (LMP) mucinous ovarian tumour. (H&E stain).* –include an arrow to show the tumour.
- Each image must be attached individually as a 'supplementary file' upon submission (not solely embedded in the accompanying manuscript) and named Fig. 1, Fig. 2, etc.

Tables

- Tables should be constructed carefully and simply for intelligible data representation. Unnecessarily complicated tables are strongly discouraged.
- Large tables will generally not be accepted for publication in their entirety. Please consider shortening and using the text to highlight specific important sections, or offer a large table as an addendum to the publication, but available in full on request from the author
- Embed/include each table in the manuscript Word file - do not provide separately as supplementary files.
- Number each table in Arabic numerals (Table 1, Table 2, etc.) and refer to consecutively in the text.
- Tables must be cell-based (i.e. not constructed with text boxes or tabs) and editable.
- Ensure each table has a concise title and column headings, and include units where necessary.
- Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Do not: Use [Enter] within a row to make 'new rows':

Rather:

Each row of data must have its own proper row:

Do not: use separate columns for *n* and %:

Rather:

Combine into one column, *n* (%):

Do not: have overlapping categories, e.g.:

Rather:

Use <> symbols or numbers that don't overlap:

References

NB: *Only complete, correctly formatted reference lists in Vancouver style will be accepted. Reference lists must be generated manually and not with the use of reference manager software. Endnotes must* ***not*** *be used.*

- Authors must verify references from original sources.
- Citations should be inserted in the text as superscript numbers between square brackets, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6]
- All references should be listed at the end of the article in numerical order of appearance in the Vancouver style (not alphabetical order).
- Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus.
- Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al.
- Volume and issue numbers should be given.
- First and last page, in full, should be given e.g.: 1215-1217 **not** 1215-17.
- Wherever possible, references must be accompanied by a digital object identifier (DOI) link). Authors are encouraged to use the DOI lookup service offered by CrossRef:
    - On the Crossref homepage, paste the article title into the 'Metadata search' box.
    - Look for the correct, matching article in the list of results.
    - Click Actions > Cite
    - Alongside 'url =' copy the URL between { }.
    - Provide as follows, e.g.: https://doi.org/10.7196/07294.937.98x

Some examples:

- *Journal references:* Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. http://dx.doi.org/10.1000/hgjr.182

- *Book references:* Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101.
- *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.
- *Internet references:* World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: WHO, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).
- Legal references

- Government Gazettes:

National Department of Health, South Africa. National Policy for Health Act, 1990 (Act No. 116 of 1990). Free primary health care services. Government Gazette No. 17507:1514. 1996.

In this example, 17507 is the Gazette Number. This is followed by :1514 - this is the notice number in this Gazette.

- Provincial Gazettes:

Gauteng Province, South Africa; Department of Agriculture, Conservation, Environment and Land Affairs. Publication of the Gauteng health care waste management draft regulations. Gauteng Provincial Gazette No. 373:3003, 2003.

- Acts:

South Africa. National Health Act No. 61 of 2003.

- Regulations to an Act:

South Africa. National Health Act of 2003. Regulations: Rendering of clinical forensic medicine services. Government Gazette No. 35099, 2012. (Published under Government Notice R176).

- Bills:

South Africa. Traditional Health Practitioners Bill, No. B66B-2003, 2006.

- Green/white papers:

South Africa. Department of Health Green Paper: National Health Insurance in South Africa. 2011.

- Case law:

Rex v Jopp and Another 1949 (4) SA 11 (N)

Rex v Jopp and Another: Name of the parties concerned

1949: Date of decision (or when the case was heard)

(4): Volume number

SA: SA Law Reports

11: Page or section number

(N): In this case Natal - where the case was heard. Similarly, (C) woud indicate Cape, (G) Gauteng, and so on.

NOTE: no . after the v

- *Other references (e.g. reports) should follow the same format:* Author(s). Title. Publisher place: Publisher name, year; pages.
- Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'.
- Unpublished observations and personal communications in the text must **not** appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

From submission to acceptance

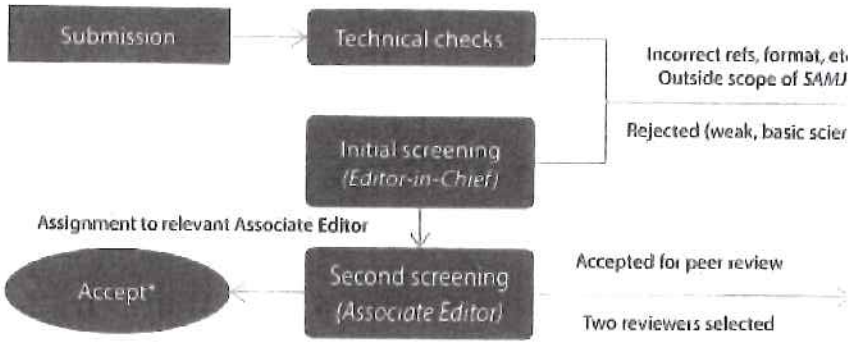
Submission and peer-review

To submit an article:

- Please ensure that you have prepared your manuscript in line with the SAMJ requirements.
- All submissions should be submitted via Editorial Manager
- The following are required for your submission to be complete:
  - Anonymous manuscript (unless otherwise stated)
  - **Author Agreement form**
  - Manuscript
  - Any supplementary files: figures, datasets, patient consent form, permissions for published images, etc.

- Once the submission has been successfully processed on Editorial Manager, it will undergo a technical check by the Editorial Office before it will be assigned to an editor who will handle the review process. If the author guidelines have not been appropriately followed, the manuscript may be sent back to the author for correcting.

Peer-review process



*Manuscripts accepted at this point are limited to Editorials, Correspondence, Obituaries, Book reviews, Abstrac
**Some minor revisions may be requested

Production process

The following process will follow:

1. An accepted manuscript is passed to a Managing Editor to assign to a copyeditor (CE).
2. The CE copyedits in Word, working on house style, format, spelling/grammar/punctuation, sense and consistency, and preparation for typesetting.
3. If the CE has an author queries, he/she will contact the corresponding author and send them the copyedited Word doc, asking them to solve the queries by means of track changes or comment boxes.
4. The authors are typically asked to respond within 1-3 days. Any comments/changes must be clearly indicated e.g. by means of track changes. Do not work in the original manuscript - work in the copyedited file sent to you and make your changes clear.
5. The CE will finalise the article and then it will be typeset.
6. Once typeset, the CE will send a PDF of the file to the authors to complete their final check, while simultaneously sending to the 2nd-eye proofreader.

7. The authors are typically asked to complete their final check and sign-off within 1-2 days. No major additional changes can be accommodated at this point.
8. The CE implements the authors' and proofreader's mark-ups, finalises the file, and prepares it for the upcoming issue.

Changing contact details or authorship

Please notify the Editorial Department of any contact detail changes, including email, to facilitate communication.

Publication

Online v. print

The *SAMJ* is an online journal. The online version of the journal is the one that has the widest circulation, is indexed by bibliographic databases including PubMed and SciELO, and is accessible in academic libraries. A printed edition , containing material selected by the Editor is also published each month and distributed to the membership of the South African Medical Association.

Online

- The full text of all accepted articles is published in full online, open access.
- Citation information of each article is based on its online publication.
- You may want to make use of the advantages of online publication e.g. specify web links to other sources, images, data or even a short video.

Print

- Not all articles will be selected for print.
- An article may be selected for print in a different month from that in which it was published online.
- Research articles will appear *in abstract form only*, if selected for a print edition.

Errata and retractions

Errata

Should you become aware of an error or inaccuracy in yours or someone else's contribution after it has been published, please inform us as soon as possible via an email to publishing@hmpg.co.za,including the following details:

- Journal, volume and issue in which published
- Article title and authors
- Description of error and details of where it appears in the published article
- Full detail of proposed correction and rationale

We will investigate the issue and provide feedback. If appropriate, we will correct the web version immediately, and will publish anerratum in the next issue. The correction will be indexed, as PubMed has a function for linking errata back to the original article. All investigations will be conducted in accordance with guidelines provided by the Committee on Publication Ethics (COPE).

Retractions

Retraction of an article is the prerogative of either the original authors or the editorial team of HMPG. Should you wish to withdraw your article before publication, we need a signed statement from all the authors.

Should you wish to retract your published article, all authors have to agree in writing before publication of the retraction.

Send an email to publishing@hmpg.co.za, including the following details:

- Journal, volume and issue to which article was submitted/in which article was published

- Article title and authors
- Description of reason for withdrawal/retraction.

We will make a decision on a case-by-case basis upon review by the editorial committee in line with international best practices. Comprehensive feedback will be communicated with the authors with regard to the process. In case where there is any suspected fraud or professional misconduct, we will follow due process as recommended by the Committee on Publication Ethics (COPE), and in liaison with any relevant institutions.

When a retraction is published, it will be linked to the original article.

Indexing

The *SAMJ* has an impact factor of 1.5.

Published articles are covered by the following major indexing services. As such articles published in the *SAMJ* are immediately available to all users of these databases, guaranteed a global and African audience:

- Index Medicus (Medline/PubMed)
- ExcerptaMedica (EMBASE)
- Biological Abstracts (BIOSIS)
- Science Citation Index (SciSearch)
- Current Contents/Clinical Medicine
- Scopus
- AIM
- AJOL
- Crossref
- Sabinet
- Scielo

Sponsored supplements

Contact claudian@hmpg.co.za for information on submitting ad hoc/commissioned supplements, including guidelines, conference/congress abstracts, Festschrifts, etc.

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

1. Named authors consent to publication and meet the requirements of authorship as set out by the journal.
2. The submission has not been previously published, nor is it before another journal for consideration.
3. The text complies with the stylistic and bibliographic requirements in **Author Guidelines**.
4. The manuscript is in Microsoft Word document format. The text is single-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
5. Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (PDF or jpeg). These must be submitted individually as 'supplementary files' (not solely embedded in the manuscript).
6. For illustrations/figures or tables that have been published elsewhere, the author has obtained written consent to republication from the copyright holder.
7. Where possible, references are accompanied by a digital object identifier (DOI).
8. An abstract has been included where applicable.
9. The research was approved by a Research Ethics Committee (if applicable)
10. Any conflict of interest (or competing interests) is indicated by the author(s).

Copyright Notice

Copyright of published material remains in the Authors' name. This allows authors to use their work for their own non-commercial purposes without seeking

permission from the Publisher, subject to properly acknowledging the Journal as the original place of publication.

Authors are free to copy, print and distribute their articles, in full or in part, for teaching activities, and to deposit or include their work in their own personal or institutional database or on-line website. Authors are requested to inform the Journal/Publishers of their desire/intention to include their work in a thesis or dissertation or to republish their work in any derivative form (but not for commercial use).

Material submitted for publication in the *SAMJ* is accepted provided it has not been published or submitted for publication elsewhere. Please inform the editorial team if the main findings of your paper have been presented at a conference and published in abstract form, to avoid copyright infringement.

Privacy Statement

The *SAMJ* is committed to protecting the privacy of the users of this journal website. The names, personal particulars and email addresses entered in this website will be used only for the stated purposes of this journal and will not be made available to third parties without the user's permission or due process. Users consent to receive communication from the *SAMJ* for the stated purposes of the journal. Queries with regard to privacy may be directed to publishing@hmpg.co.za.

The South African Medical Journal | Online ISSN: 2078-5135 | Print ISSN: 0256-9574 | © 2014 Health & Medical Publishing Group

This journal is protected by a Creative Commons Attribution - NonCommercial Works License (CC BY-NC 4.0) | Read our privacy policy.

Our Journals: South African Medical Journal | African Journal of Health Professions Education | South African Journal of Bioethics and Law | South African Journal of Child Health | Southern African Journal of Critical Care | South African Journal of Obstetrics and Gynaecology |