SELECTIVE SCREENING OF INBORN ERRORS OF METABOLISM AMONG CLINICALLY SUSPECTED CASES IN CHILDREN AGED 1 TO 18 YEARS AT THE KENYATTA NATIONAL HOSPITAL

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DECLARATION

This dissertation is my original work and has not been published elsewhere or presented for a degree in any other university.

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ABBREVIATIONS

AA	Amino Acid
CoQ	Coenzyme Q10
CDG	Congenital Disorders of Glycosylation
FAO	Fatty Acid Oxidation
IEMs	Inborn Errors of Metabolism
IMDs	Inherited Metabolic Diseases
LSD	Lysosomal Storage Disorders
NBS	New-born Screening
PC	Pyruvate Carboxylase
PBD	Peroxisomal disorders
PDH	Pyruvate Dehydrogenase
PPP	Pentose Phosphate Pathway
NADPH	Nicotinamide adenine dinucleotide phosphate
VLCFA	Very Long Chain Fatty Acids
MCADD	Medium Chain Acyl CoA Dehydrogenase Deficiency

DEFINITIONS OF TERMS

Catabolism – this is the breakdown of complex molecules to smaller unites that may either be used in other anabolic reactions or to create energy for the cell

Krebs cycle – a series of chemical reactions in aerobic that breakdown fats, proteins, or carbohydrates to produce energy through oxidation of acetyl co-A

Metabolism – these are chemical reactions that occur in the living organisms that aim to sustain life e.g., respiration, digestion

Monogenic – involving or controlled by only one gene

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

List of Tables

List of Figures

ABSTRACT

Background: Inborn Errors of metabolism comprises a group of disorders which are as a result of a disfunction in the metabolic pathway. Waters D et al estimated global birth prevalence of Inborn errors of metabolism is 50.9 per 100 000 live births while the estimated case fatality rate is 33% or higher(1). No study has been done in Kenya to determine the prevalence of inborn errors of metabolism in the Kenyan population.

Study Justification and Utility: Despite the description of inborn errors of metabolism across the world, there remains no data available in the Kenyan population. This study sought to determine the prevalence of inborn errors of metabolism in a Kenyan hospital as well provide the clinical characteristics of the Kenyan children suffering from these conditions.

Objectives: The main objective of this study was to determine the prevalence of inborn errors of metabolism among clinically suspected cases in children aged 1 to 18 years at the Kenyatta National Hospital. This study also determined the characteristics and the spectrum range of inborn errors of metabolism in children aged 1 to 18 years at the Kenyatta National Hospital.

Study Design: This is an observational cross-sectional study.

Methods: It was carried out at the four general paediatric wards and outpatient clinics at the Kenyatta National Hospital, a national referral teaching and research hospital located in Nairobi Kenya. The study population included children aged 0 months 18 years with inborn errors of metabolism at Kenyatta National hospital. Data collection was be carried out by the principal investigator and a research assistant using patient's history, a short questionnaire and observation.

Data management and analysis: Data collected by questionnaire was coded and analysed using R statistical software. Descriptive statistics included continuous variables e.g., mean with Standard deviation; Median with interquartile. Proportions were used to describe binary categorical variables. Quantitative data was presented in percentages and frequency tables

Results: A high number of patients (22/78 (27%)) were confirmed with 9 different types of IEMs. The most presenting features were intellectual disability and abnormal

posture at 68.2% (n = 15) followed by those with hypotonia at 54.5% (n = 12). The least presenting features were visual impairment, ventricular dysfunction and cataracts among others 4.5% (n = 1). The majority of the patients 40.9% (n = 9) had Mucopolysaccharidosis type 2. The second most prevalent inborn error of metabolism was congenital adrenal hyperplasia 13.6% (n = 3).

Conclusions: The creation of a national screening program for IEMs is essential for early discovery of these potentially treatable illnesses, timely and appropriately timed therapeutic intervention, and the avoidance of severe neurological sequelae.

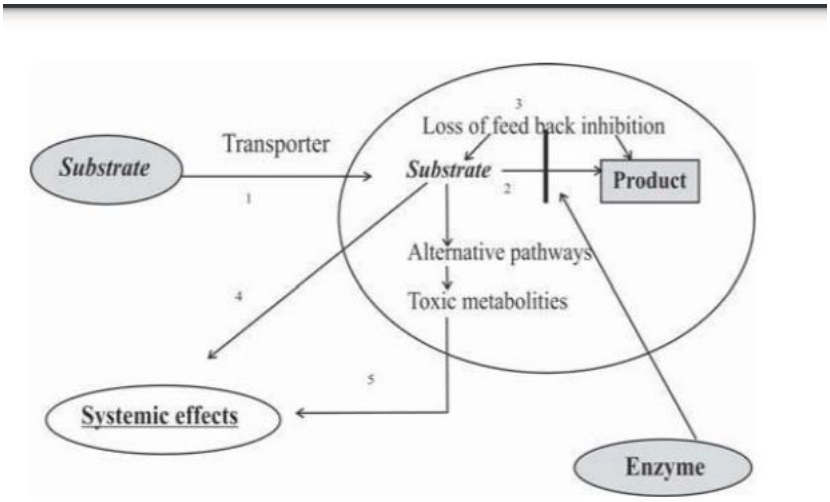
CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

Background

Inborn Errors of metabolism comprises a group of disorders which are as a result of a dysfunction in the metabolic path. Walters D et al estimated global birth prevalence of Inborn errors of metabolism is 50.9 per 100 000 live births while the estimated case fatality rate is 33% or higher (1). Ramao A et al found the mean age at presentation to be 4.3 ± 4.7 years with initial signs being cognitive impairment convulsions, growth retardation, developmental delay and hepatomegaly (2). There is paucity of data in Africa. One 12-year study done in Libya, AlObaidy described 46 metabolic disorders among 55,442 live births including amino acids disorders, carbohydrate disorders lysosomal storage diseases organic aciduria and energy metabolic defects (3). No study has been done in Kenya to determine the prevalence of inborn errors of metabolism in the Kenyan population.

Pathophysiology of Inborn Errors of Metabolism

Inborn Errors of metabolism are caused by a single enzyme deficiency that disrupts one step of a metabolic pathway. This disruption may lead to the accumulation of metabolites preceding the interrupted step.



1. Substrate is transported into a cell with the help of transporter, deficiency of transporter leads to IEM. 2. Substrate is converted to product in the presence of catalyst, if the enzyme is deficient which leads to IEM. 3. The substrate is converted to product, the accumulation of product obtains in case of loss of feed back inhibition leads to metabolic disorders. 4. Due to metabolic defects, substrate is not converted to product and accumulation of substrate leads to systemic effects. 5. If substrate is not converted to product due to enzyme or cofactor deficiency, it enters to alternative pathway and produce toxic metabolites which lead to systemic effects in turn causes presenting features of inborn errors of metabolism.

Source (4)

Figure 1 : Pathophysiology of Inborn Errors of Metabolism

Classification of Inborn Errors of Metabolism

Inborn Errors of Metabolism can be classified into three groups(5). Disorders which give rise to intoxication include errors of amino acid (AA) catabolism (phenylketonuria, maple syrup urine disease, homocystinuria, tyrosinemia, etc.), congenital urea cycle defects (UCD), sugar intolerances (galactosemia, hereditary fructose intolerance), and metal intoxication (Wilson's disease). These are metabolic errors that cause an accumulation of small molecules near the metabolic block, resulting in acute or progressive intoxication in body tissues e.g. in the brain(6). They do not interfere with

prenatal life but present with clinical signs of intoxication after a symptom-free period early in life.

Disorders involving energy metabolism include congenital lactic acidemias, mitochondrial respiratory chain disorders, fatty acid oxidation and ketone body defects.

The third category includes all lysosomal storage disorders (LSD), intracellular trafficking peroxisomal disorders (PBD), and processing disorders such as alpha-1-antitrypsin. These diseases disrupt the re-modelling, synthesis, and catabolism of complex molecules, found in cellular organelles. Symptoms are often chronic, progressive and unrelated to food intake

Clinical Presentation of IEM

IEMs can present as from neonatal age to adulthood(7). Age at clinical presentation and symptoms are not constant and vary according to type of disease and severity of the disease. Age at clinical presentation and symptoms are not constant and vary according to type of disease and severity of the disease. To assess the early manifestations of inborn errors of metabolism, Ramao A et al (2) studied 141 children and found cognitive impairment and seizures were the initial signs and symptoms, followed by growth retardation, neuropsychomotor developmental delay, seizures and hepatomegaly. The main laboratory abnormalities in the diagnosis were hyperammonemia and metabolic acidosis.

The table below shows the symptoms associated with IEM, physical anomalies associated with inborn errors of metabolism and clinical manifestations in neonates (4) as per Rao et al.

Symptoms Indicating Possibility of an IEM	Symptoms indicating strong possibility of an IEM
1. Infant becomes acutely ill after period of normal behaviour and feeding. This may occur within hours or weeks.	1. Persistent or recurrent vomiting. 2. Failure to thrive (failure to gain weight or weight loss).

2. Neonate or infant with seizures and/or hypotonia, especially if seizures are intractable. 3. Neonate or infant with an unusual odour.	3. Apnoea or respiratory distress (tachypnea) 4. Jaundice or hepatomegaly. 5. Lethargy. 6. Coma (Particularly intermittent). 7. Unexplained haemorrhage. 8. Family history of neonatal deaths or of similar illness, especially in siblings. 9. Parental consanguinity. 10. Sepsis (especially E. Coli)

Table 1: Physical anomalies associated with acute onset inborn errors of metabolism (4)

Inborn errors of metabolism can also present in association with some congenital anomalies. Some anomalies associated with IEMs are Ambiguous genitalia, macrocephaly, facial dysmorphia and many more.

The following table shows congenital anomalies associated with possible IEMs.

Anomaly	Possible IEM
1. Ambiguous genitalia. Hair and/or skin problems (alopecia, dermatitis). 2. Structural brain abnormalities (agenesis of corpus callosum, cortical cysts). 3. Macrocephaly. 4. Renal cysts, facial dysmorphia. 5. Facial dysmorphia.	1. Congenital adrenal hyperplasia. 2. Multiple carboxylase deficiency, biotinidase deficiency, arginosuccinic aciduria. 3. Pyruvate dehydrogenase deficiency. 4. Glutaric aciduria, type I. 5. Glutaric aciduria, Type II; (Zellweger syndrome). 6. Galactosemia, Lowe syndrome. 7. Peroxisomal disorders. 8. Sulphite oxidase deficiency, Molybdenum cofactor deficiency.

6. Cataract. 7. Retinopathy. 8. Lens dislocation, seizures. 9. Facial dysmorphia, congenital heart disease, vertebral anomalies.	9. 3-OH-isobutyric CoA deacylase deficiency.

Source (4)

Table 2: congenital anomalies associated with possible IEMs

Family history

Important history details suggestive of IEM include history of maternal eclampsia , family history of consanguinity, unexplained neonatal or infantile deaths, Past medical history of delayed child development, unexplained hypoglycaemia, encephalopathy, protein aversion, self-injurious behaviour, psychiatric symptoms and seizure disorder(8)

Physical examination

The clinical manifestations of IEM may include findings in virtually every system.

Neurologic — Neurologic manifestations of IEM include lethargy, coma, seizures, developmental delay or regression, peripheral neuropathy, abnormalities of tone, motor problems, ataxia, and neuropsychiatric manifestations.

Gastrointestinal — Gastrointestinal presentations of IEM include recurrent episodes of vomiting or dehydration, poor feeding, failure to thrive, decreased gastrointestinal motility, hepatomegaly or hepatosplenomegaly, and jaundice

Gastrointestinal — Gastrointestinal presentations of IEM include recurrent episodes of vomiting or dehydration, poor feeding, failure to thrive, decreased gastrointestinal motility, hepatomegaly or hepatosplenomegaly, and jaundice.

Cardiomyopathy

Ophthalmologic — Ophthalmologic presentations of IEM include cataracts, corneal opacities or clouding, cherry-red spots, retinitis pigmentosa, and dislocated lenses

Dermatologic — Dermatologic manifestations of IEM may include ashes photosensitivity, hyperkeratosis and ichthyosis, skin ulceration, skin angiokeratoma, pearly papules and hypopigmentation

Diagnosis of IEM

Molecular genetic testing

This is the gold standard of diagnosis of IEMs is the use of molecular genetic testing. This involves DNA sequencing(9). There are 2 methods used. The traditional DNA sequencing (sanger sequencing) and a newer more advanced method called Next Generation Sequencing. The CENTOGENE genetic testing panel has as sensitivity of 99.5% and specificity of 99.9%

Laboratory Diagnosis

Routine laboratory tests that should be always ordered when an IEM is suspected
1. Total Blood count
2. Complete blood count with differential
3. Liver function tests
4. Renal function tests
5. Ammonia
6. Blood gases
7. Anion gap
8. Glucose
9. Lactate Urine and blood ketones

Table 3: Routine laboratory tests when suspecting an IEM in a patient with a metabolic stress state

This table represents the most useful routine laboratory tests when suspecting an IEM in a patient with a metabolic stress state. Source (10)

Results of these tests may indicate the underlying pathophysiology and narrow the focus of additional testing to identify a metabolic disorder or category of disorders.

Missed Diagnosis of IEM

Diagnosis of IEMS is a challenge in many countries. In a study by Fatma Zohra Chioukh in Tunisia, 31% of the patients had unidentified IEMs because of difficulty to perform certain analyses(11). Morbidity and mortality can be reduced by early diagnosis, which is not usually the case as demonstrated by Chi-Ju Yang in a 2 year period in China where Tandem Mass spectrometry was used to screen 100,077 neonates(12). In this study 56 out of the 1313 new-borns with suspected IEM were diagnosed with IEM, highlighting the need for suspected cases to be tested for IEM.

Sharma et al concluded that neonates with inborn errors of metabolism present with severe illness characterised by poor feeding, drowsiness, lethargy or hypotonia(13). These clinical manifestations can also be attributed to more common illnesses which present at this time e.g., neonatal sepsis, birth asphyxia or congenital heart disease. As a result, misclassification of the illness occurs.

In a systematic literature review of all reports of IEM presenting as cerebral palsy, Leach et al found that 57% of treatable IEM were reported as cerebral palsy. This study showed that IEM can present as "CP mimics" yet would have responded to targeted therapy(14).

Similarly, Martins noted that although greater than 300 human diseases are due to IEM the incidence of the same has not been rising in parallel because diagnosis is often missed(15). He related the high rate of misdiagnosis to the conception that individually, the diseases are rare, thus diagnosis is only considered after ruling out other more common conditions. In many cases, the clinical features are nonspecific or intermittent; and can be attributed to other frequently encountered conditions. Furthermore, diagnosis in many cases is reliant on the collection of blood and urine during specific times, which is most often missed. Martins also cited the delay in occurrence of severe symptoms until adulthood, e.g., propionic academia which presents infrequently with vomiting in childhood but in adulthood manifests with chorea and dementia. Finally, misdiagnosis of IEM is also attributed to the lack of

availability of diagnostic methods. This is because definitive diagnosis of IEM is dependent on specialised enzyme assays or the identification of molecular defects.

Assessment of Inborn Errors of Metabolism

Methods of assessment of Inborn Errors of Metabolism

Investigation	**Advantages**	**Disadvantages**
1. Genetic sequencing	• Gold standard	• Expensive
2. Enzyme Assay	• Diagnostic accuracy (97.6%) Jyotsna	• Inaccurate
3. Tandem Mass Spectrometry	• Easy to use • inexpensive	• Not always diagnostic

Table 4: Methods of assessment of Inborn Errors of Metabolism

Studies on Inborn Errors of Metabolism

STUDY DESCRIPTION			KEY FINDINGS
Country, Author Year	Study Population	Setting, Study design	(Mean=M) (Prevalence of elevated SF (%) =P
Global Donald Waters et all 2018	49 studies	systematic literature review of birth prevalence and case fatality of IEM globally	50.9 per 100 000 live births
Zhang et al 2019	42,257 new-borns	A 7-Year Report of Spectrum of Inborn Errors of Metabolism on Full-Term and Premature Infants in a Chinese	The prevalence of IEMs in total, full-term, and premature infants was 1:640, 1:446, and 1:2,584, respectively

STUDY DESCRIPTION			KEY FINDINGS
Country, Author Year	Study Population	Setting, Study design	(Mean=M) (Prevalence of elevated SF (%) =P
		Neonatal Intensive Care Unit	
Fatemeh Keyfi et al 2018	13,327 infants	Frequency of Inborn Errors of Metabolism in a North-eastern Iranian Sample with High Consanguinity Rates	60 different IEMs were diagnosed in 1,118 infants
A Applegarth 2000	400,000 births	Incidence of inborn errors of metabolism in British Columbia, 1969-1996	40 cases per 100 000 live births
Laila A. et al	3380	Selective screening for inborn errors of metabolism by tandem mass spectrometry in Egyptian children: A 5-year report	6% were confirmed with 17 different types of IEMs

Table 5: Studies on Inborn Errors of Metabolism

CHAPTER 2: STUDY JUSTIFICATION, RESEARCH QUESTIONS AND STUDY OBJECTIVES

Study Justification

Despite the description of inborn errors of metabolism across the world, there remains no data available in the Kenyan population. This study sought to determine the prevalence of inborn errors of metabolism in a Kenyan hospital as well provide the clinical characteristics of the Kenyan children suffering from these conditions.

Inborn metabolic errors are one of the most common forms of genetic defects, according to anecdotal evidence, and are associated with a variety of diseases. The prevalence of in KNH, on the other hand, is unknown. These issues are compounded by severe nutritional issues and a wide pool of idiopathic disorders. The control of inborn errors of metabolism could be improved by providing details and recording features such as disease conditions.

Furthermore, although anecdotal findings show that the prevalence among many paediatric conditions is high, little attention has been paid by Kenyan health care professionals who need to recognize that their treatment approaches have significant implications for the overall management of many paediatric and adolescent diseases often found to be associated with innate errors This is significant because IEMs can lower one's quality of life and increase morbidity and mortality.

To our knowledge, no research in Kenya or the KNH has attempted to relate disease conditions to inborn errors of metabolism (IEM). The study highlighted the following aspects of metabolism errors in patients: age, sex, geographical distribution, and the proportion of each of the diseases. The results of this study are useful to further investigate the innate mistakes of metabolism and associated diseases perhaps elsewhere as well as in Kenya.

Furthermore, the study's persuasive rationale is based on the treatment of inborn metabolic errors in the context of certain diseases. It is preferable to treat the underlying disorder rather than just the symptoms. However, in cases where the probable cause is unknown, this may be expensive. Nutrition therapy is another type of management component. This may be a simple option for proven triggers or when the IEM is serious. Symptom control, on the other hand, should be avoided. This will

necessitate a framework for decision-making, and the findings of this study will provide some insight into these consequences.

Since IEM is a multifactorial disease that occurs in a variety of clinical settings, this research identified the most common relationship, assisting in differential diagnosis and enhancing overall case management. It's likely that certain disorders occur more often or in conjunction with others due to the large number of disease associations with inborn metabolic errors. As a result, this research will aid in the ranking and sorting of the most popular associations.

Research Question

What is the prevalence of inborn errors of metabolism among clinically suspected cases in children aged 1 to 18 years at the Kenyatta National Hospital?

Study Objectives:

Primary objective

To determine the prevalence of inborn errors of metabolism among clinically suspected cases in children aged 1 to 18 years at the Kenyatta National Hospital.

Secondary objectives

1. To evaluate the characteristics of inborn errors of metabolism in children aged 1 to 18 years at the Kenyatta National Hospital.

2. To determine the spectrum range of inborn errors of metabolism in children aged 1 to 18 years at the Kenyatta National Hospital.

CHAPTER 3 RESEARCH METHODS

Study Design

This is an observational cross-sectional study.

Study Setting

Patients were recruited from the Kenyatta National Hospital outpatient clinics (Neurology, Cardiac, Endocrine) and the General Wards.

KNH is the Kenya referral teaching and research hospital in Nairobi Kenya with 1800 bed capacity. It has been in existence since 1901. There are four general paediatric wards i.e., 3A, 3B, 3C and 3D. Admissions are done daily from the paediatric emergency unit at the paediatric filter clinic by a paediatric trainee doctor. There are approximately 14,000 admissions to the paediatric ward each year of children aged 0-12 years. Patients receive inpatient care provided majorly by 70-80 paediatric registrars who are supervised by about 25 paediatricians. The nursing care is provided by a total of 126 nurses, with 12- 24 working per shift.

Study Population

The study population involved children aged 0 months 18 years suspected to have inborn errors of metabolism at Kenyatta National Hospital.

- Patients with a diagnosis of IEM by genetic studies
- Suggestive history suggestive of IEMS
- Suggestive clinical presentation and physical examination
- Suggestive initial laboratory tests

Study participation was be voluntary.

Inclusion Criteria

Children aged 0 to 18 years with:

- IEMs as confirmed with genetic studies as per their hospital records
- History suggestive of IEMs
- Family history suggestive of IEMs
- Physical examination suggestive of IEMs
- The paediatric and adolescent caregivers had consented to participate in the study

Exclusion Criteria

- Refusal to give consent.
- No clinical impression of IEMs on history or physical examination.

Case Definition

Inborn error of metabolism referred to a hereditary disease with suggestive history, physical features and biochemical characteristics as defined in the outcomes of interest

Key Outcomes of Interest

- **History suggestive of IEM** was defined as history of maternal eclampsia, family history of consanguinity, unexplained neonatal or infantile deaths, Past medical history of delayed child development, unexplained hypoglycaemia, encephalopathy, protein aversion, self-injurious behaviour, psychiatric symptoms and seizure disorder(8)

- **Physical examination suggestive of IEMs** were defined by any of the following features:

System	**Suggestive features of IEMs**
Neurologic manifestations	Lethargy, coma, seizures, developmental delay, peripheral neuropathy, abnormalities of tone,

	motor problems, ataxia, and neuropsychiatric manifestations.
Gastrointestinal manifestations	recurrent vomiting, poor feeding, failure to thrive, decreased gastrointestinal motility, hepatomegaly or hepatosplenomegaly, and jaundice
Cardiac	Cardiomyopathy
Ophthalmologic manifestations	cataracts, corneal opacities or clouding, cherry-red spots, retinitis pigmentosa, and dislocated lenses
Dermatologic manifestations	Rashes, photosensitivity, hyperkeratosis and ichthyosis, skin ulceration, skin angiokeratoma, pearly papules and hypopigmentation

Table 6: Physical examination suggestive of IEMs

- **Biochemical characteristics suggestive of IEMs** was defined as the presence of the following in the presence of suggestive history, family history and suggestive physical manifestations: hyperammonia, metabolic acidosis, high anion gap, hypoglycaemia, elevated lactate levels, elevated urine and blood ketones
- **Genetic disorders shall be defined** by detection of abnormal DNA sequences as detected by CENTOGENE (a molecular genetic sequencing test).

Sample Size Calculation

Selim et al, in a study done over 5 years found the prevalence of inborn errors of metabolism among clinically suspected cases in children to be 6% over a period of 5 years.

$$n=\frac{(Z)^2\ p(1-p)}{MOE^2}=\frac{1.96^2\ X\ (0.06x0.094)}{0.05x0.05}=\ 78$$

z-standard deviation at 95% confidence interval

p-sample proportion using Laila A. Selim et al. study in Egypt an average proportion of 6% were diagnosed with IEMs over a period of 5 years (16).

MOE-margin of error or probability value

Sampling Technique

Consecutive sampling was carried out. All eligible children who presented to the clinics or the wards were enrolled consecutively.

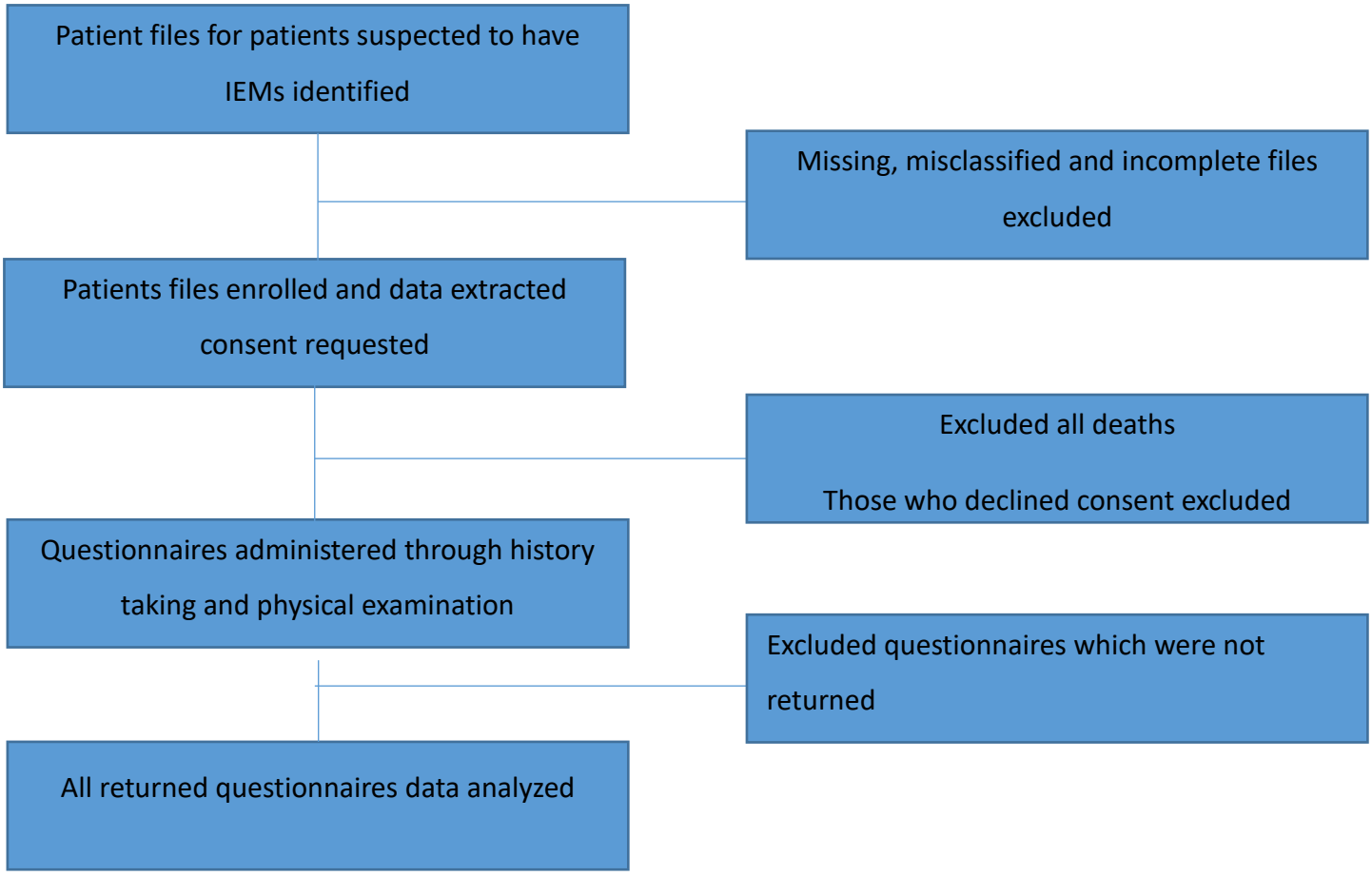
Study Procedure

Patient recruitment

Files of patients with suspected Inborn Errors of Metabolism were retrieved from the health records department by the health records. Mortality files were also retrieved. Once the files were retrieved, the participants were contacted for consent and assent. Extraction of information on age, sex, age at diagnosis, haematological features, biochemical features, and genetic diagnosis were extracted from the files. The research assistant then took history and also did physical examination of the participants using the data collection tool provided.

Retrieval of this information was done at the Health Records Department in a particular room allocated to researchers.

Figure 2: Study procedure indicating patient enrolment



Study Instruments

Questionnaire

This was used to record the participants' demographic characteristics, including age, sex, history, physical examination findings and investigations done. It also captured the genetic diagnosis of the participants.

Data Management

Pre-testing and Piloting

The study instrument was pre-tested at KNH paediatric ward. The pre-test gave feedback on whether the areas in the study had been adequately captured well. Omissions were identified as well as any need for addition of some items for adequate information gathering in the study.

Data collection took place with the help of a research assistant. The research assistant was hired with an aim to aid the principal investigator with data collection. Research assistant was registered clinical officer. The principal investigator trained and supervised the research assistant on how to administer the questionnaire. Precaution was taken to ensure that the research assistant was able to demonstrate competency and accuracy.

Data Scrutiny

A scrutiny of the completed questionnaire was done and confirmed with the patients' medical records. Data that was missing from a given section of the questionnaire was not included in the analysis of those particular areas. Editing to detect errors and omissions was also done to assure accuracy and consistency with other facts that were be gathered.

Tabulation of data involved arranging data in concise and logical order. This was important because it conserved space, reduced explanations, and facilitated

comparison, summation and detection of errors as well as provided a basis for various statistical computations

Data Analysis

Data collected by questionnaire was coded and analysed using R statistical software. Descriptive statistics included continuous variables e.g., mean with Standard deviation; Median with interquartile. Proportions were used to describe binary categorical variables. Quantitative data was presented in percentages and frequency tables.

Ethical Considerations

We sought approval from the Joint University of Nairobi and Kenyatta National Hospital Research and Ethics committee before we started the study. The purpose of the study was explained to participants who then signed consent.

Confidentiality of the respondents was maintained by ensuring the subjects remained anonymous and their individual identity did not feature in the study. All information obtained was treated with utmost confidentiality and respondents were not be identified by their names, but coding was done. The data was be kept under lock and key and for digital data, secure computing practices like use of a password were done.

Full information on the purpose of the study, any foreseen risk and benefits was given to the participants to ensure voluntary informed consent and participation. Participation in this study was purely by choice. The participants were free to be included and also were free to leave the study anytime they want to do so. Parental approval was obtained in order to protect the children and adolescents. Assurance was given to them that there would be penalty for refusal or withdrawal, study did not pose any physical or psychological harm, though data on clinical diagnosis will be considered confidential by some, as such, participants were free to consent or to decline without any prejudice or any consequences whatsoever. Written informed consent to participate in the study was obtained from all the participants.

Study Dissemination Plan

Study findings were disseminated to the relevant authority at KNH as well as presentation of findings as part of the thesis defence to the Department of Paediatrics, University of Nairobi in both hard and soft copies.

Control of Errors and Biases

The following measures were taken to reduce different forms of bias and errors.

- Participant enrolment was done using consecutive sampling on all eligible patients from the minute the clinic opens so as to reduce sampling bias.
- Standard case record form was used on every study participant to ensure uniformity and standardization.
- The principal investigator ensured validity of collected data and accurate transcription of the laboratory reports by utilizing a cross checking method.
- Thorough perusal of the patients records as an attempt to overcome recall bias as pertains to history of blood transfusion which may rely heavily on patient recall.

CHAPTER 4: RESULTS

This study had a sample size of 78 participants. 98 participants were included in the study. 4 files of the participants were missing, misclassified or incomplete. Consent was sought for 94 participants. 3 participants declined consent, while 4 had died at the time of the study. 87 questionnaires were administered, out of which 9 questionnaires were not returned. The study participants were aged between 1 and 18 years. The majority of the study participants were female, 51.3% (n = 40) while the rest were males. In terms of age categories, majority of the patients were aged between 5 and 10 years 46.2% (n = 36) while those above 15 years were the least.

Demographic characteristics of study participants

Variable	Frequency/median (IQR) N = 78	Percentage (%)
Gender: Male	38	48.7
Female	40	51.3
Age in years:	Median 6.2 (5.2)	
Age categories: <5 years	25	32.1
5-10	36	46.2
years	10	12.
11-15	7	8.9
years		
>15		
years		

Table 7: Demographic characteristics of study participants

Age distribution

The age of the study participants was right skewed with median 6.2 years and an interquartile range of 5.2 years. The mean age of the participants was 7.2 years.

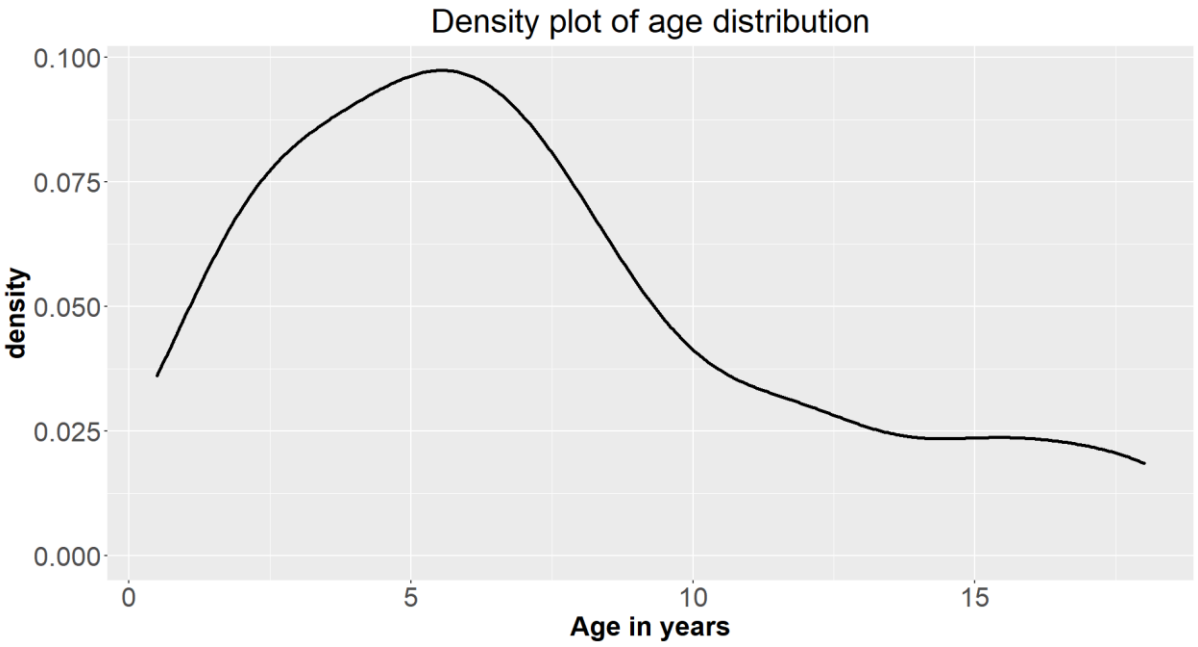


Figure 3: Density plot of age distribution

Age distribution for the two genders

Figure 4 below shows that the age for the two genders was right skewed. There were more males below age 7.5 years than females. Both ganders decreased as age advanced and females remained relatively more than males throughout beyond age 7.5 years.

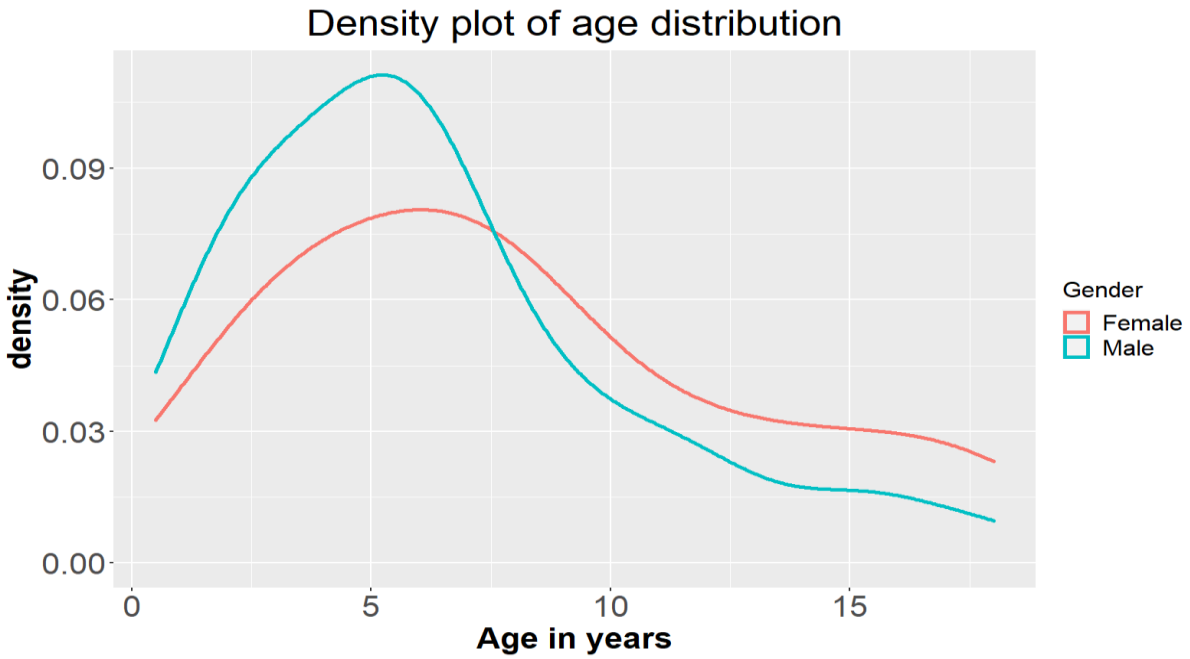


Figure 4: Density plot for age distribution of the two genders

Prevalence of inborn errors of metabolism among clinically suspected cases in children aged 1 to 18 years at the Kenyatta National Hospital

Of the total study participants, 73% (n = 57) were negative for inborn errors of metabolism while the rest were positive (figure 3). In our study, the prevalence of inborn errors of metabolism was 27% (95% CI 18%, 38%).

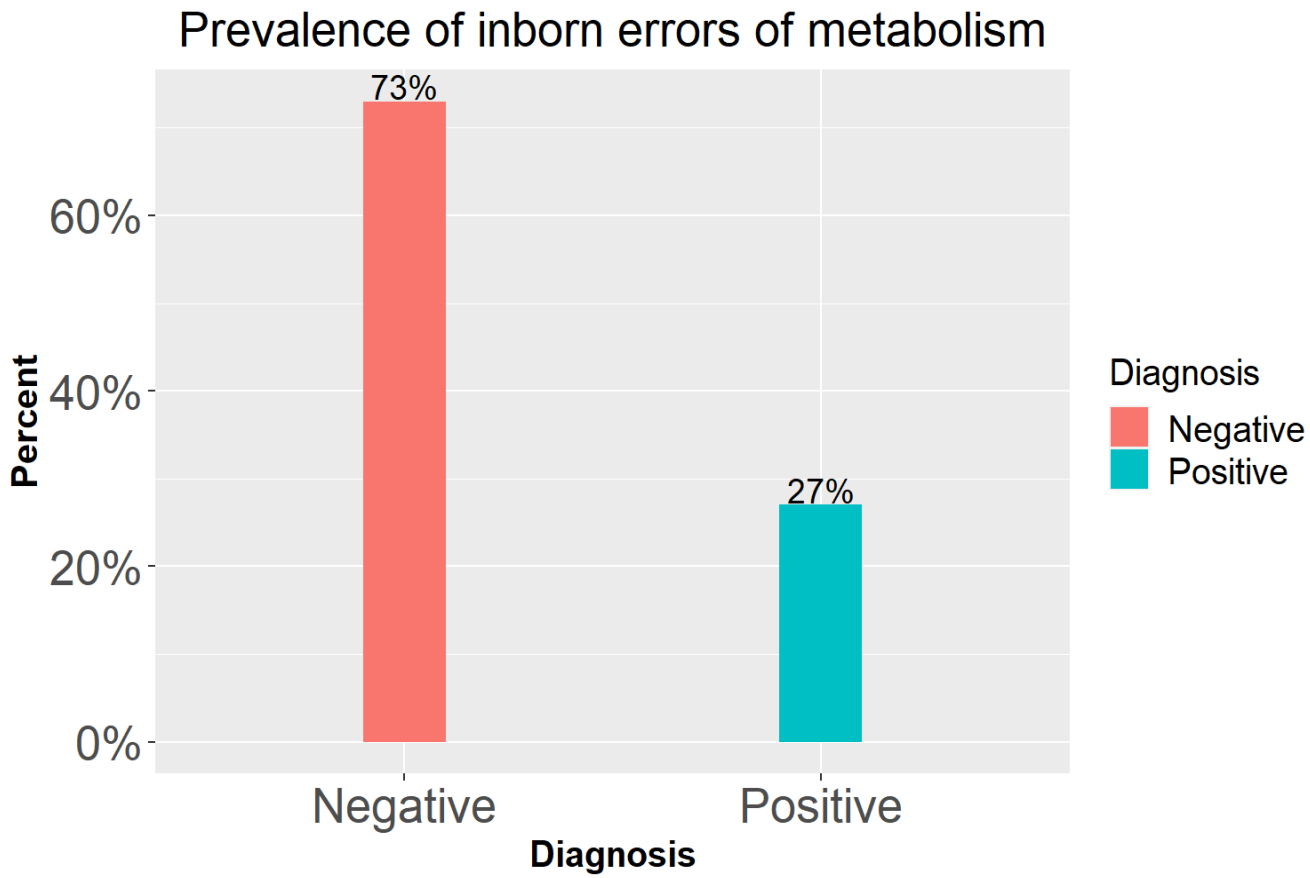


Figure 5: Prevalence of inborn errors of metabolism

Bivariate analysis

Comparison of inborn errors of metabolism between males and females

Gender	Inborn errors of metabolism		Chi square value	p-value
	Negative N = 49	Positive N = 29		
Female	30	10	0.02	0.89

Male	27	11

Table 8: Comparison of inborn errors of metabolism between males and females

Pearson's Chi square produced a p-value of 0.89 at significance level 0.05. since the p-value is greater than 0.05, we conclude that there was no statistically significant association between gender and inborn errors of metabolism.

Association between age and inborn errors of metabolism

In figure 4 below, we compare median ages between those diagnosed positive and negative for inborn errors of metabolism using Mann-Whitney U-test. The p-value produced by this test is 0.003 at 5% significance level. These leads us to conclusion that there was a significant difference in median age between those who were positive and those who were negative for inborn errors of metabolism (figure 4).

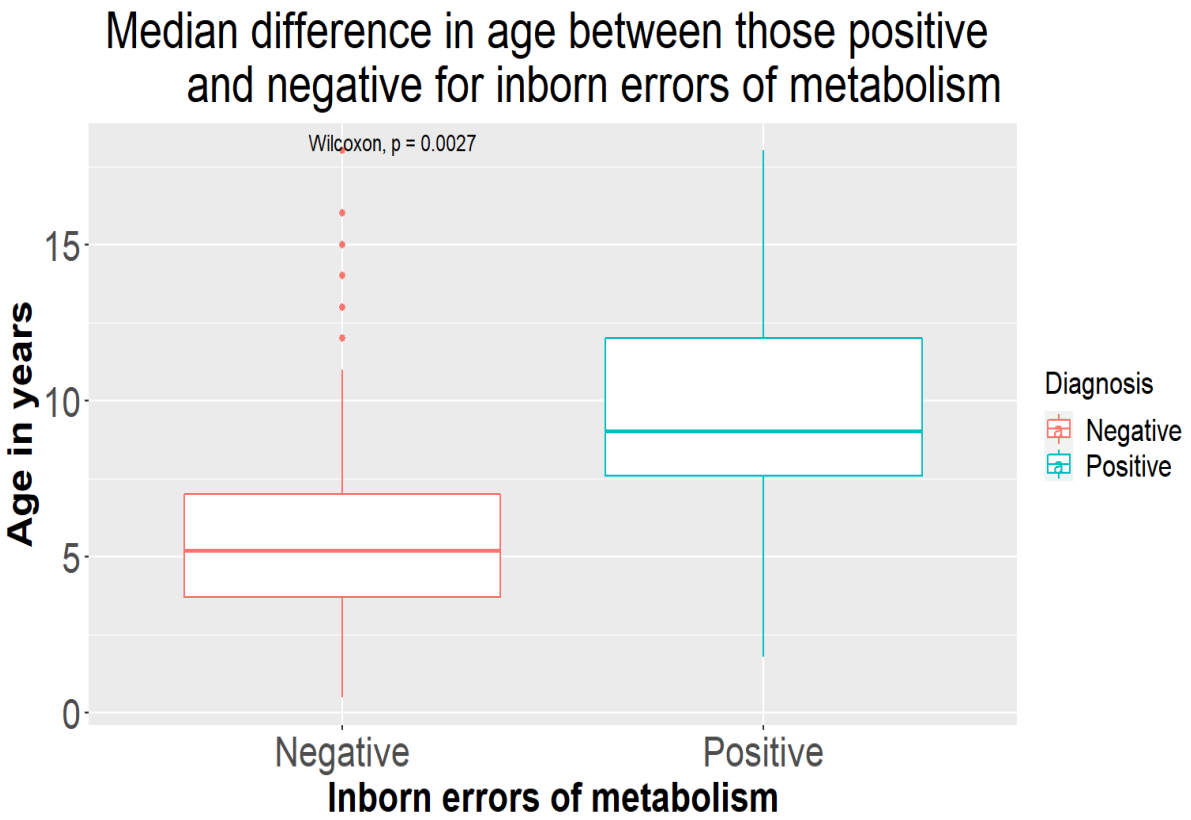


Figure 4: Median difference in age between those positive and negative for inborn errors of metabolism

Clinical features of inborn errors of metabolism in children aged 1 to 18 years at the Kenyatta National Hospital

Clinical characteristics of the study participants

Feature	**Frequency N = 78**	**Percentage% (95% CI)**
Visual		
Visual impairment: Yes	1	1.3 (0.07,7.9)
Presence of cataracts: Yes	1	1.3 (0.07,7.9)
Photosensitivity	4	5.1 (1.7,13.3)
Blood		
Has acidosis: Yes	1	1.3 (0.07,7.9)
Cardiovascular features		
Ventricular dysfunction: Yes	1	1.3 (0.07,7.9)
Cardiomyopathy: Yes	4	5.1 (1.7,13.3)
Neurological features		
Intellectual disability: Yes	52	66.7 (55.0, 76.7)
Experiences convulsions: Yes	46	59.0 (47.3, 69.8)
Abnormal posture: Yes	47	60.3 (48.5, 71.0)
Hypotonia: Yes	47	60.3 (48.5, 71.0)
Hypertonia: Yes	24	30.8 (21.1, 42.4)
Speech appropriate for age: No	29	37.2 (26.7, 48.9)
Musculoskeletal features		
Flared nostrils: Yes	4	5.1 (1.7,13.3)
Claw-like hands: Yes	5	6.4 (2.4, 15.0)
Carpal tunnel syndrome: Yes	3	3.8 (1.0, 11.6)
Joint stiffness: Yes	7	9.0 (4.0, 18.2)
Difficulty walking: Yes	19	24.4 (15.7, 35.6)
High forehead: Yes	8	10.3 (4.8, 19.7)
Large anterior fontanelle: Yes	8	10.3 (4.8, 19.7)

Hypoplastic supraorbital ridges: Yes	8	10.3 (4.8, 19.7)
Epicanthal folds: Yes	4	5.1 (1.7,13.3)
Low broad nasal bridge: Yes	6	7.7 (3.2, 16.5))
High arched plate: Yes	3	3.8 (1.0, 11.6)
Scoliosis/kyphosis: Yes	7	9.0 (4.0, 18.2)
Gastrointestinal features		
Vomiting: Yes	12	15.4 (8.5, 25.7)
Jaundice: Yes	6	7.7 (3.2, 16.5)
Splenomegaly: Yes	7	9.0 (4.0, 18.2)
Hepatomegaly: Yes	7	9.0 (4.0, 18.2)
Respiratory manifestations		
Upper RTIs: Yes	15	19.2 (11.5, 30.0)
Difficulty in breathing: Yes	14	17.9 (10.5, 28.6)
Nasal flaring: Yes	4	5.1 (1.7,13.3)
Dermatological manifestations		
Rashes: Yes	8	10.3 (4.8, 19.7)
Skin ulceration: Yes	9	11.5 (5.7, 21.3)
Skin nodules: Yes	7	9.0 (4.0, 18.2)
Angiokeratoma: Yes	3	3.8 (1.0, 11.6)
Hypopigmentation: Yes	6	7.7 (3.2, 16.5)
Pebble-like nodular skin: Yes	6	7.7 (3.2, 16.5)
Thick Skin: Yes	8	10.3 (4.8, 19.7)
Genito-urinary features		
Hypospadias: Yes	6	7.7 (3.2, 16.5)
Facial abnormalities		
Deformed earlobes: Yes	6	7.7 (3.2, 16.5)
Cleft palate: Yes	6	7.7 (3.2, 16.5)
Protruding tongue: Yes	47	60.3 (48.5, 71.0)

Thick lips: Yes	4	5.1 (1.7,13.3)

Table 9: Clinical characteristics of the study participants

The majority of the patients presented with intellectual disability 66.7% (n = 52) followed by those with abnormal posture, hypotonia and protruding tongue at 60.3% (n = 47) each. The least number of patients presented with visual impairment, cataracts, acidosis and ventricular dysfunction at 1.3% (n = 1) each.

Clinical characteristics of children who had confirmed diagnosis of inborn errors of metabolism

Feature	**Frequency N = 22**	**Percentage% (95% CI)**
Visual features		
Visual impairment: Yes	1	4.5 (0.2, 24.0)
Presence of cataracts: Yes	1	4.5 (0.2, 24.0)
Cardiovascular features		
Ventricular dysfunction: Yes	1	4.5 (0.2, 24.0)
Cardiomyopathy: Yes	1	4.5 (0.2, 24.0)
Neurological features		
Intellectual disability: Yes	15	68.2 (42.8, 82.8)
Experiences convulsions: Yes	10	45.5 (23.9, 65.1)
Abnormal posture: Yes	15	68.2 (42.8, 82.8)
Hypotonia: Yes	12	54.5 (31.1, 72.6)
Hypertonia: Yes	5	22.7 (8.3, 44.2)
Speech appropriate for age: No	6	27.3 (11.0, 48.7)
Large anterior fontanelle: Yes	2	9.1 (1.5, 29.5)
Musculoskeletal features		
Claw-like hands: Yes	1	4.5 (0.2, 24.0)
Joint stiffness: Yes	4	18.2 (5.7, 39.5)
Difficulty walking: Yes	9	40.9 (20.5, 61.2)

High forehead: Yes	2	9.1 (1.5, 29.5)
Hypoplastic supraorbital ridges: Yes	2	9.1 (1.5, 29.5)
Epicanthal folds: Yes	1	4.5 (0.2, 24.0)
Low broad nasal bridge: Yes	1	4.5 (0.2, 24.0)
Scoliosis/kyphosis: Yes	2	9.1 (1.5, 29.5)
Gastrointestinal features		
Jaundice: Yes	2	9.1 (1.5, 29.5)
Splenomegaly: Yes	4	18.2 (5.7, 39.5)
Hepatomegaly: Yes	4	18.2 (5.7, 39.5)
Respiratory features		
Upper RTIs: Yes	5	22.7 (8.3, 44.2)
Difficulty in breathing: Yes	4	18.2 (5.7, 39.5)
Nasal flaring: Yes	1	4.5 (0.2, 24.0)
Dermatological manifestations		
Rashes: Yes	2	9.1 (1.5, 29.5)
Skin ulceration: Yes	3	13.6 (3.4, 34.7)
Skin nodules: Yes	2	9.1 (1.5, 29.5)
Hypopigmentation: Yes	1	4.5 (0.2, 24.0)
Pebble-like nodular skin: Yes	1	4.5 (0.2, 24.0)
Thick Skin: Yes	3	13.6 (3.4, 34.7)
Facial abnormalities		
Deformed earlobes: Yes	1	4.5 (0.2, 24.0)
Cleft palate: Yes	1	4.5 (0.2, 24.0)
Protruding tongue: Yes	1	4.5 (0.2, 24.0)
Thick lips: Yes	1	4.5 (0.2, 24.0)

Table 10: Clinical characteristics of the study participants

After selecting the patients who had turned positive for inborn errors of metabolism, the most presenting features were intellectual disability and abnormal posture at 68.2% (n = 15) followed by those with hypotonia at 54.5% (n = 12). The least presenting features still remained visual impairment, ventricular dysfunction and cataracts among others 4.5% (n = 1). From table 4 above, it is clear that all the patients who had visual impairment, ventricular dysfunction and cataracts were those with inborn errors of metabolism. Some features e.g., acidosis, vomiting, photosensitivity, angiokeratoma, arched palate and hypospadias were not present among patients with inborn errors of metabolism.

Clinical presentation of children with inborn errors of metabolism

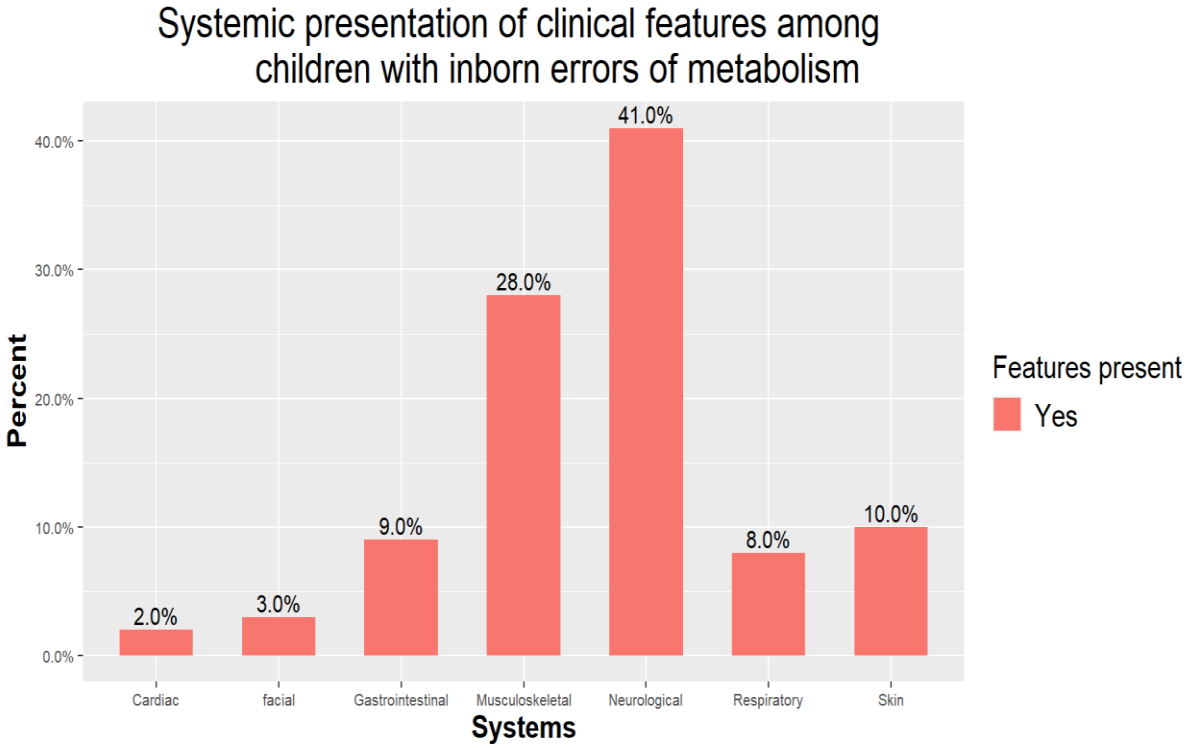


Figure 5: Clinical presentation of the study participants

The majority of the patients presented with neurological features i.e., 41.0% followed by the musculoskeletal features at 28.0%. The least presenting feature was in the cardiovascular systems at 2.0% each.

The spectrum range of inborn errors of metabolism in children aged 1 to 18 years at the Kenyatta National Hospital

Inborn error of metabolism	Frequency N = 22	Percent (%)
Autosomal Dominant COL2A1Related Disorder	1	4.5 (0.2, 24.0)
Autosomal Dominant FGFR3-Related Disorder	1	4.5 (0.2, 24.0)
Autosomal recessive Gaucher Disease	2	9.1 (1.5, 29.5)
Autosomal recessive Bordel-Biedl Syndrome type 19	2	9.1 (1.5, 29.5)
CASK Disorders	1	4.5 (0.2, 24.0)

Congenital Adrenal Hyperplasia	3	13.6 (3.4, 34.7)
Mucopolysaccharidosis	9	40.9 (20.5, 61.2)
X-linked Dominant G6PD deficient haemolytic anaemia	2	9.1 (1.5, 29.5)
X-linked Dominant Hypophosphatemic Rickets	1	4.5 (0.2, 24.0)

Table 11: Spectrum of inborn errors of metabolism among study participants

In terms of spectrum for the inborn errors of metabolism, there were a total of 12 variants. The majority of the patients 40.9% (n = 9) had Mucopolysaccharidosis type 2. The second most prevalent inborn error of metabolism was congenital adrenal hyperplasia 13.6% (n = 3). The other variants are presented in table 5 above.

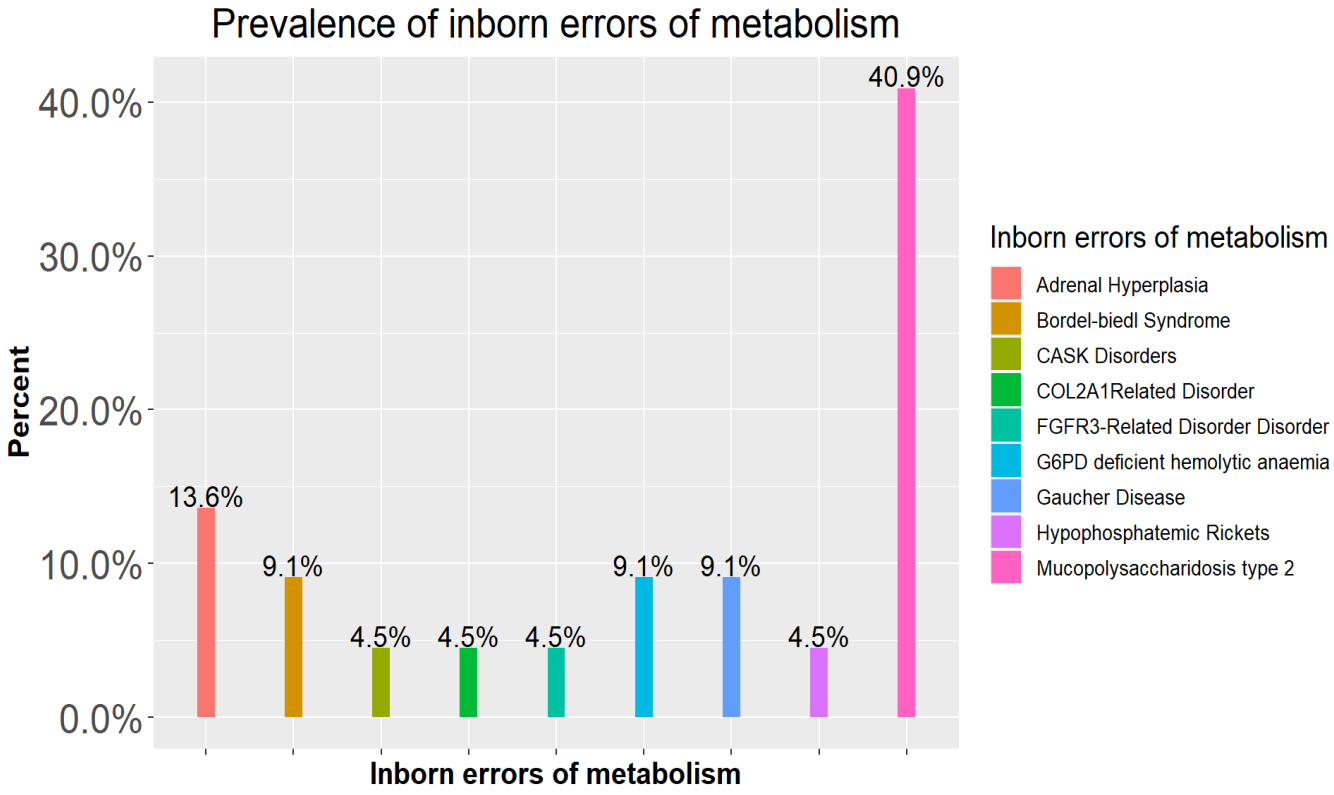


Figure 6: Inborn errors of metabolism

Other genetic diseases found among study participants

Other than the inborn errors of metabolism, six other genetic diseases were found among some of the patients who participated in this study. Each of these variants appeared only once 12.5% (n = 1).

Genetic disease	Frequency N = **8**	Percentage (%)
Autosomal Dominant 16P13.11	1	12.5 (0.7, 53.3)
Autosomal Dominant Coffin-Seri**e**s Syn**d**rome 12	1	12.5 (0.7, 53.3)
Autosomal Dominant Developmental and epileptic encephalopathy 2	1	12.5 (0.7, 53.3)
Autosomal Dominant Glass-Syndrome	1	12.5 (0.7, 53.3)
Variance of Uncertain Significance	1	12.5 (0.7, 53.3)
Willians-Beuren Syndrome	1	12.5 (0.7, 53.3)
Autosomal Dominant Microcephaly	1	12.5 (0.7, 53.3)
Autosomal Dominant susceptibility autism type 18	1	12.5 (0.7, 53.3)

Table 12: Other genetic diseases found among study participants

CHAPTER 5: DISCUSSION

Results

In this study, 21 patients were diagnosed with IEMs out of 78 children suspected to have IEMs pediatric patients with a prevalence of 21%. This is a high prevalence in comparison to Laila et al who found the prevalence to be 6% in an Egyptian population. This wide variation could be explained by the inconsistent diagnostic strategies, by the different testing panels and also by the prevalence of these disorders. In our study we used results obtained from genetic sequencing, while in most of the previous studies the testing was done using screening methods.

Mucopolysaccharidosis in our study accounted for 40.9% of total positive cases. This is not in keeping with what Laila et al found with PKU being the most common type (49.3%). This is attributed to the difference in ethnicity which could influence the type of IEMs in different regions. We also note that the Egyptians study was conducted in high consanguinity area which also would influence the prevalent type of IEM.

In this study Neurological features were the most common presenting features at 43%. This is in keeping with the findings of Laila et al (75%)

Strengths of the Study

To the best of our knowledge, this is the first of such study describing Kenyan children with Inborn errors of metabolism.

The use of data collection by use of a hospital files combined history taking and physical examination improved the quality of our study and the results.

Limitations of the study

The study population was mainly be drawn from KNH, a tertiary referral hospital, and thus the results may not be generalizable to lower-level facilities or community settings.

Patient selection was based on attending clinicians' diagnoses and we may have missed out on those patients that the clinicians were not able to identify.

Some eligible patients may refuse to participate in the study

Mitigatory Measure to study limitations

Because the study was conducted in a national referral hospital, the study population included both patients from the KNH catchment area, and lower-level facilities, and thus inclusive. Hence results of the study can be generalizable even to lower-level facilities and community settings.

The utility and benefits of the study were clearly explained to the patients and their parents and guardians, and they were encouraged to participate in the study. However, those who declined to participate were not coerced in any manner.

Conclusions

To the best of our knowledge, this is the first study describing Kenyan children with IEMs diagnosed by genetic testing. This study indicated the magnitude of IEMs among suspected Kenyan pediatric patients. This warrants the development of a nationwide newborn screening program for IEMs as well as education among healthcare workers to increase their index of suspicion and for referral of these patients for genetic testing. Early detection and early intervention of individuals at risk of IEMs before the onset of symptoms can prevent, or at least, reduce serious neurological and developmental sequelae.

Recommendations

The creation of a national screening program for IEMs is essential for early discovery of these potentially treatable illnesses, timely and appropriately timed therapeutic intervention, and the avoidance of severe neurological sequelae.

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APPENDIX

Appendix 1: Study Timelines

No.	Activity	Month
1	Development of Proposal and presentation	June to Aug 2021
2	Proposal Submission for ethical review and approval	Sept 2021 to March 2022
3	Data Collection	March 2022
4	Data analysis and reporting	April 2022
5	Thesis Writing	April 2022
7	Thesis Submission	April 2022

Appendix 2: Study Budget

The following is the budget used for the study

Category	Remark	Qty	Unit cost	Total (Ksh)
Proposal development	Printing drafts	5	5,000.00	25,000.00
	Proposal copies	8	5,000.00	40,000.00
Data collection	Stationery	10	500.00	5,000.00
	Training research assistants	5000	1.00	5,000.00
	Research assistant (20 weeks @1500/week)	1500	20	30,000.00
Lab tests	Specimen Bottles	20	100	2,000.00
	Lab Assistant	100	100	10,000.00
	Syringes	20	100	2,000.00
	Needles	20	100	2,000.00
	Cotton Wool (Roll)	200	1	200.00
	Surgical Spirit (Liters)	1000	5	5,000.00
Data entry	Data clerk	7000	1	7,000.00
Data analysis	Statistician	30000	1	30,000.00
Thesis write up	Printing drafts	5	1000	5,000.00
	Printing thesis	1500	10	15,000.00
Contingency	10% Contingency			18,320.00
			Total	201,520.00

SOURCE OF FUNDS: Personal Savings

Appendix 3: Parental/Guardian Consent Form

INFORMATION FORM

Study Title: SELECTIVE SCREENING OF INBORN ERRORS OF METABOLISM AMONG CLINICALLY SUSPECTED CASES IN CHILDREN AGED 1 TO 18 YEARS AT THE KENYATTA NATIONAL HOSPITAL

Patients study identification number: ----------

KNH/UON ERC Protocol number: ----------

Principal investigator: Dr. Cleopas Kaumbulu
Paediatric Resident University of Nairobi.

Supervisor Details: Dr. Lucy Mungai;
Senior Lecturer, Department of Paediatrics
University of Nairobi
Phone number: 0724 654135

Introduction

I am conducting a study on Inborn Errors of Metabolism Disorders in Children seen at the Kenyatta national Hospital. Your child is being requested to participate in the study because they meet the conditions required to be included in the study.

The purpose of this form is to give you the information you will need to help you decide whether or not to be a participant in the above listed study. You can ask any questions to clarify the purpose of the research, what happens if your child participates in the study, the possible risks and benefits and on your rights as a volunteer.

This process is called 'informed consent'. Once you understand and agree to be in the study, I will request you to sign your name on this form.

Your decision is voluntary, it will not affect your access to health services in the hospital and furthermore, you can withdraw from the study any time without having to give a reason.

If your child is above 7 years, he/she will also be required to also agree to participate in the study after being fully informed about it.

What is the purpose of the study?

This study is informed by the need to estimate the proportion of children living with an inherited disease which is referred to as Inborn errors of metabolism. This study also seeks to confirm the diagnosis for those children suspected to have these condition.

There will be approximately 87 participants.

We are requesting for your consent to consider participating in this study.

What will happen if you decide you want your child to be in this research study?

If you consent to participate in this study, I will proceed to ask a series of questions and will subsequently note your responses in writing. I will then conduct a physical examination of your child.

2 ml of blood will then be withdrawn for tests. The blood sample will be used to carry out to check for 201 genetic mutations which are known to lead to Inborn Errors of metabolism. This will help us to make a diagnosis in your child.

You will be informed about the results and a copy of the results will be placed in your records.

Are there any risks associated with this study?

Your child may feel some pain or discomfort when blood is being drawn from him/her. A small bruise or swelling may also develop at the site which is temporary.

Are there any benefits being in this study?

This study will provide a chance for your child to get free genetic testing for inborn errors of metabolism

The results will assist in improving the management of your child

It will not cost you anything in terms of financial resources neither is there a reimbursement for participation.

If you have any questions in the future, you can call or send a text message to the number given at the bottom of this page.

The role of University of Nairobi and Kenyatta National Hospital Research and Ethics committee (KNH-UoN ERC)

We will seek approval from the Joint University of Nairobi and Kenyatta National Hospital Research and Ethics committee (KNH-UoN ERC) before we start the study. To contact the KNH-UoN ERC use the following contact: Email uonknh_erc@uonbi.ac.ke; Website: http:/www.erc.uonbi.ac.ke

For more information, contact the investigator Dr. Cleopas Mutua, Department of Paediatrics and Child Health, University of Nairobi or the supervisor, Dr. Lucy Mungai from 9-3pm, every Monday to Friday.

STATEMENT OF CONSENT

The person being considered for study is unable to consent for him/herself because he/she is a minor. You are therefore requested to give your permission to include your child in this study.

Parent / guardian statement

I have read this consent form or had the information read to me. I have had the chance to discuss this study and my questions have been answered in a language that I understand. The risks and benefits have been explained to me. I understand that my participation in this study is voluntary and that I may choose to withdraw any time. I freely agree to participate in this research study. I understand that all efforts will be made to keep information regarding my personal identity confidential.

By signing this consent form, I have not given up any of the legal rights that I have as a participant in a research study.

I voluntarily agree to sending of my child's sample to Germany for analysis YES NO

Participant printed name----------

Participant signature / Thumb stamp ---------- Date ----------

I voluntarily agree to my child's participation in this research study YES NO

I agree to have my child undergo blood tests YES NO

I have agreed to provide contact information for follow-up YES NO

Participant printed name----------

Participant signature / Thumb stamp ---------- Date ----------

Investigator's Declaration

I, the undersigned, have fully explained the relevant details of this research study to the participant named above and believe that the participant has understood and has willingly and freely given his/her consent.

Principal investigator's Name: ----------

Signature----------

Date: ----------

FOMU YA IDHINI

Kiambatisho cha 1: Fomu ya Idhini ya Mzazi

FOMU YA HABARI

Kichwa cha Utafiti: UCHUNGUZI CHAGU WA MAKOSA YA KUZALIWA YA UMETABOLI MIONGONI MWA KESI ZINAZOTOSIKIWA KITABIBU KWA WATOTO WA UMRI WA MIAKA 1 HADI 18 KATIKA HOSPITALI YA TAIFA YA KENYATTA.

Nambari ya utambulisho wa wagonjwa wa utafiti: ----------

Nambari ya Itifaki ya KNH/UON ERC: ---------- -

Mpelelezi Mkuu: Dk Cleopas Kaumbulu
Chuo Kikuu cha Mkaazi wa Watoto cha Nairobi

Nambari ya simu: 0725822269

Maelezo ya Msimamizi: Dk Lucy Mungai;
Mhadhiri Mkuu, Idara ya Magonjwa ya Watoto
Chuo Kikuu cha Nairobi
Nambari ya simu: 0724 654135

Utangulizi

Ninafanya utafiti kuhusu Makosa ya Kuzaliwa kwa Matatizo ya Kimetaboliki kwa Watoto yanayoonekana katika Hospitali ya kitaifa ya Kenyatta. Mtoto wako anaombwa kushiriki katika utafiti kwa sababu anatimiza masharti yanayohitajika ili kujumuishwa katika utafiti.

Madhumuni ya fomu hii ni kukupa taarifa utakayohitaji ili kukusaidia kuamua kama kuwa mshiriki au la katika utafiti ulioorodheshwa hapo juu. Unaweza kuuliza maswali yoyote ili kufafanua madhumuni ya utafiti, nini kitatokea ikiwa mtoto wako atashiriki katika utafiti, hatari na manufaa yanayoweza kutokea na juu ya haki zako kama mtu aliyejitolea.

Utaratibu huu unaitwa 'kibali cha taarifa'. Ukishaelewa na kukubali kuwa katika utafiti, nitakuomba utie sahihi jina lako kwenye fomu hii.

Uamuzi wako ni wa hiari, hautaathiri ufikiaji wako wa huduma za afya hospitalini na zaidi ya hayo, unaweza kujiondoa kwenye utafiti wakati wowote bila kulazimika kutoa sababu.

Ikiwa mtoto wako ana umri wa zaidi ya miaka 7, atahitajika pia kukubali kushiriki katika utafiti baada ya kufahamishwa kikamilifu kuuhusu.

Madhumuni ya utafiti ni nini?

Utafiti huu unatokana na hitaji la kukadiria idadi ya watoto wanaoishi na ugonjwa wa kurithi ambao unajulikana kama makosa ya kuzaliwa ya kimetaboliki. Utafiti huu pia unatafuta kuthibitisha utambuzi kwa wale watoto wanaoshukiwa kuwa na hali hizi. Kutakuwa na takriban washiriki 87.

Tunaomba idhini yako ili kuzingatia kushiriki katika utafiti huu.

Nini kitatokea ukiamua unataka mtoto wako awe katika utafiti huu?
Ukikubali kushiriki katika utafiti huu, nitaendelea kuuliza msururu wa maswali na nitazingatia majibu yako kwa maandishi. Kisha nitafanya uchunguzi wa kimwili wa mtoto wako.
2 ml ya damu itatolewa kwa vipimo. Sampuli ya damu itatumika kuchunguza mabadiliko 201 ya kijeni ambayo yanajulikana kusababisha Makosa ya Kuzaliwa kwa kimetaboliki. Hii itatusaidia kufanya uchunguzi katika mtoto wako.
Utajulishwa kuhusu matokeo na nakala ya matokeo itawekwa kwenye rekodi zako.

Je, kuna hatari zozote zinazohusiana na utafiti huu?
Mtoto wako anaweza kuhisi maumivu au usumbufu wakati damu inatolewa kutoka kwake. Mchubuko mdogo au uvimbe unaweza pia kutokea kwenye tovuti ambayo ni ya muda mfupi.

Je, kuna manufaa yoyote katika utafiti huu?
Utafiti huu utatoa nafasi kwa mtoto wako kupata uchunguzi wa kinasaba bila malipo kwa hitilafu alizozaliwa nazo za kimetaboliki
Matokeo yatasaidia katika kuboresha usimamizi wa mtoto wako
Haitakugharimu chochote katika suala la rasilimali za kifedha wala hakuna malipo ya ushiriki.
Ikiwa una maswali yoyote katika siku zijazo, unaweza kupiga simu au kutuma ujumbe wa maandishi kwa nambari iliyotolewa chini ya ukurasa huu.
Kwa maelezo zaidi, wasiliana na Dkt. Cleopas Mutua, Idara ya Magonjwa ya Watoto na Afya ya Mtoto, Chuo Kikuu cha Nairobi. Kuanzia 9-3pm, kila Jumatatu hadi Ijumaa.

Jukumu la Chuo Kikuu cha Nairobi na kamati ya Utafiti na Maadili ya Hospitali ya Kitaifa ya Kenyatta (KNH-UoN ERC)

Tutaomba idhini kutoka kwa Chuo Kikuu Kishiriki cha Nairobi na kamati ya Utafiti na Maadili ya Hospitali ya Kitaifa ya Kenyatta (KNH-UoN ERC) kabla ya kuanza utafiti. Ili kuwasiliana na KNH-UoN ERC tumia anwani ifuatayo: Barua pepe uonknh_erc@uonbi.ac.ke; Tovuti: http://www.erc.uonbi.ac.ke

Kwa maelezo zaidi, wasiliana na mpelelezi Dkt. Cleopas Mutua, Idara ya Magonjwa ya Watoto na Afya ya Mtoto, Chuo Kikuu cha Nairobi au Msimamizi, Dkt. Lucy Mungai kuanzia saa 9-3 jioni, kila Jumatatu hadi Ijumaa.

TAARIFA YA RIDHAA

Mtu anayezingatiwa kusoma hana uwezo wa kujikubali kwa sababu yeye ni mtoto. Kwa hivyo unaombwa kutoa idhini yako ya kujumuisha mtoto wako katika utafiti huu.

Taarifa ya mzazi/mlezi

Nimesoma fomu hii ya idhini au nimesomewa maelezo. Nimepata nafasi ya kujadili utafiti huu na maswali yangu yamejibiwa kwa lugha ninayoielewa. Hatari na faida zimeelezewa kwangu. Ninaelewa kuwa ushiriki wangu katika utafiti huu ni wa hiari na kwamba ninaweza kuchagua kujiondoa wakati wowote. Ninakubali kwa uhuru kushiriki katika utafiti huu. Ninaelewa kuwa juhudi zote zitafanywa ili kuweka taarifa kuhusu utambulisho wangu wa kibinafsi kuwa siri.
Kwa kutia saini fomu hii ya idhini, sijaacha haki zozote za kisheria nilizo nazo kama mshiriki katika utafiti wa utafiti.

Ninakubali kwa hiari kutumwa kwa sampuli ya mtoto wangu Ujerumani kwa uchambuzi NDIYO HAPANA

Jina la mshiriki limechapishwa---------- ----------
Sahihi ya mshiriki / Muhuri wa kidole gumba ----------Tarehe----------

Ninakubali kwa hiari ushiriki wa mtoto wangu katika utafiti huu NDIYO HAPANA
Ninakubali mtoto wangu afanyiwe vipimo vya damu NDIYO HAPANA

Nimekubali kutoa maelezo ya mawasiliano kwa ufuatiliaji
NDIYO HAPANA

Jina la mshiriki limechapishwa---------- ----------
Sahihi ya mshiriki / Muhuri wa kidole gumba ---------- Tarehe -----
----

Kauli ya mtafiti

Mimi, niliyetia sahihi chini, nimeeleza kikamilifu maelezo muhimu ya utafiti huu kwa mshiriki aliyetajwa hapo juu na ninaamini kuwa mshiriki ameelewa na ametoa ridhaa yake kwa hiari na kwa uhuru.

Jina la Mpelelezi Mkuu: ----------Tarehe: -- ----------
Sahihi----------

Appendix 4 Child Information/Assent Form

Study Title: SELECTIVE SCREENING OF INBORN ERRORS OF METABOLISM AMONG CLINICALLY SUSPECTED CASES IN CHILDREN AGED 1 TO 18 YEARS AT THE KENYATTA NATIONAL HOSPITAL

Patients study identification number: ----------

KNH/UON ERC Protocol number: ----------

Principal investigator: Dr. Cleopas Kaumbulu
Paediatric Resident University of Nairobi.

We are conducting this research to learn more about children who get sick sometimes like you do and its not clear what exactly the disease is even after many blood tests. 78 children will be part of the study.

If you agree to be part of this study, we will ask you some questions about how you have been feeling, and we will also examine you. It won't take long.

We will also need to remove some blood from you which we will send a lab in Germany for testing. You will feel some little pain when the blood is being removed.

The good thing about being in this study is you will help us understand a bit more about what happens when you get sick and it may help some other children, maybe even you in the future.

You do not have to agree to be part of this study.

When we are finished, we will write a report of what we learn but we will not put your name or that you were in the study.

If after you agree you want to change your mind and stop being in the study, it is also fine, and you will still continue being treated today in the clinic.

Your parents also know about the study. You can ask me any question you want.

If you agree you want to be in this study, please sign your name.

I ----------want to be in this study.

Signature/ Thumbprint ---------- Date ---------

Appendix 5: Questionnaire

Selective screening of Inborn errors of metabolism

RESEARCHER: Dr. Kaumbulu Cleopas Mutua

SERIAL NO…… Date of Interview …..... /……../……..

Date sample taken……/……/……...

1. Age (year(s) / month(s): ……...../…….
2. Height: _____ (in cm)
3. Weight: _____ (in Kgs)
4. Gender: MALE _____ FEMALE _____
5. Area of residence: _____
6. Genetic diagnosis:
    a. Positive result for _____
    b. Negative results _____
7. What is the participant being treated for currently?

    _____
8. NEUROLOGICAL MANIFESTATIONS: Evaluate the participant for the presence of the following symptoms and signs.
    a. Answer YES or NO in the following questions:
        i. Is the speech appropriate for age: YES, or NO?
        ii. Is the participant mentally retarded: YES, or NO?
        iii. Any convulsions experienced: YES, or NO?
        iv. Any abnormal walking posture: YES, or NO?
    b. Examine the participant for the following
        i. hypotonia: YES, or NO?
        ii. hypertonia: YES, or NO?
9. FACIAL MANIFESTATIONS: Examine the participant for presence of the following:
    a. Large protruding tongue: YES, or NO
    b. Thicken lips: YES, or NO

c. Flared nostrils with broad noses and prominent supraorbital ridges: YES, or NO

10. Skeletal features
    a. Examine the participant for the presence of the following:
    b. Claw like hands: YES, or NO
    c. Carpal tunnel syndrome: YES, or NO
    d. Joint stiffness/ contractures: YES, or NO
    e. Difficulty in walking/abnormal gait: YES, or NO
    f. Spine instability/ scoliosis/kyphosis: YES, or NO
11. Abdominal features
    a. Does the participant experience vomiting: YES, or NO?
    b. Examine the participant for the presence of the following:
        i. Jaundice: YES, or NO
        ii. Hepatomegaly: YES, or NO
        iii. splenomegaly: YES, or NO
12. Respiratory features
    a. Do you suffer recurrent upper respiratory infections: YES, or NO?
    b. Does the participant experience difficulty in breathing: YES, or NO?
13. Skin features
    a. Does the participant experience Photosensitivity: YES, or NO?
    b. Examine the participant for the presence of the following
        i. Rashes: YES, or NO?
        ii. Skin ulceration: YES, or NO?
        iii. Skin nodules: YES, or NO?
        iv. Angiokeratoma: YES, or NO?
        v. Hypopigmentation: YES, or NO?
        vi. Pebble-like nodular skin lesions over shoulder blades: YES, or NO
        vii. Thickened skin: YES, or NO
    c. Dysmorphic features
        i. High forehead: YES, or NO

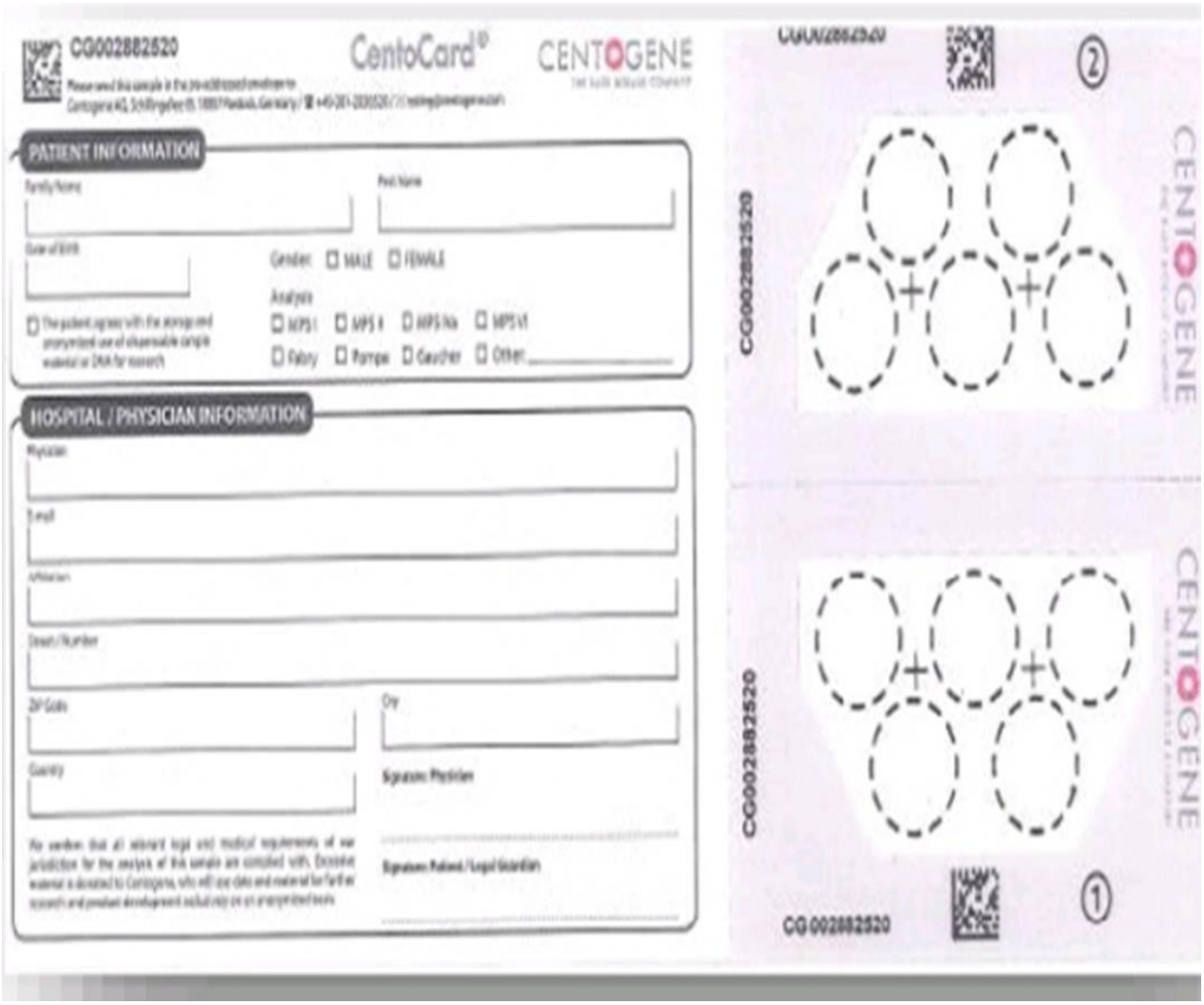
ii. Large anterior fontanelle: YES, or NO
iii. Hypoplastic supraorbital ridges: YES, or NO
iv. Epicanthal folds: YES, or NO
v. Low and broad nasal bridge: YES, or NO
vi. High-arched palate: YES, or NO
vii. Deformed ear lobes: YES, or NO
viii. Cleft palate: YES, or NO
ix. Hypospadias: YES, or NO
x. Polydactyly/syndactyly: YES, or NO

14. Acid-base disorders, hyperammonemia, and hypoglycemia: Check in the file for:
    a. Acid-base disorders: YES, or NO
    b. Hyperammonemia: YES, or NO
    c. Hypoglycemia: YES, or NO
15. Hematologic abnormalities: Check in the file for
    a. Macrocytic anemia: YES, or NO
    b. Normocytic anemia: YES, or NO
    c. Predominant or isolated neutropenia: YES, or NO
    d. Predominant Pancytopenia: YES, or NO
16. At what age did the first manifestation begin? Age (year(s) / month(s): ……/…… ……. /……/…….

Interviewer's name: _____

Signature: _____

Appendix 6: Sample of a filter paper



Appendix 7: Procedure for Blood sample collection onto a filter paper

1. Enter unique coded participant's particulars and clinical information onto the requisition form attached to the filter paper.
2. Disinfect the participant's finger.
3. Prick the chosen finger using a sterile needle.
4. Allow 3 drops of blood from the finger onto the circle. Ensure the finger does not touch the filter paper and the entire circle is uniformly saturated.
5. Continue the procedure until full saturation of the 10 required blood spots. After that air dry the card for at least two hours. The samples should be sent to CENTOGENE by two weeks.
6. Once the sample is spotted on the filter card and it is dried, it is mandatory to store the dry filter paper sealed in the plastic bag at room temperature (+18°C to +28°C). Accepted ranges: -10°C to +30°C; no direct sun light. Out of these ranges the enzymes may be damaged.

Appendix 8: Procedure: Metabolic Diseases Covered

What genes and disorders are targeted by CentoMetabolic®?

CentoMetabolic® targets close to 200 metabolic disorders. The content and design of the panel is based on our continuously enhanced medical expertise and knowledge in rare metabolic diseases.

The following table shows the distribution of genes and targeted metabolic disorders depending on 19 different disease categories.

TYPE OF METABOLIC DISORDERS COVERED	NUMBER OF GENES
Congenital disorders of glycosylation and other disorders of protein modification	2
Defects in Cholesterol and Lipoprotein Metabolism	2
Defects in Hormone Biogenesis or Function	7
Disorder of phosphate, calcium and vitamin D metabolism	3
Disorders in the metabolism of purines, pyrimidines and nucleotides	6
Disorders in the metabolism of trace elements and metals	6
Disorders in the metabolism of vitamins and (non-protein) cofactors	10
Disorders of amino acid and peptide metabolism	33
Disorders of carbohydrate metabolism	35
Disorders of energy metabolism	6
Disorders of fatty acid and ketone body metabolism	3
Disorders of lipid and lipoprotein metabolism	8
Disorders of neurotransmitter metabolism	1
Disorders of porphyrin and haem metabolism	8
Disorders of the metabolism of sterols	16
Lysosomal disorders	48
Peroxisomal disorders	16
Porphyria and Bilirubinemia	1

GENES INCLUDED

ABCA1, ABCB4, ABCC2, ABCD1, ABCD4, ABCG5, ABCG8, ACAT1, ADA, AGA, AGL, AGPS, AGXT, ALAD, ALAS2, ALDH4A1, ALDOA, ALDOB, ALG3, ALPL, ANTXR2, APOA2, APOA5, APOB, APOC2, APOE, ARG1, ARSA, ARSB, ASAH1, ASL, ASS1, ATP7A, ATP7B, BCKDHA, BCKDHB, BTD, CBS, CD320, CETP, CLN3, CLN5, CLN6, CLN8, CPOX, CPS1, CPT1A, CTNS, CTSA, CTSD, CTSK, CYP11B1, CYP17A1, CYP19A1, CYP21A2, DBT, DDC, DHCR7, DIABLO, DLX4, DNAJC5, DPYD, ENO3, ENPP1, EPHX2, ETHE1, FAH, FBP1, FECH, FGF23, FUCA1, G6PC, G6PD, GAA, GALC, GALE, GALK1, GALNS, GALT, GAMT, GATM, GBA, GBE1, GHR, GK, GLA, GLB1, GM2A, GNPAT, GNPTAB, GNPTG, GNS, GUSB, GYG1, GYS1, GYS2, HCFC1, HEXA, HEXB, HFE, HJV, HGD, HGSNAT, HLCS, HMBS, HPD, HPRT1, HSD3B2, HYAL1, IDS, IDUA, ITIH4, IVD, KHK, LAMP2, LCAT, LDHA, LDLR, LDLRAP1, LIPA, LIPC, LIPI, LMBRD1, LPA, LPL, MAN2B1, MANBA, MCOLN1, MFSD8, MMAA, MMAB, MMACHC, MMADHC, MMUT, NAGA, NAGLU, NAGS, NEU1, NPC1, NPC2, OTC, PAH, PCSK9, PDHB, PEX1, PEX10, PEX12, PEX13, PEX14, PEX16, PEX19, PEX2, PEX26, PEX3, PEX5, PEX6, PEX7, PFKM, PGAM2, PGK1, PGM1, PHKA1, PHKA2, PHKB, PHKG2, PKLR, PNPO, POR, PPOX, PPP1R17, PPT1, PRKAG2, PSAP, PYGL, PYGM, RBCK1, SGSH, SI, SLC17A5, SLC22A5, SLC25A13, SLC25A15, SLC25A20, SLC25A36, SLC2A1, SLC2A2, SLC2A3, SLC37A4, SLC3A1, SLC3A2, SLC40A1, SLC6A19, SLC6A8, SLC7A7, SLC7A9, SLCO1B1, SLCO1B3, SMPD1, SUMF1, TAT, TFR2, TPP1, UGT1A1, UMPS, UROD, UROS

Appendix 9: Procedure for Genetic Testing

Genetic testing is completed by fully sequencing the specific gene associated with inborn errors of metabolism, followed by deletion/duplication testing and analysis.

Step 1 – Full gene sequencing, covers the entire coding region, exon/intron boundaries and 200 bp of the gene promoter

Step 2 – Deletion/duplication testing – covers large deletions and duplications that cannot be detected by full gene sequencing

● Based on the screening outcome, Principal Investigator will be issued with one of the following reports:

Normal – a biochemistry report

Pathogenic – a biochemistry and genetic analysis report

- CENTOGENE will keep all information generated and the unused sample for at least twenty years.
- Medical confidentiality will be observed in the participant's generated results and the unused samples.
- At any time, the participant can request stoppage of processing of results and destruction of samples without victimization.

Appendix 10: Certificate of accreditation 1

COLLEGE of AMERICAN PATHOLOGISTS

CERTIFICATE OF ISO 15189 ACCREDITATION

Centogene GmbH
Rostock, Germany

CAP # 8005167

The organization named above is granted this accreditation in accordance with the recognized International Standard ISO 15189:2012, Medical Laboratories – Requirements for quality and competence. This accreditation demonstrates competence for a defined scope and the operation of a laboratory quality management system.

Effective From August 6, 2021 through August 6, 2024

Gaurav Sharma MD, FCAP
Chair, CAP 15189 Committee

Patrick Godbey, MD, FCAP
President, College of American Pathologists

The scope of this accreditation includes Quality Management System and the disciplines of Clinical Biochemical Genetics and Molecular Pathology.

Appendix 11: Certificate of Accreditation 2

CENTERS FOR MEDICARE & MEDICAID SERVICES
CLINICAL LABORATORY IMPROVEMENT AMENDMENTS

CERTIFICATE OF ACCREDITATION

LABORATORY NAME AND ADDRESS
CENTOGENE GMBH
AM STRANDE 7
ROSTOCK 18055
GERMANY

CLIA ID NUMBER
99D2049715

EFFECTIVE DATE
04/03/2021

LABORATORY DIRECTOR
PETER A BAUER M.D.

EXPIRATION DATE
04/02/2023

Pursuant to Section 353 of the Public Health Services Act (42 U.S.C. 263a) as revised by the Clinical Laboratory Improvement Amendments (CLIA), the above named laboratory located at the address shown herein (and other approved locations) may accept human specimens for the purposes of performing laboratory examinations or procedures.

This certificate shall be valid until the expiration date above, but is subject to revocation, suspension, limitation, or other sanctions for violation of the Act or the regulations promulgated thereunder.

CMS

Monique Spruill, Director
Division of Clinical Laboratory Improvement & Quality
Quality & Safety Oversight Group
Center for Clinical Standards and Quality

254 cwlw2_090721

If you currently hold a Certificate of Compliance or Certificate of Accreditation, below is a list of the laboratory specialties/subspecialties you are certified to perform and their effective date:

LAB CERTIFICATION (CODE)	EFFECTIVE DATE
VIROLOGY (140)	05/18/2020
ROUTINE CHEMISTRY (310)	04/03/2013
HEMATOLOGY (400)	04/03/2013
CYTOGENETICS (900)	04/03/2013

LAB CERTIFICATION (CODE)	EFFECTIVE DATE

CMS

FOR MORE INFORMATION ABOUT CLIA, VISIT OUR WEBSITE AT WWW.CMS.GOV/CLIA
OR CONTACT YOUR LOCAL STATE AGENCY. PLEASE SEE THE REVERSE FOR
YOUR STATE AGENCY'S ADDRESS AND PHONE NUMBER.
PLEASE CONTACT YOUR STATE AGENCY FOR ANY CHANGES TO YOUR CURRENT CERTIFICATE.

Appendix 12: Certificate of Accreditation 3

Australian Government

Department of Health

Therapeutic Goods Administration

Australian Register of Therapeutic Goods Certificate

Issued to

Emergo Asia Pacific Pty Ltd T/a Emergo Australia

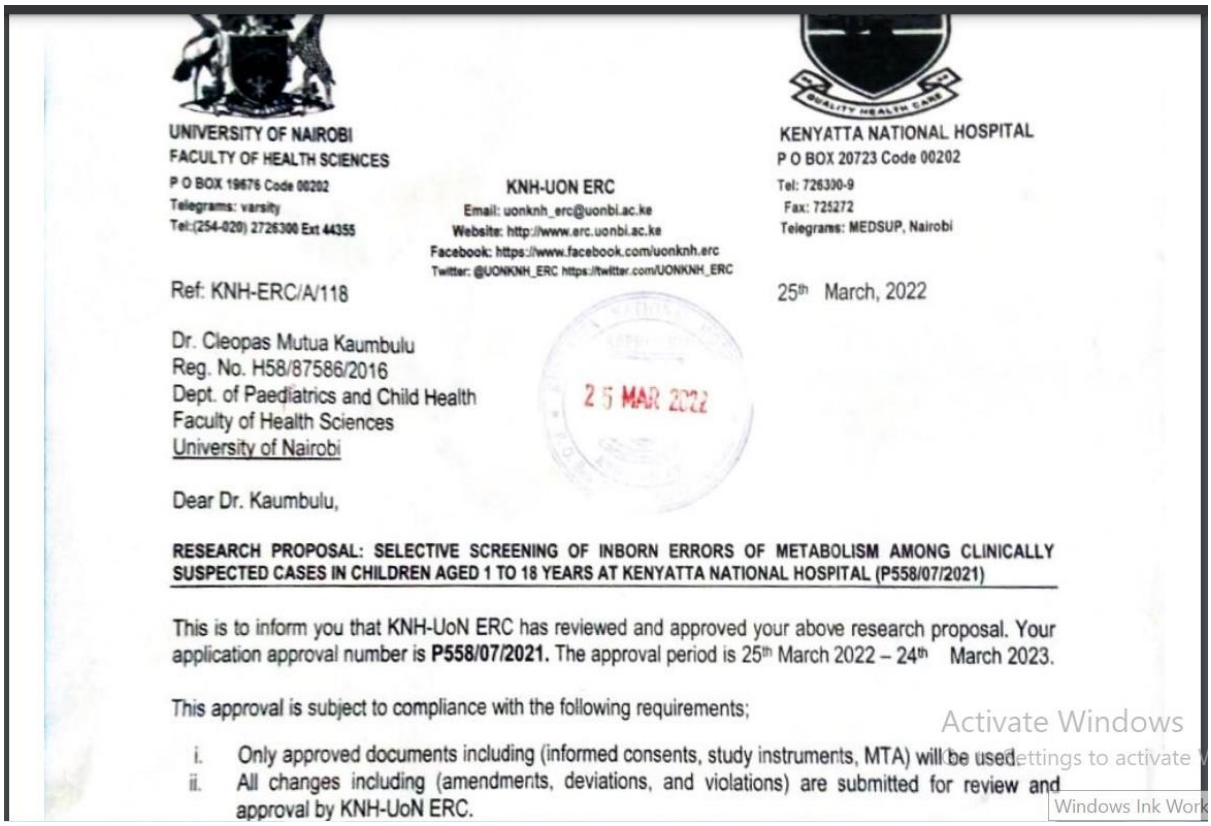
for approval to supply

Specimen receptacle IVDs

ARTG Identifier	279167
ARTG Start date	15/08/2016
Product Category	Medical Device Included - IVD Class 1
GMDN	CT936
GMDN Term	Specimen receptacle IVDs
Intended Purpose	The CentoCard Sample Collection Device is intended to be used as a medium to collect and transport whole blood specimen spots to a laboratory in genetic and biochemical testing. The device includes a tear apart form for collection of demographic information, 1 plastic sleeve, 1 pre addressed envelope for shipping, 1 consent, 1 instruction sheet.

Manufacturer Details	Address	Certificate number(s)
Centogene AG	Schillingallee 68 , Rostock, 18057 Germany	

Appendix 13: Research Proposal Approval KNH-UON ERC (P558/07/2021)



UNIVERSITY OF NAIROBI
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Tel:(254-020) 2726300 Ext 44355

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Website: http://www.erc.uonbi.ac.ke
Facebook: https://www.facebook.com/uonknh.erc
Twitter: @UONKNH_ERC https://twitter.com/UONKNH_ERC

KENYATTA NATIONAL HOSPITAL
P O BOX 20723 Code 00202
Tel: 726300-9
Fax: 725272
Telegrams: MEDSUP, Nairobi

Ref: KNH-ERC/A/118

25th March, 2022

Dr. Cleopas Mutua Kaumbulu
Reg. No. H58/87586/2016
Dept. of Paediatrics and Child Health
Faculty of Health Sciences
University of Nairobi

25 MAR 2022

Dear Dr. Kaumbulu,

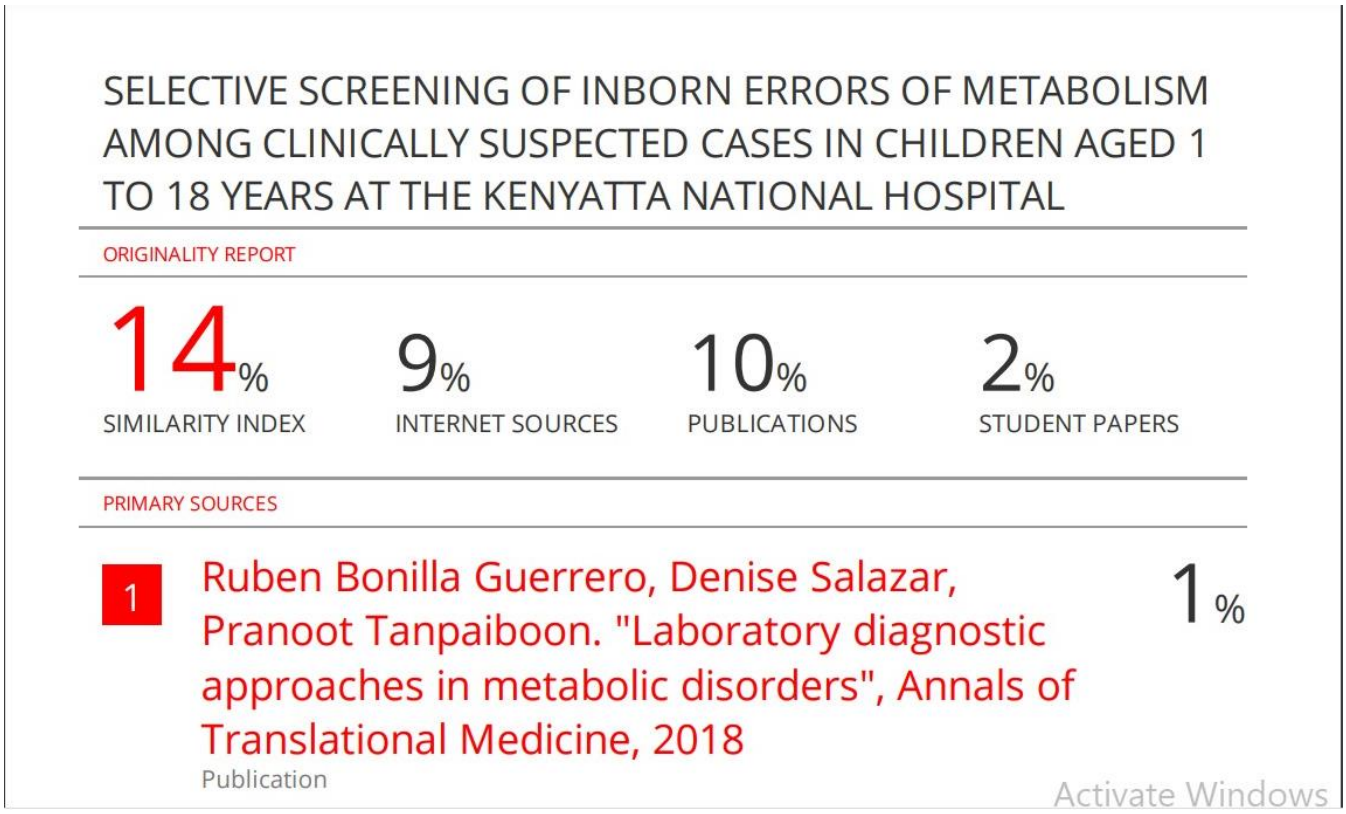
RESEARCH PROPOSAL: SELECTIVE SCREENING OF INBORN ERRORS OF METABOLISM AMONG CLINICALLY SUSPECTED CASES IN CHILDREN AGED 1 TO 18 YEARS AT KENYATTA NATIONAL HOSPITAL (P558/07/2021)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P558/07/2021.** The approval period is 25th March 2022 – 24th March 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.

Appendix 14: Turnitin Similarity Index



SELECTIVE SCREENING OF INBORN ERRORS OF METABOLISM AMONG CLINICALLY SUSPECTED CASES IN CHILDREN AGED 1 TO 18 YEARS AT THE KENYATTA NATIONAL HOSPITAL

ORIGINALITY REPORT

14%	9%	10%	2%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Ruben Bonilla Guerrero, Denise Salazar, Pranoot Tanpaiboon. "Laboratory diagnostic approaches in metabolic disorders", Annals of Translational Medicine, 2018 Publication	1%

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