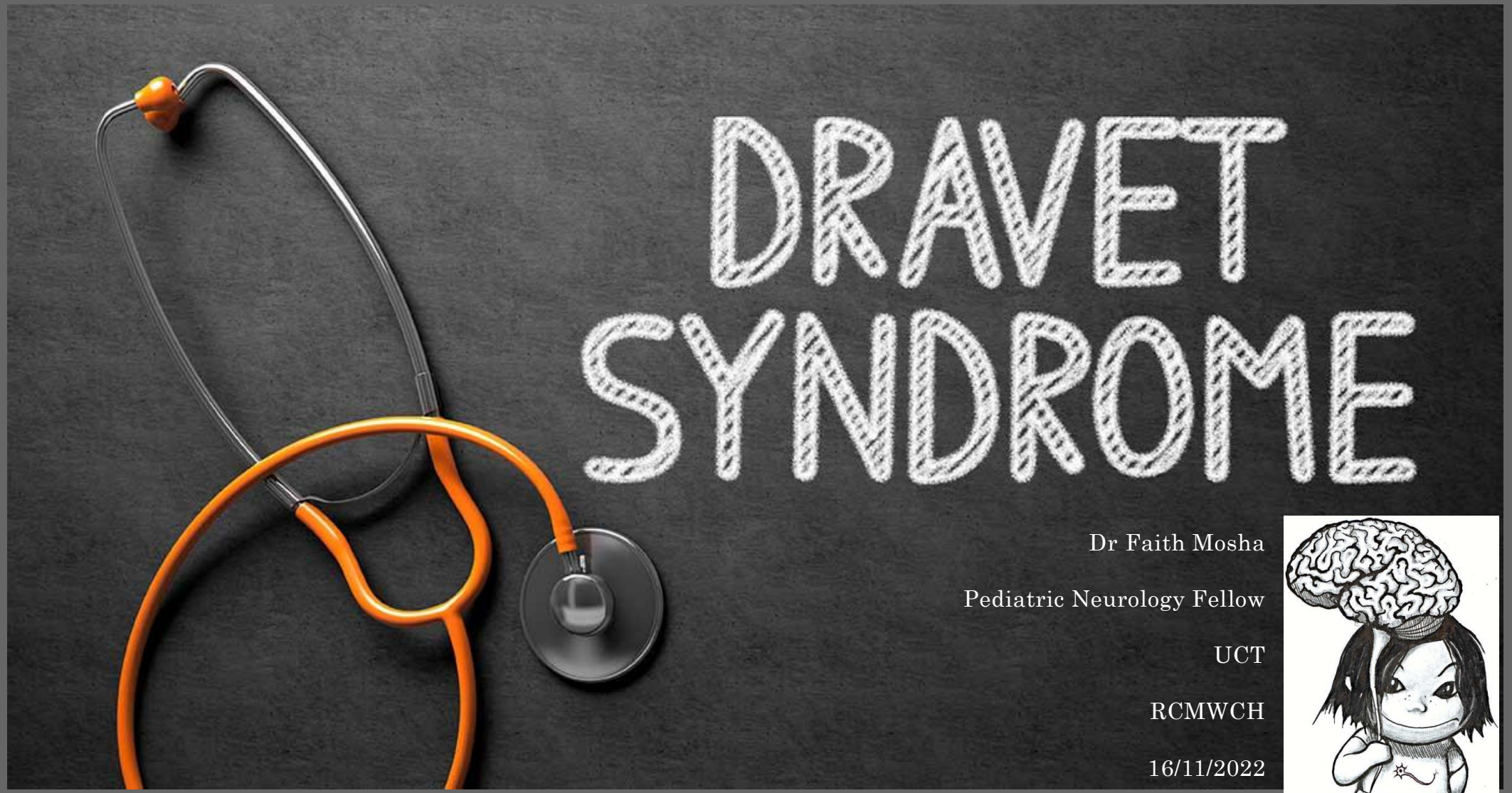



Dr Faith Mosha

Pediatric Neurology Fellow

UCT

RCMWCH

16/11/2022

# Background

## Definition of Epilepsy

***Practical Definition of Epilepsy***

**Table 2. Operational (practical) clinical definition of epilepsy**

Epilepsy is a disease of the brain defined by any of the following conditions

1. At least two unprovoked (or reflex) seizures occurring >24 h apart
2. One unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
3. Diagnosis of an epilepsy syndrome

Epilepsy is considered to be *resolved* for individuals who had an age-dependent epilepsy syndrome but are now past the applicable age or those who have remained seizure-free for the last 10 years, with no seizure medicines for the last 5 years.

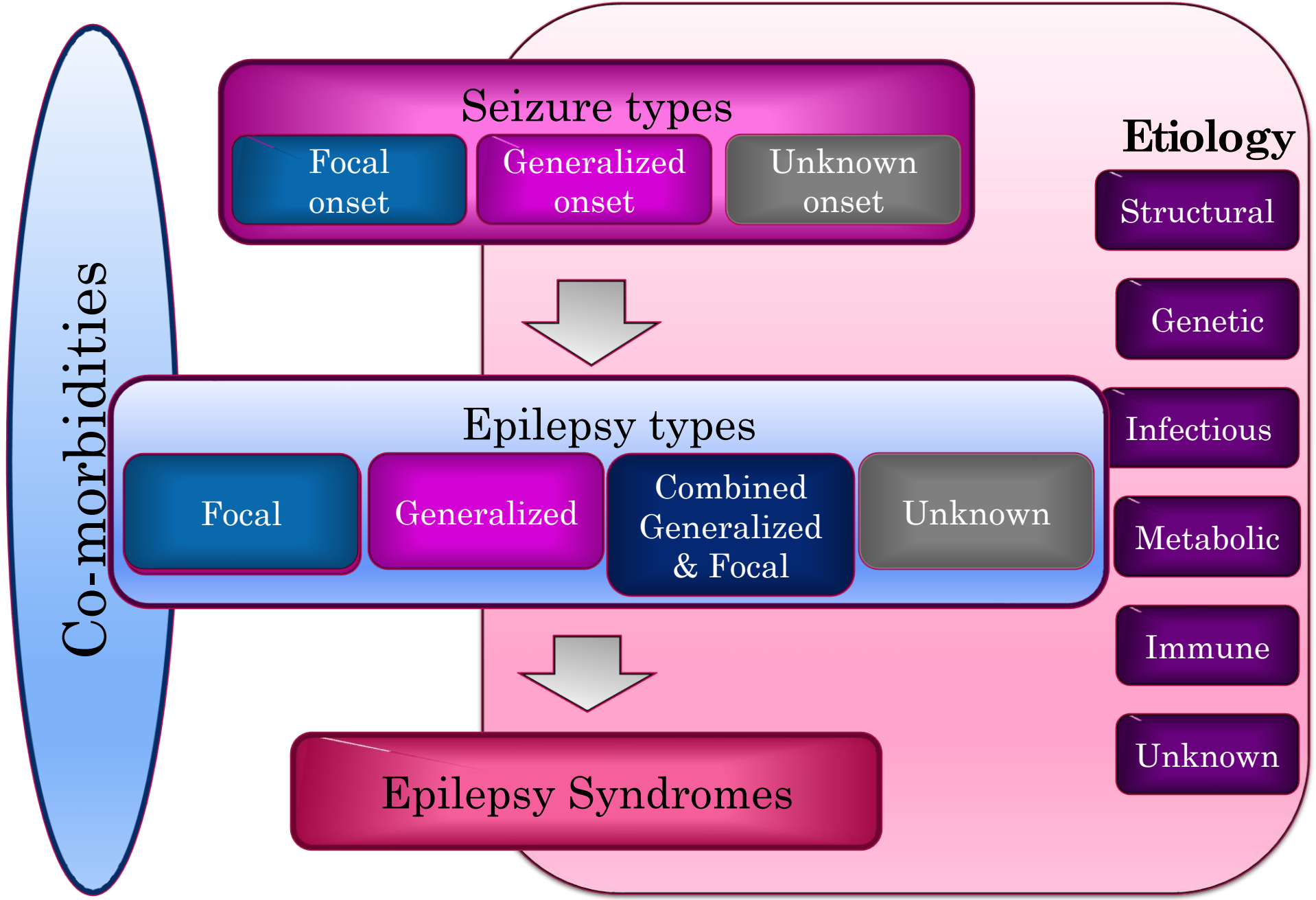
(Fisher et al., 2014)

# Background cont'd

- Epilepsy
  - broad group of disorders with diverse etiologies, electroclinical presentations and marked variability in clinical outcomes
  - classified into epilepsy types based on semiology and underlying etiologies;
  - semiology aids further categorisation into syndromes.

- The 2017 ILAE Classification of the Epilepsies defined 3 diagnostic levels with etiology and comorbidities being considered at each level:
  1. Seizure type
  2. Epilepsy type
  3. Epilepsy syndrome

(Scheffer et al., 2017)


Co-morbidities
Seizure types
Focal onset
Generalized onset
Unknown onset
Epilepsy types
Focal
Generalized
Combined Generalized & Focal
Unknown
Epilepsy Syndromes
Etiology
Structural
Genetic
Infectious
Metabolic
Immune
Unknown

"a characteristic cluster of clinical and EEG features, often supported by specific etiological findings (structural, genetic, metabolic, immune, and infectious)." The diagnosis of a syndrome in an individual with epilepsy frequently carries prognostic and treatment implications. Syndromes often have age-dependent presentations and a range of specific comorbidities.

# Definition of an Epileptic Syndrome

(Scheffer et al., 2017; Wirrell et al., 2022)

# Background cont'd

- Epilepsy syndromes described accordingly by the ILAE revised in 2022:

1. Epilepsy syndromes with onset in
   a) Neonates and infants (up to age 2 years)
   b) Childhood
   c) Variable ages (both paediatric and adults)
   d) Idiopathic generalized epilepsies

2. Subdivided based on
   a) Seizure types - focal, generalized, focal-generalized
   b) Syndromes with **developmental and epileptic encephalopathy (DEE)** or progressive neurological deterioration

(Wirrell et al., 2022)

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DOI: 10.1111/epi.17241

Epilepsia

SPECIAL REPORT

# International League Against Epilepsy classification and definition of epilepsy syndromes with onset in childhood: Position paper by the ILAE Task Force on Nosology and Definitions

Nicola Specchio[1] | Elaine C. Wirrell[2] |
Kate Riney[5,6] | Pauline Samia[7] | Mari
Sameer M. Zuberi[10] | Jo M. Wilmshurst[11]
Edouard Hirsch[14] | Samuel Wiebe[15] |
Solomon L. Moshé[19] | Paolo Tinuper[20,21]

Received: 23 April 2021 | Revised: 20 March 2022 | Accepted: 21 March 2022
DOI: 10.1111/epi.17239

Epilepsia

SPECIAL REPORT

# ILAE classification and definition of epilepsy syndromes with onset in neonates and infants: Position statement by the ILAE Task Force on Nosology and Definitions

Sameer M. Zuberi[1] | Elaine Wirrell[2]
Nicola Specchio[5] | Kate Riney[6,7] |
Pauline Samia[11] | Edouard Hirsch[12]
O. Carter Snead[15] | Samuel Wiebe[16]
Ingrid E. Scheffer[21] | Emilio Perucca
Rima Nabbout[27]

Received: 23 April 2021 | Revised: 18 March 2022 | Accepted: 21 March 2022
DOI: 10.1111/epi.17236

Epilepsia

SPECIAL REPORT

# ILAE definition of the Idiopathic Generalized Epilepsy Syndromes: Position statement by the ILAE Task Force on Nosology and Definitions

Edouard Hirsch[1] | Jacqueline French[2] | Ingrid E. Scheffer[3] | Alicia Bogacz[4] |
Taoufik Alsaadi[5] | Michael R. Sperling[6] | Fatema Abdulla[7] | Sameer M. Zuberi[8] |
Eugen Trinka[9,10] | Nicola Specchio[11] | Ernest Somerville[12] | Pauline Samia[13] |
Kate Riney[14,15] | Rima Nabbout[16] | Satish Jain[17] | Jo M. Wilmshurst[18] |
Stephane Auvin[19,20] | Samuel Wiebe[21] | Emilio Perucca[22,23] |
Solomon L. Moshé[24] | Paolo Tinuper[25,26] | Elaine C. Wirrell[27]

## Self-limited epilepsies

- Self-limited neonatal epilepsy (SeLNE)
- Self-limited familial neonatal-infantile epilepsy (SeLFNIE)
- Self-limited infantile epilepsy (SeLIE)
- Genetic epilepsy with febrile seizures plus (GEFS+)
- Myoclonic epilepsy in infancy (MEI)

## Developmental and epileptic encephalopathies (DEE)

- Ealy infantile developmental and epileptic encephalopathy (EIDEE)
- Epilepsy in infancy with migrating focal seizures (EIMFS)
- Infantile epileptic spasms syndrome (IESS)
- Dravet syndrome (DS)

# Organization of epilepsy syndromes that begin in neonates and infants

### Etiology-specific syndromes

- *KCNQ2*-DEE
- Pyridoxine-dependent (*ALDH7A1*)-DEE (PD-DEE)
- Pyridox(am)ine 5'-Phosphate Deficiency (PNPO)-DEE (P5PD-DEE)
- *CDKL5*-DEE
- *PCDH19* clustering epilepsy
- Glucose Transporter 1 Deficiency Syndrome (GLUT1DS)
- Sturge Weber syndrome (SWS)
- Gelastic seizures with hypothalamic hamartoma (GS-HH)

(Zuberi et al., 2022)

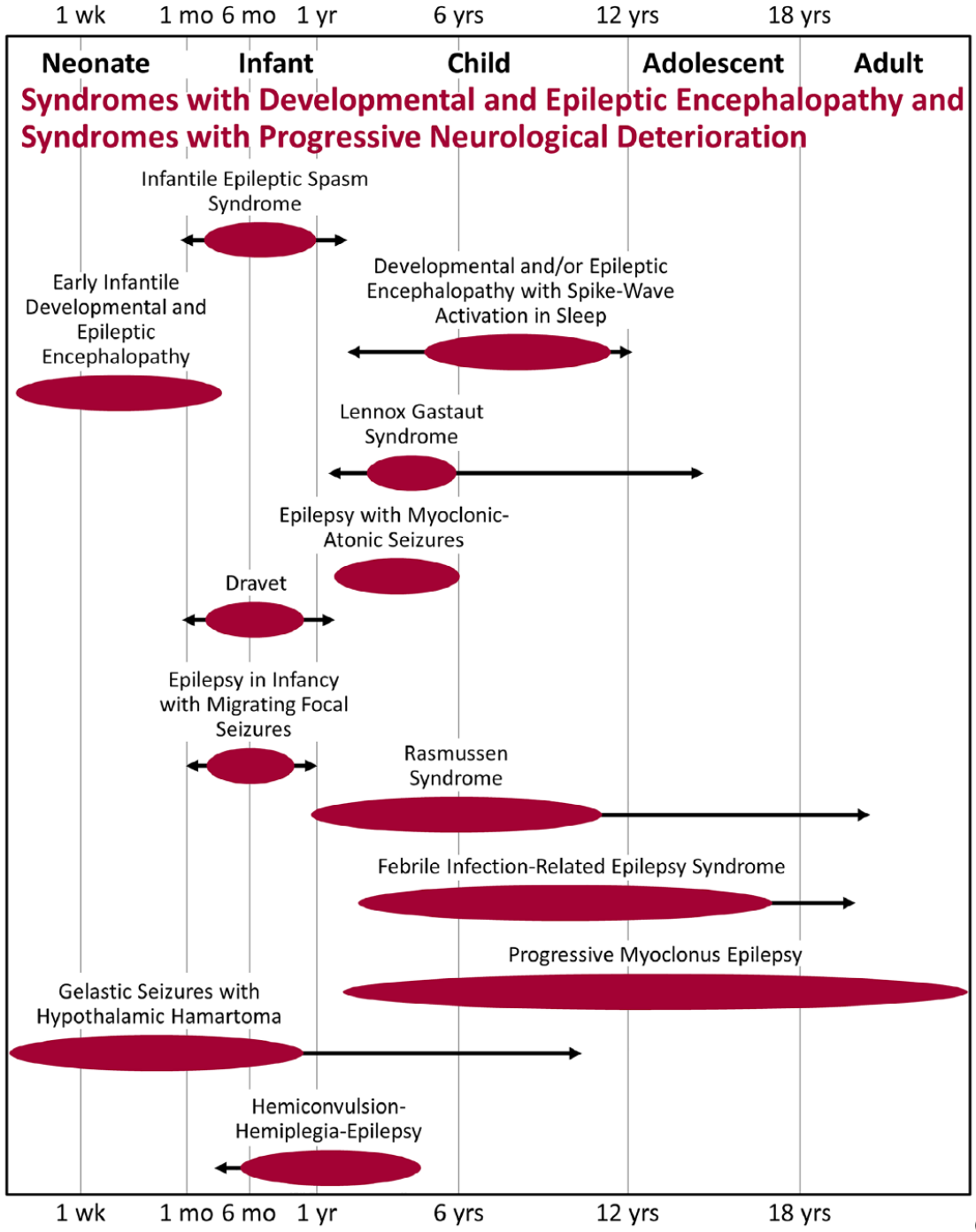
# Developmental and Epileptic Encephalopathy

- DEE is an epilepsy associated with developmental impairment that may be due to
  - underlying etiology (developmental encephalopathy) **and** superimposed epileptic activity (epileptic encephalopathy).

- Most DEEs present very early in life during early infancy

- In most patients with DEE, the most common cause is of genetic origin
  - genetic variant is responsible for both cognitive impairment and epilepsy severity
  - despite seizure control, the cognitive outcome is expected to be poor.

(Zuberi et al., 2022) (Raga et al., 2021)



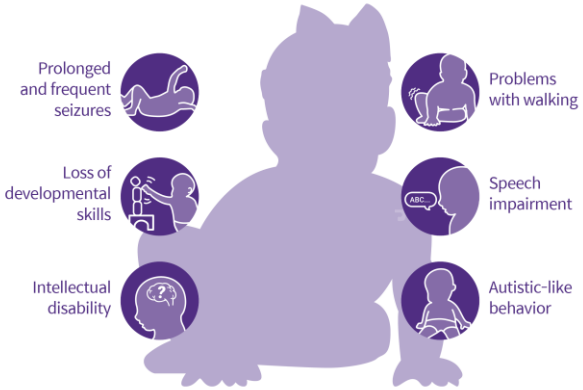

(Wirrell et al., 2022)

# Dravet Syndrome

- An epilepsy syndrome under the umbrellas of "**Developmental and Epileptic Encephalopathies**"
- First described in 1978 as severe myoclonic epilepsy of infancy (SMEI) by Charlotte Dravet
- Later renamed to Dravet syndrome in 1989
  - myoclonic component not always present and some variability has been observed in the symptomatology
- Rare form of early-onset genetic epilepsy syndrome
  - manifests in infancy as intractable epilepsy and neurodevelopmental delays

(Dravet, 2011;Anwar et al., 2019)

# Dravet Syndrome




- Main characteristics

  - Onset - recurrent prolonged febrile and then afebrile seizures from 3 months of age in a child with normal growth and development

  - Subsequent seizures - multiple types
    - intractable focal or generalized clonic or hemiclonic seizures with alternating laterality
    - myoclonic and atypical absences between the age of 1 and 4 years
    - behavioural and cognitive regression usually from the age of 2 years onwards

  - Majority have drug-resistant epilepsy and other associated symptoms greatly impacting their QOL

(Anwar et al., 2019; Wirrell et al., 2022)

# Epidemiology of DS

- Limited data
  - USA
    - An estimated 1 in 15,700 individuals, 80-90% have both SCN1A mutation and clinical phenotype
  - Scotland
    - Incidence of 6.5 per 100,000 live births, all patients diagnosed with DS had a de novo pathogenic variant in the SCN1A gene
  - In Africa – unknown incidence
    - Lack of awareness, limited epilepsy research and/or genetic testing
    - Study in SA by Alina et al in 2018 – identified 25 children with DS based on clinical phenotype; genetic analysis showed 41% had a SCN1A gene mutation

(Wu et al., 2015; Symonds et al., 2021; Esterhuizen et al., 2018)

Seizure: European Journal of Epilepsy 62 (2018) 99–105

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Seizure: European Journal of Epilepsy

journal homepage: www.elsevier.com/locate/seizure


# Dravet syndrome in South African infants: Tools for an early diagnosis

Alina I. Esterhuizen[a,b,*], Heather C. Mefford[c], Rajkumar S. Ramesar[a,b], Shuyu Wang[d], Gemma L. Carvill[e], Jo M. Wilmshurst[f,g]

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Esterhuizen, A. I., Mefford, H. C., Ramesar, R. S., Wang, S., Carvill, G. L. & Wilmshurst, J. M. 2018. Dravet Syndrome In South African Infants: Tools For An Early Diagnosis. *Seizure,* 62, 99-105.

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*Keywords:*
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Fbrile seizures
Epileptic encephalopathy
Sub-Saharan Africa
Genetic epilepsy
*SCN1A*

ABSTRACT

*Purpose:* Dravet syndrome (DS) is a well-described, severe genetic epileptic encephalopathy with an increased risk of SUDEP. The incidence and genetic architecture of DS in African patients is virtually unknown, largely due to lack of awareness and unavailability of genetic testing. The clinical benefits of the available precision medicine approaches to treatment emphasise the importance of an early, correct diagnosis. We investigated the genetic causes and clinical features of DS in South African children to develop protocols for early, cost-effective diagnosis in the local setting.

*Method:* We selected 22 South African children provisionally diagnosed with clinical DS for targeted re-sequencing of DS-associated genes. We sought to identify the clinical features most strongly associated with *SCN1A*-related DS, using the DS risk score and clinical co-variates under various statistical models.

*Results:* Disease-causing variants were identified in 10 of the 22 children: nine *SCN1A* and one *PCDH19*. Moreover, we showed that seizure onset before 6 months of age and a clinical DS risk score of $> 6$ are highly predictive of *SCN1A*-associated DS. Clinical reassessment resulted in a revised diagnosis in 10 of the 12 variant-negative children.

*Conclusion:* This first genetic study of DS in Africa confirms that *de novo SCN1A* variants underlie disease in the majority of South African patients. Affirming the predictive value of seizure onset before 6 months of age and a clinical DS risk score of $> 6$ has significant practical implications for the resource-limited setting, presenting simple diagnostic criteria which can facilitate early correct treatment, specialist consultation and genetic testing.

Esterhuizen, A. I., Mefford, H. C., Ramesar, R. S., Wang, S., Carvill, G. L. & Wilmshurst, J. M. 2018. Dravet Syndrome In South African Infants: Tools For An Early Diagnosis. *Seizure,* 62**,** 99-105.

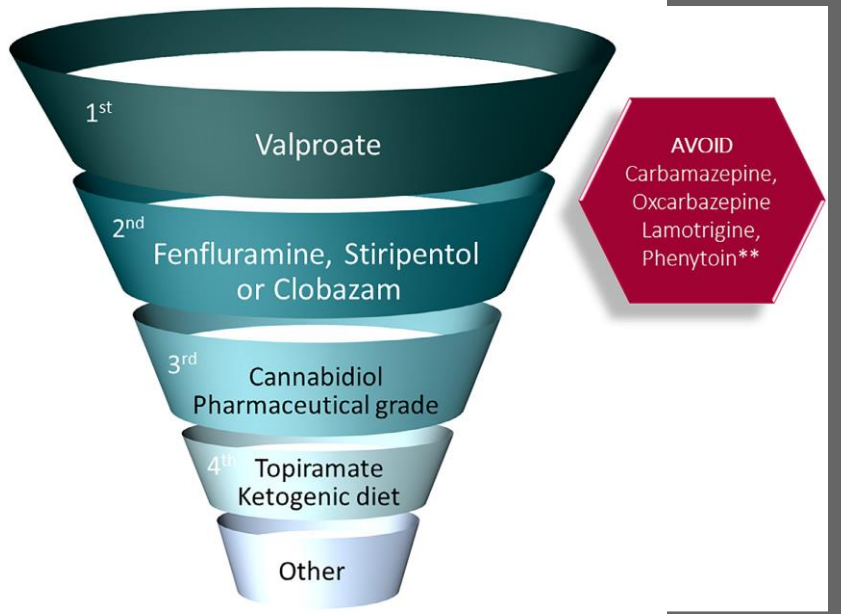
# Treatment of DS

- Treatment of DS is challenging and largely empirical mainly targeted at seizure control based on trial and error

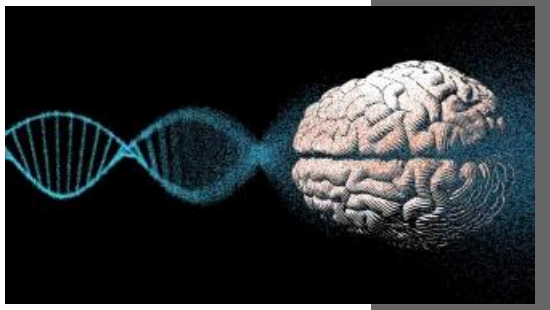
- DS children often have hemiclonic seizures and are often inappropriately managed
  - Main target is seizure control, worsening uncontrolled seizures aggravates cognitive impairment
  - 1st line ASMs – CBZ, Phenobarbitone and Lamotrigine can exacerbate seizures
  - Good seizure control improves patient and family's overall quality of life

- Several studies looking into existing safe and effective medication
  - FDA approved between June 2018 – August 2020
  - Stiripentol, flenfluramine, pharmaceutical cannabidiol
  - Disease modifying agents targeting affected sodium channel (STK-001, ETX-101)
    - Reduced overall mortality in animal mice models, human trials are future enterprises

(Esterhuizen et al., 2018; Wirrell et al., 2022)



# Genetic testing - DS



- Genetic basis of DS was discovered in a study done by Claes et al in 2001 in 7 unrelated DS patients

- Genetic mutations discovered:
  - Mutation in the voltage-gated sodium channel, alpha-1 subunit (*SCN1A*) gene on chromosome 2q24
  - More than 90% were de novo mutations
  - Missense familial mutations were located in only 5%-10%
  - The difference in phenotype and severity is reflected in the nature of *SCN1A* mutations identified in patients

- Screening test for predicting DS before 1yr of age developed in 2007 by Hattori et al
  - designed to be used by general paediatricians
  - help predict Dravet syndrome before one year of age
  - a clinical risk score of ≥6 → high risk of DS and recommend genetic analysis testing

(Claes et al., 2001; Hattori et al., 2008)

*Epilepsia*, 49(4):626–633, 2008
doi: 10.1111/j.1528-1167.2007.01475.x

**FULL-LENGTH ORIGINAL REASARCH**

# A screening test for the predict[illegible] of Dravet syndrome before one yea[illegible]

*Junri Hattori, †Mamoru Ouchida, *Junko Ono
¶Nobuyoshi Mimaki, *Yoko Ohts

Departments of *Child Neurology and †Molecular Genetic
Pharmaceutical Sciences, Okayama University, Okayama, Japan
Takamatsu, Kagawa, Japan; §Matsuyama Red Cross Hospital, Pe
Pediatrics, Okayama, Japan; and **Department of Physiolog
Pharmaceutical Sciences, Okayama U

**Table 3. A proposed risk score for a screening test**

| Predictive risk factors | Risk score |
|---|---|
| Clinical score | |
| Onset ≤ 7 months | 2 |
| Total number of seizures ≥ 5 | 3 |
| Hemiconvulsion | 3 |
| Focal seizure | 1 |
| Myoclonic seizure | 1 |
| Prolonged seizure | 3 |
| Hot water–induced seizure | 2 |
| Genetic score | |
| SCN1A missense mutation | 1 |
| SCN1A truncated mutation | 2 |

**Clinical risk score of ≥6 → high risk of DS and recommend genetic analysis testing**

*Epilepsia*, 49(4):626–633, 2008
doi: 10.1111/j.1528-1167.2007.01475.x

(Hattori et al., 2008)

# Genetic testing - DS cont'd

- >80% of children with suspected DS have a de novo pathogenic variant in the alpha-1 subunit of the *SCN1A* gene,
  - however, not all children with *SCN1A* variants have DS
  - Other variants in other genes – *SCN2A, PCDH19, GABRA1, GABARG2* are associated with the syndrome

- Recent studies and consensus for high suspicion of DS and mandates for genetic testing:
  - Infants aged 2-15 months presenting with
    - first onset of a prolonged hemiclonic seizure or convulsive status epilepticus of unknown cause, provoked with fever or following vaccination

(Hattori et al., 2008; Wirrell et al., 2022)

**TABLE 1** Clinical presentation: in a developmentally normal child, who presents with seizures of unknown cause (normal magnetic resonance imaging, normal laboratory studies, ± normal cerebrospinal fluid studies), genetic testing to exclude DS should be performed with the following seizure types

| Seizure | Age 2–5 months | | | Age 6–15 months | | |
|---|---|---|---|---|---|---|
| | Without fever | With fever | After vaccination | Without fever | With fever | After vaccination |
| Single seizure | | | | | | |
| Prolonged (5–29 min) GTCS | 63%[a] | 74%[b] | 74%[b] | 63%[a] | 58%[a] | 68%[b] |
| Prolonged (5–29 min) hemiclonic seizure | 68%[b] | 84%[c] | 95%[c] | 68%[b] | 84%[c] | 89%[c] |
| Focal or generalized convulsive status epilepticus (≥30 min) | 74%[b] | 84%[c] | 89%[c] | 74%[b] | 84%[c] | 89%[c] |
| Recurrent seizures | | | | | | |
| Recurrent brief (<5 min) convulsive seizures | 63%[a] | 58%[a] | | 58%[a] | 58%[a] | |
| Recurrent brief (<5 min) hemiclonic seizures | 68%[b] | 74%[b] | | 79%[b] | 79%[b] | |
| Recurrent prolonged focal or generalized convulsive seizures (5–29 min) | 89%[c] | 100%[c] | | 84%[c] | 95%[c] | |
| Recurrent focal or generalized convulsive status epilepticus (≥30 min) | 89%[c] | 95%[c] | | 89%[c] | 95%[c] | |

*Note:* Based on 19 physician responses.

Abbreviations: DS, Dravet syndrome; GTCS, generalized tonic–clonic seizure.

[a]Responses indicate no consensus for genetic testing for DS.

[b]Responses indicate Moderate consensus for genetic testing for DS.

[c]Responses indicate Strong consensus for genetic testing for DS.

(Wirrell et al., 2022)

# Importance of genetic testing in DS

- Early treatment is important and can improve the overall developmental outcome and quality of life

- In resource limited settings, burden of disease from seizures is still the highest in Africa
  - In South Africa,
    - high burden of infections, likely that most seizures are provoked
    - infants with DS are at risk of not being recognised, diagnosed, and treated timeously thus leading to worse outcomes.

- Universal consensus on the impact for precision medicine in children with DS
  - potentially reduce the frequency of seizures
  - reduce the occurrence of comorbidities associated with DS:
    - intellectual disability, gait and sleep problems and behavioural concerns
  - improve the overall quality of life for the child and the family

(Esterhuizen et al., 2018; )

# Importance of genetic testing in DS

- The clinical utility of genetic testing
  - provides a foundation for a precision diagnosis
  - promotes capacity for precision medical therapy
  - enables exploration of further product development based on insight into the underlying gene function
  - overall provides diagnostic closure and targeted knowledge to be relayed to the affected family.

(Jeffrey et al., 2021)

- In sight of this, there is limited research looking into the personal implications of genetic testing, that is, the psychological and social value of genetic testing of the patient and parent/caregiver

# Implications of access to genetic testing in children with Dravet Syndrome

By: Dr. Faith Mosha

Supervisors: Prof Jo Wilmshurst

Alina Esterhuizen

# Problem Statement

- Epilepsy genetic testing is not routinely available in South Africa in the public sector.
- Study done in SA in 2018 achieved these results from a research study on epilepsy genetics when the screening was set up in-house or via named patient motivation through an overseas genetic testing resource, Invitae.
- Both processes are no longer routinely available and access to genetic studies for DS and other genetic epilepsy is even more limited as a result.
- Parents/caregivers of children with DS play the role of primary caregiver, advocate, and decision maker in their child's care. Their experience and insight is important – it guides and shapes the overall understanding of what the most meaningful aspect of their child's life for which treatment could have the greatest impact.

# Motivation of the study

- In light of this, this study aims to understand the impact of genetic testing – potential gains and implications to patient care and the relevance of access to definitive genetic testing.

- To understand whether the genetic results:-

  ✓ had a positive or negative impact on the parents/caretakers – personal psychological and social aspect, improved QOL, follow-ups/lost to follow up

  ✓ affected overall treatment management (changes, additions) and outcomes of children with DS (clinical utility, developmental assessment, rehabilitation therapy and improvement in ADLs)

# Aim

To explore and justify the implications of access to genetic testing in children with Dravet Syndrome

# Research Questions

- *What are the implications of access to genetic testing in children with Dravet Syndrome?*

- *Can we justify the implication of access to genetic testing in children with DS?*

# Specific objectives

1. To determine the incidence of children with clinically and genetically confirmed DS recruited from the epilepsy genetic study done in the Epilepsy Clinic at RCWMCH from 2016 to 2022. (HREC 232/2015)

2. To identify the type of treatment given, seizure control and clinical outcomes of children with clinically and genetically confirmed DS

3. To describe the impact of genetic testing in children with DS on the patient and family/caregiver – change in treatment, change in management outcomes

4. To explore the personal psychological and social implications of genetic testing in children with DS on the patient and parent/caregiver

# Methodology

## Study design

- Mixed methods sub study of a larger study that was previously conducted in the Epilepsy Clinic at RCWMCH between 2016 and 2022 identifying all children with clinically and genetically confirmed DS. (HREC 232/2015)

## Quantitative

- Data collected from pre-existing hospital records
  - Retrospective and prospective
  - Incidence, treatment given, seizure control, clinical outcomes

## Qualitative

- Prospective patient-oriented research
  - In-depth semi-structured questionnaires
  - Face-to-face interviews

# Methodology

## Study area

- RCWMCH, a tertiary teaching hospital affiliated with the University of Cape Town, the largest dedicated children`s hospital with the only specialised Pediatric Epilepsy clinic in sub-Saharan Africa
- The neurology service and clinic predominantly manages children and adolescents from the Western Cape and the remainder from further afield

## Study population

- All children with clinically phenotypic and/or genetically confirmed DS will be recruited as a direct result of the epilepsy genetic study done in the Epilepsy Clinic at RCWMCH between 2016 and 2022 (HREC 232/2015) and a smaller number subsequent to this who were screened via the named patient motivation for Invitae testing.

# Methodology

## Sampling method

- Convenience sampling method - all children recruited from the previous cohort study as a direct result of the epilepsy genetic study done between 2016 and 2022 in the Epilepsy clinic at RCWMCH will be enrolled. (n=25 children)

## Inclusion criteria

- All children with clinically phenotypic and/or genetically confirmed DS recruited from previous study done at RCWMCH with obtained consent

## Exclusion criteria

- Children with clinically phenotypic and/or genetically confirmed DS whose parents do not consent to the study
- Children with clinical phenotypical DS with inadequate hospital record notes
- Children with clinical phenotypical DS who are lost to follow up

# Methodology: Data management

## Quantitative Data collection

- Data will be collected from the previous DS study with genetically identified children with DS (n=25) and entered into a REDCap database
  - clinical demographics, seizure semiology, seizure evolution, seizure control, treatment history, family history, clinical risk score, investigations, genetic results and clinical outcome

## Qualitative Data collection

- Self-constructed semi-structured questionnaires – open and closed ended questions
  - General experience, impact on overall personal psychological and social aspect of the patient and the parent/caregiver
- Written informed consent for participation
- Interview will be no longer than 30 minutes, undertaken on days when the family are attending for clinic
- Families given the option of holding the interview in English, Afrikaans or IsiXhosa
- All interviews will be transcribed and translated by the researcher (me) accordingly.

# Methodology: Data management

## Quantitative analysis

- Data  analysis will be conducted using Statistical Software for Social Science (SPSS )
- Descriptive statistics including frequencies and means will be generated and summarised in tables and figures
- Any associations will be explored using the Chi-square or Fisher exact test (p-values will be considered significant if less than 0.05) where applicable.

## Qualitative analysis

- Data obtained will be transcribed verbatim to gain general understanding of the content, identify emerging themes and develop a structured coding framework
- Patterns of meaning/themes will be identified with aim of capturing shared understandings of the implications of access to genetic testing while highlighting each participants' individuals experience variation
- Coded information will be analyzed with appropriate software associated with qualitative method anaylsis to ensure accuracy

# Ethical considerations

- This study proposal will be submitted to the RCWMCH Research committee for approval then to the University of Cape Town Faculty of Health Science Human Research and Ethics Committee for review and approval before study commencement then submitted to the hospital administration for clearance.
- The patients will be de-identified from the data collection tool to ensure that anonymity and confidentiality is maintained, unique numerical identifiers will be used instead.
- The data analysis will be combinations of findings and will not be in a form to permit individuals to be identified.
- All parents will be asked to give consent for their children's details to be collected and to take part in the qualitative survey and where possible the children provide assent. Translated consent forms in the local language will be included.
- Parents will be able to choose the language of their choice for the interviews.
- The study will not require additional interventions to the children and will not result in an additional cost to the hospital or the parents of the affected children.

# Limitations

- Some families may no longer be accessing the clinic or may decline to be interviewed.
- The caregiver may not be the person most involved in the home care of the child and every attempt will be made to ensure that the interview is with the primary caregiver.
- The study numbers may be too small to measure effective statistical outcomes for this rare disease.

# Dissemination

- The research will be presented to the Department of Paediatrics and Child Health Research days and any relevant congress/ scientific conferences in 2022/2023.

- In addition, the study will be published in a peer-reviewed journal.

- A bound thesis will be submitted to the University of Cape Town in partial fulfilment for the award of an MPhil.

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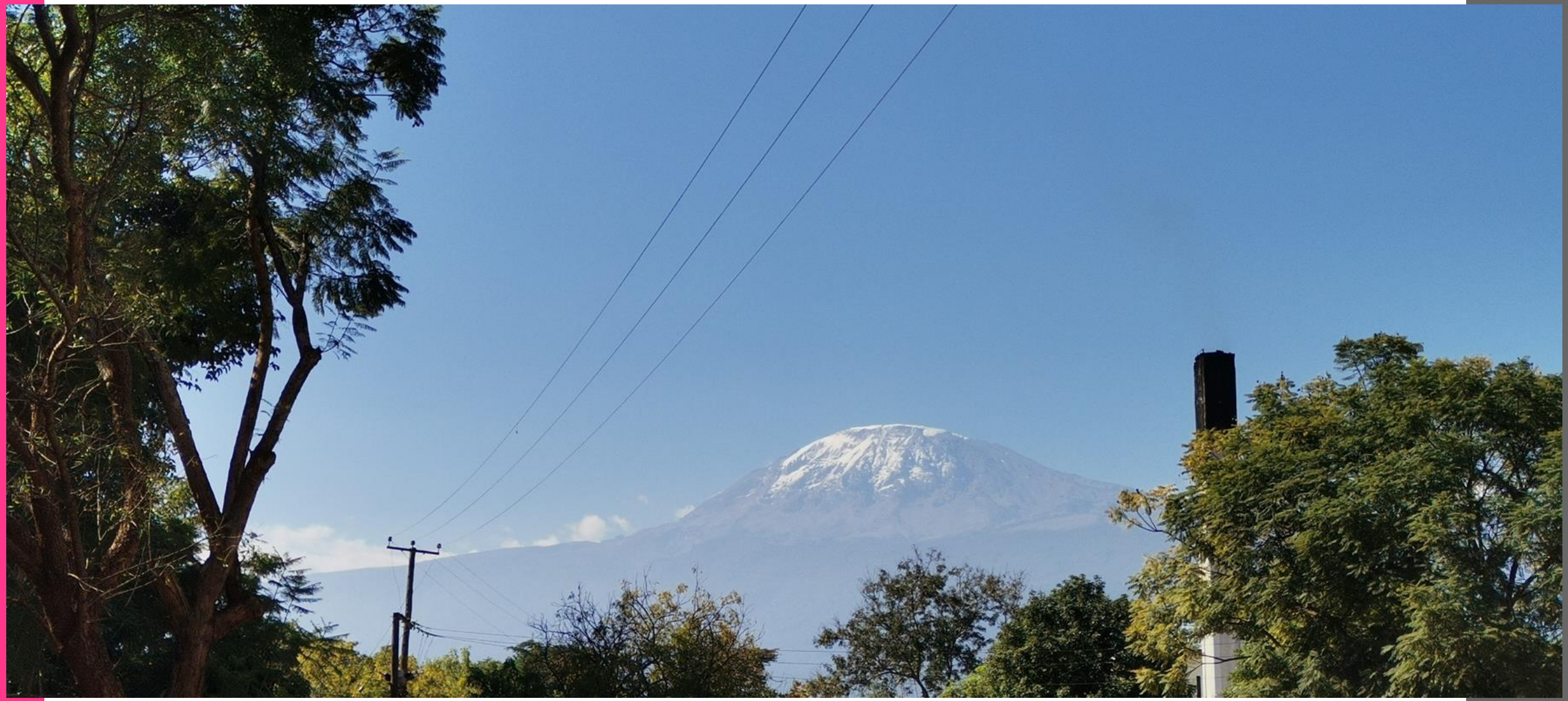

# Thank you