RARE DISEASES MANAGEMENT FRAMEWORK

DEPARTMENT OF HEALTH & FAMILY WELFARE
GOVERNMENT OF KERALA

KERALA.HEALTH

Contents

Contribution

Centre of Excellence for RARE Disease , SAT hospital,

Government Medical College, Thiruvananthapuram

Dr SANKAR V H	Professor & HOD, Department of Medical Genetics, SAT hospital, Government Medical College, Thiruvananthapuram Nodal Officer, COE for Rare Disease
Dr BINDU S	Superintendent, SAT hospital Government Medical College, Thiruvananthapuram
Dr P K JABBAR	Principal, Government Medical College, Thiruvananthapuram
Dr BINDU G S	Professor & HOD, Department of Paediatrics SAT hospital, Government Medical College, Thiruvananthapuram
Dr MARY IYPE	Professor & HOD, Department of Paediatric Neurology, SAT hospital, Government Medical College, Thiruvananthapuram (In charge – SMA Clinic – SAT hospital)
Dr ARUN SREE PARAMESWARAN	Assistant Professor, Department Of Medical Genetics, SAT Hospital, Government Medical College, Thiruvananthapuram
Dr PIO JAMES	Assistant Professor, Department of Obstetrics & Gynaecology, SAT hospital, Government Medical College, Thiruvananthapuram (In Charge- SHRDHA clinic- foetal medicine)
Dr VINITHA A O	Associate Professor, Department of Paediatrics, SAT hospital, Government Medical College, Thiruvananthapuram

Dr DEEPA	Director in Charge, Child Development Centre, Thiruvananthapuram
Dr RAHUL U R	State Nodal Officer, Child Health Division and RARE Disease, Government of Kerala
Smt. ASUNDHA	Public Relations Officer . RARE Disease cell, SAT Hospital,
Smt. SHERRIN T ALEX	Genetic Counsellor and Patient coordinator Genetic lab, CDC, Trivandrum
Smt. ATHIRA	Staff Nurse, SHRDA Clinic (USG and Prenatal procedures) CDC Trivandrum
Dr ASWATHY	Molecular Geneticist, Genetics LAB, CDC
Smt. REMYA S	Cytogeneticist, Genetics LAB, CDC
Smt. HARITHA DASARADH	Biochemist, Genetics LAB, CDC
Dr VINEETHA	Research Associate, ICMR Registry
Dr ANJANA	Molecular Geneticist, NIDAN KENDRA (DBT) Genetic LAB, Department of Medical Genetics
Dr DEEPA	Molecular Geneticist, NIDAN KENDRA (DBT) Genetic LAB, Department of Medical Genetics
Smt. AJITHA ROSE	Cytogeneticist, Genetic LAB, MDRL
Mr.HARILAL	Accounts Officer, Government Medical College, Thiruvananthapuram
Mr. ANILKUMAR G	Lay Secretary, SAT Hospital

Foreword

Health Departments faces various challenges all the time. It is round the clock emergency handling department. Out of these challenges to work out rare disease program was a tough task.

However, without getting overwhelmed by the difficulties, the team along with Dr Sankar V H , Dr Sreehari, Dr Asheel and others started detailed study and initiated a set of actions to work on this area. Hon High Court took the cognisance and asked for the personal appearance of the Secretary. The Hon Court studied the whole science of rare disease and given a direction by facilitating opening of crowd funding mechanism exclusively for rare disease management. We respectfully thank the judge for giving the guidance. The approach taken by the State later on adopted by the Ministry of Health and Family Welfare and a national policy was rolled out. This initiative got further strengthened with the Government commitment to work out a program to tackle rare diseases KARe (Kerala against Rare diseases). Dr Vinay MD KMSCL and SMD NHM, Dr Rahul State nodal officer for child health , Dr Arun General Manager KMSCL coordinated the program.

Kerala health continued its effort by taking up the matter with Director General Patent and Trademark, Drug Controller of India, Director General ICMR and Secretary Health & Family Welfare Govt of India with a request to work on compulsory licensing, generic formulations, so that all the cases in the country can be dealt with properly. We hope it will materialize soon.

We sincerely appreciate the wholehearted support of people and other CSR donors who donate the amount for rare disease. We thank KMSCL who do management of drug procurement and supplies to the hospitals.

I take this opportunity to acknowledge the work done by Dr Sankar by constantly giving the guidance and continuously working to build the Department of Genetics and laying the foundation of futuristic interventions to tackle the diseases.

This book presents a comprehensive information regarding evolution of rare disease management, governance mechanism evolution, service delivery processes, and advocacy with the authorities at Government of India level.

I am confident that it will serve as a valuable reference for policymakers and administrators, supporting evidence-based planning and further strengthening the program to make it accessible to many families all over the country.

Dr Rajan Khobragade IAS

Addl Chief Secretary

Health and Family Welfare

Government of Kerala

A rare disease is any disease of low prevalence that affects a small number of people compared with other prevalent diseases in the general population. It comprised of approximately 7,000 different rare diseases and disorders affecting more than 300 million people worldwide according to the Global Genes Project . Though rare diseases are of low prevalence and individually rare, collectively they affect considerable proportion of the population of any country, around 6-8%. Many of the rare disease are life-threatening or chronically debilitating. Most rare diseases are genetic (80%), and thus are present throughout the person's entire life, even if symptoms do not immediately appear. Many rare diseases appear early in life (50%), and about 30 percent of children with rare diseases will die earlier. Only about 400 rare diseases have therapies and about 80% have a genetic component. Work over the past 25 years has resulted in the identification of genes responsible for ~50% of the estimated 7,000 rare monogenic diseases. Improved understanding of rare diseases is key for accurate and timely diagnosis.

1. Rationale: Challenges in rare diseases

1.1 Definition and lack of epidemiological data

WHO defines rare disease as often debilitating lifelong diseases or disorder with a prevalence of 1 or less, per 1000 population. However, different countries have their own definitions to suit their specific requirements and in context of their population, health care systems and resources. For arriving at a proper definition of rare disease, we need to consider prevalence, disease qualifier and treatment options. In India, at present we are not having any definition based on prevalence data due to lack of epidemiological studies and National Policy for RARE disease (NPRD 2021) uses operational definition based on availability of treatment. This underscores the need for a state wide registry for the rare diseases.

1.2 Diagnosis of rare Disease

Diagnosis of a rare disease may take up to several years, owing to difficulty in diagnostic modalities and lack of awareness among doctors. The mean time to diagnosis the rare diseases is about 6 years and patients receive several incorrect diagnoses during this time. A multiplicity of factors renders diagnosing a rare disease extremely difficult. Symptoms are often hidden behind more common illnesses and initially, may appear to be of only minor concern. Delays in diagnosis can lead to inappropriate management as well as disease progression. Misdiagnosis can also lead to additional intervention. An accurate and timely diagnosis is the first step to improving care for people with rare diseases and their families. Genetic testing is very important to confirm the disease. Family history

and genetic testing of the parents will help to ensure an earlier diagnosis, and prenatal screening can be ensured.

1.3 Challenges in Treatment

Despite the advances in medical sciences, no effective and safe treatment is available for many rare diseases. Of the 7000 rare disorders, less than 300 have therapies available to treat them. Where drugs available, they are prohibitively expensive, placing immense strain on resources of families, health systems and donor agencies. Since the affected people are very small, the pharmaceutical industry reluctant to invest money in research and development of drugs for these conditions. There are no domestic manufactures of drugs for rare diseases in India. Since most of these rare disorders are genetic, genetic counselling should be offered to families affected with these disorders. Moreover, if one child with disorder identified in the family, prenatal diagnosis can be done on the next pregnancy or other family members which will reduce the burden of the conditions in the family and society. The facility for the genetic counselling and prenatal diagnosis should be increased in our state so that all families will get this benefit. Similarly, most of the rare disease patients can be supported with a good multidisciplinary care and support to have a better life.

1.4 Challenges in Research and Development

There is little known about the natural history and pathophysiology of most of the rare diseases. Moreover, we don't have any epidemiological data on the prevalence of rare diseases in our state and also any specific rare diseases in any population. Similarly, research avenues should be created for early detection and new treatment modalities. Since prevalence of rare diseases is low, multicentric studies and collaborations with other centers in the country/international should be done for better understanding of these diseases.

1.5 Objectives & Scope

A. **Developing a centre of excellence in rare diseases for diagnosis, Management and genetic Counselling to families affected with the RARE Diseases**

   Under this centre of Excellence, we should be able to provide comprehensive services for the patient and their families affected with the rare diseases.

   1. **Rare Disease Clinic/OP:** There will be a rare disease clinic /OPD in the centre of excellence where clinical services to the patients and families will be provided.
   2. **Diagnosis:** Diagnostic facility should be available with state-of-the-art Genetic laboratory where conventional tests (cytogenetics & Molecular genetics) and advanced teats like microarray/Next generation sequencing are available.

3. **Genetic Counselling:** All families with rare disease should be provided with Genetic counselling by a trained qualified specialist. The antenatal mothers with ultrasound detected malformations and other high-risk factors for genetic disorders also will be counselled in the counselling centre.

4. **Management:** Treatment of rare diseases should be provided in the centre of excellence with targeted therapy including gene therapy. A multidisciplinary clinic should be formed with the help of other departments to manage these patients. Specific treatment options will be considered for the conditions where ever it is available, and measures will be taken to administer based on the availability of the drug/facility and cost of the drug.

5. **Prenatal Diagnosis:** The prenatal diagnostic facility should be available for all families affected with chromosomal disorders and monogenic disorders, to prevent the disorder to second child.

B. A network of rare disease clinic in all Medical Colleges in the state as a "hub- and spoke" model for decentralisation and better patient compliance

The Centre of Excellence for diagnosis and management facility will be created at the tertiary care centre in the state. Other four major medical colleges should be identified as treatment centres where drug administration, multidisciplinary care and follow up is possible. This will be a help to patients who need to travel a long distance for getting the treatment for rare diseases. The centre of excellence will act as a "HUB" where diagnosis of the condition, and treatment plan will be initiated whereas regular drug administration with follow-up will be the responsibility of the rare disease clinic/treatment centre at the other medical colleges "SPOKE".

C. Creating a patient registry for rare diseases in the state for policy making and funding perspective

Disease registries have become an essential tool for relevant health care stake holders to deliver improved quality patient outcomes. The rare diseases individually have a low prevalence, however when taken collectively have a significant disease burden in any country. Even though more than 7000 rare diseases are identified and reported, no single institution has sufficient numbers of patient to undertake generalizable clinical and translational research. In our country because of large birth cohort and high degree of consanguineous marriage the incidence and prevalence of genetic diseases/ rare diseases will be significantly high. A state wide rare disease registry will help the policy makers to identify the priority areas to be tackled to reduce the infant mortality/ morbidity rate and to improve the quality of life.

D. Strategies for prevention of rare diseases in the community

Most of these rare diseases are genetic disorders and genetic counselling including the options for prenatal diagnosis should be an integral part of management. This will reduce the burden of rare disease in the community.

Primordial Prevention: IEC activities to increase the general awareness among public and health care practitioners to have practices that will reduce the burden of genetic disorders like avoidance of Consanguineous marriages, Carrier screening of Common Genetic disorders like SMA, periconceptional folic acid supplementation, pre-pregnancy evaluation to detect disorders like Diabetes, and to avoid teratogenic drugs.

Primary prevention: Antenatal detection of genetic disorders and formal decision on continuation of pregnancy in high-risk population is a strategy to reduce the burden of the genetic disease. Facilities and trained manpower should be created for the prenatal diagnosis and Genetic Counselling.

Secondary prevention: Early detection of the condition and management to prevent complication. Neonatal screening of conditions where treatment is available like congenital adrenal hyperplasia and Galactosemia.

Tertiary Prevention: Multidisciplinary care and rehabilitation of conditions where definitive treatment is not available or supportive treatment is required

E. Taking measures to improve research and development for treatment, diagnostic modalities, and supportive care

Newer treatment modalities should be made available to our community through participating into drug trails. Newer diagnostic modalities should be tried in the larger populations for early diagnosis of treatable rare disease. Screening also should be streamlined for early identification of carriers in the population followed by genetic counselling and prenatal diagnosis. Supportive therapy for chronic debilitating diseases should be part of the health system for benefit of the families affected with theses rare diseases.

F. Creating awareness among public, health workers and other stake holders; also encouraging funding support from PSUs and corporate sector.

This facility will take care of training needs of the health care workers and students on various aspects of rare genetic disorders. We can have regular training programs like fellowships and certificate programs and In-service training program for the doctors and health staff. IEC activities should be planned for creating awareness among the public regarding the importance of rare diseases and its prevention. The advocacy with corporate sector and PSUs for

encouraging funding support for the various activities related to RARE DISEASES should be encouraged.

1.6 Case Definition and Classification

A rare disease, also known as orphan disease, generally defined as a condition that affects a small percentage of population. Globally the definition varies in different countries. WHO defines rare disease as often debilitating lifelong disease or disorder with a prevalence of 1 or less, per 1000 population. However, different countries have their own definitions to suit their specific requirements and in context of their own population, health care system and resources. In the US, rare diseases are defined as a disease or condition that affects fewer than 200,000 patients in the country (6.4 in 10,000 people). EU defines rare diseases as a life-threatening or chronically debilitating condition affecting no more than 5 in 10,000 people. Japan identifies rare diseases as diseases with fewer than 50,000 prevalent cases (0.04%) in the country. The use of varying definitions and diverse terminology can result in confusion and inconsistencies and has implications for access to treatment and for research and development.

Table1: Definition of rare Disease in different countries

Country	Prevalence per less than 10,000 population
USA	6.4
Europe	5.0
Canada	5.0
Japan	4.0
South Korea	4.0
Australia	1.0
Taiwan	1.0

Source: The I.C. Verma Sub-Committee Report 'Guidelines for Therapy and Management'

However along with prevalence of the disease other factors like severity of the condition, availability and sustainability of the treatment and cost benefit ratio of the treatment also should be considered. Another important factor to be considered change in the population- a condition rare in one population may be a common condition in another population. This underscores the importance of rare disease epidemiology in our country for better defining the rare diseases. The national Registry of rare and inherited disorders is a real window through which this can be achieved.

Broadly rare disease is categorized into different group based on aetiology

1. Genetic diseases (e.g.: Cystic fibrosis, Spinal muscular atrophy, Gaucher Disease)
2. Rare Cancers (ego: Certain types of leukaemia or sarcoma)
3. Autoimmune disorders (e.g.: lupus with rare manifestations , rare rheumatological disorders)
4. Infectious Disease (e.g.: tetanus and rabies)

80 % of rare diseases are genetic Disorders and most are presentations in paediatric age group. In the NPRD policy 2021, 63 disorders are included in the list of rare diseases where most are genetic disorders. The inclusion of the condition is based on the availability of a curative treatment and sustainability of the treatment. The new conditions can be included in the NPRD policy based on the availability and sustainability of the treatment through a rigorous process by the technical committee.

The 63 conditions are divided into the 3 GROUPS based on the availability of treatment.

As per the national rare disease policy 2021, the rare diseases should be classified under three heading and support should be given

- **Group 1:** Disease where one-time expensive treatment like liver transplantation and bone marrow transplantation for genetic disorders like metabolic disorders and Primary Immunodeficiency disorders
- **Group 2:** Rare disorders with management options available like dietary therapy and drug therapy with reasonable cost
- **Group3:** Rare genetic disorders where very expensive treatment with few studies available

The entire list of disorders in the NPRD policy is attached with Appendix 1

1.7 Burden of cases in Kerala & India

In India congenital anomalies and genetic disorders have become important causes of childhood morbidity and mortality. As per the neonatal perinatal database of the National Neonatology Forum (NNF) congenital malformations were the second commonest cause (9.9%) for mortality among stillbirths and the fourth commonest cause (9.6%) of neonatal mortality. There are almost 24 million births per year in India and a large number of infants with genetic disorders are born annually. Three percent of all pregnancies result in a child with a birth defect, 10% of all paediatric and adult hospital admissions involves diseases with significant genetic component. Genetic disorders are more common than generally appreciated. With increasing control of communicable diseases and subsequently infant mortality; inherited abnormalities are assuming a proportionately greater importance.

At present infant mortality rate (IMR) in Kerala is 6. Further reduction of IMR is possible only by better neonatal care and reduction of congenital anomalies. If we consider our own data, 10-15% of newborn problems are associated with genetic disorder. Along with other subspecialty services like paediatric cardiology, paediatric neurology and paediatric nephrology, genetic services will help to reduce the mortality and morbidity in newborn care. Tertiary hospital like Medical College also should have good perinatology services in which Genetic services and genetic counselling is an integral part.

From the available information from hospital based data and our registry in the centre of excellence for rare diseases, Spinal muscular atrophy, Duchenne muscular atrophy, haemophilia, Pompe disease, Mucopolysaccharidosis, Gaucher disease, GM1 gangliosidosis, osteogenesis imperfecta, osteopetrosis, skeletal dysplasia, Maple syrup urine disease, congenital adrenal hyperplasia , Wilsons disease, Fanconi anaemia, primary immunodeficiency disorders, cystic fibrosis, primary hyperoxaluria, cystinosis, Familial HLHS and Hereditary angioneurotic oedema are some of the disorders commonly seen in our population.

Table 2: Number of registered patients in some rare diseases in our Hospital (Jan 2023 – March 2026)

Sl No	Diagnosis	2023	2024	2025	2026
1	Primary Immunodeficienc	2	3	8	1
2	Cystic Fibrosis	1	3	4	-
3	Cystinosis	-	3	3	-
4	Duchenne Muscular Dystrophy	11	1	6	1
5	Fabrys Disease	1	1	2	-
6	Glycogen Storage Disorde	1	2	-	-
7	Gaucher Disease	5	1	4	-
8	Hereditary Angioedema	2	1	5	-
9	Mucopolysaccharidoses	17	6	7	-
10	Primary Hyperoxaluria	5	4	-	2
11	IEM	1	1	7	1
12	Noonan Syndrome	3	2	15	2
13	Pompe Disease	6	3	2	-
14	Prader Willi Syndrome	2	2	10	2
15	Spinal Muscular Atrophy	104	62	9	1
16	Turner Syndrome	4	12	17	4
17	Wilsons Disease	3	2	1	-
18	X linked Hypophosphatemia	1	-	1	-
19	X linked Adrenoleukodystrophy	1	-	2	-

20	Growth Hormone Deficiency	-	5	29	3

With the introduction of rare disease policy 2021, the diagnosis, treatment and counselling of families affected with rare genetic disorders is paramount importance including prenatal diagnosis. Since 80% of rare diseases are contributed by genetic disorders, we should have sufficient infrastructure facility and manpower to manage the genetic disorders. Since newer molecular therapy (gene therapy) are increasingly introduced like spinal muscular atrophy (SMA) a greater number of clinicians experienced in genetics is the need of the hour. There is a huge manpower gap which should be addressed at the earliest so that by 5 years we should have sufficient trained faculty in this specialty of medical genetics.

Chapter 2. Rare Disease Management

The overall concept of treatment of rare diseases envisaged in India's National Policy for Rare Diseases (NPRD), 2021 is not a single uniform treatment model, but a stratified, pragmatic approach that balances *clinical feasibility, affordability, and sustainability* within India's public health system.

2.1 Core Treatment Philosophy of NPRD 2021

A. Treatment prioritised based on clinical nature of the disease

Rather than promising universal coverage for all rare diseases, the policy recognises that:

- Many rare diseases are extremely expensive to treat
- Some have curative options, while others need lifelong therapy
- Public funding must therefore be targeted and rationalised

This led to a group-based treatment strategy.

B. Three-tier treatment approach (disease grouping)

The policy categorises rare diseases into **three groups**, each with a different treatment concept:

Group 1 – Disorders amenable to one-time curative treatment:

- Diseases amenable to definitive, one-time interventions (e.g., bone marrow transplant, Liver transplant)
- Government support is prioritised here
- Rationale: *High upfront cost, but potentially lifelong cure*
- *This group forms the backbone of the policy's treatment focus.*

Group 2 – Group 2: Diseases requiring long term / lifelong treatment having relatively lower cost of treatment and benefit has been documented in literature and annual or more frequent surveillance is required:

- Diseases requiring chronic therapy (e.g., Special diets. Drug management of CAH)
- Treatment costs are relatively lower and recurring

Group 3 – Diseases for which definitive treatment is available but challenges are to make optimal patient selection for benefit, very high cost and lifelong therapy.

- Conditions where treatment exists but:
  - Optimal patient selection is complex, or
  - Outcomes vary significantly

Treatment decisions are to be made by expert committees at Centres of Excellence

Focus is on careful resource allocation and ethical decision-making

C. Strong emphasis on non-curative care

The treatment concept goes beyond drugs:

- Symptomatic management
- Rehabilitative services
- Physiotherapy, nutritional support, and palliative care
- Psychological and social support for families

Quality of life is recognised even when cure is not possible.

Long-term vision: reduce treatment dependence

Rather than only funding treatment, the policy promotes:

- Early diagnosis and prevention
- Prenatal and newborn screening
- Genetic counselling
- Indigenous research and local drug manufacturing

The ultimate goal is to reduce incidence and cost burden over time.

2.2 Early Identification & Diagnosis

Early identification and accurate diagnosis of rare diseases are essential to reduce disability, avoid unnecessary treatments, and improve survival and quality of life. It was brought about by working with a health-system–led approach rather than reliance on individual specialists or families.

2.2.1. Strengthened awareness at the first point of care

Most patients with rare diseases first present to:

- Primary health centres
- District hospitals
- Paediatric and general outpatient services

Early identification is brought about by -

- Sensitising frontline health workers to recognise *warning signs* such as unexplained developmental delay, recurrent hospitalisations, poor growth, or family history of similar illness
- Encouraging early referral when common conditions do not explain symptoms

The emphasis was not on making a diagnosis at the primary level, but on recognising when a case may be uncommon.

2.2.2. Use of structured screening programmes

Role of population-based screening was highlighted as a key tool for early detection.

This includes:

- Newborn screening, especially for conditions where early treatment can prevent irreversible damage
- Screening during infancy and early childhood through existing child health programmes
- Identification of affected children through District Early Intervention Centres (DEICs) under national child health initiatives

Such screening allowed identification before symptoms become severe, reducing long-term care costs.

2.2.3. Tiered referral and diagnosis through specialised centres

Rare diseases require expertise that is not widely available at all health facilities.

Thus, it was accomplished by:

- A referral pathway from primary and district levels to designated Centres of Excellence (CoEs)
- Concentration of diagnostic services, including advanced laboratory and genetic testing, at these centres
- Multidisciplinary evaluation to ensure accurate and timely diagnosis

This avoids repeated testing, delays, and misdiagnosis across multiple facilities.

2.2.4. Access to appropriate diagnostic technologies

Accurate diagnosis of rare diseases often requires specialised tests that are not part of routine care.

The policy supported:

- Upgrading diagnostic capacity at selected centres
- Rational use of advanced testing only when clinically indicated
- Reducing out-of-pocket expenditure by limiting unnecessary investigations

The aim is targeted and efficient diagnosis, rather than indiscriminate testing.

2.2.5. Role of genetic counselling and family history assessment

Many rare diseases have a genetic basis.

Early identification is strengthened by:

- Systematic documentation of family history
- Genetic counselling to help families understand the condition, recurrence risk, and available options
- Identification of at-risk siblings or future pregnancies

This approach also supports prevention and informed decision-making.

2.2.6. National registry and data systems

Rare diseases are often under-reported.

To address this, it promotes:

- Creation of a national hospital-based rare disease registry
- Standardised reporting of diagnosed cases by Centres of Excellence
- Use of data to improve planning, research, and future screening strategies

Better data enables earlier recognition at a population level.

2.2.7. Integration with existing public health programmes

Rather than creating parallel systems, it was encouraged:

- Integration of rare disease identification into existing maternal, child health, and non-communicable disease programmes
- Use of established health infrastructure for referral and follow-up
- This ensures sustainability and scalability.

2.3 Treatment of Rare Diseases in Kerala: Diseases, Therapies, and Impact on Quality of Life

Kerala's rare disease programme focuses primarily on severe, childhood-onset genetic disorders where treatment can significantly improve survival, function, or long-term quality of life. Most interventions are delivered through tertiary government hospitals, especially the Centre of Excellence at Government Medical College, Thiruvananthapuram (SAT Hospital).

2.3.1. Spinal Muscular Atrophy (SMA)

Nature of disease

- A severe neuromuscular genetic disorder
- Causes progressive muscle weakness, respiratory failure, and early death if untreated
- Most severe forms present in infancy

Treatment provided in Kerala

- Disease-modifying drug therapy (SMN-targeted treatment)
- Initiated as early as possible, including pre-symptomatic treatment in newborns
- Supportive care: respiratory support, physiotherapy, nutritional support

Impact on quality of life

- Dramatic improvement in survival
- Children who would otherwise not sit, stand, or breathe independently can achieve major motor milestones
- Reduced need for ventilatory support and hospitalisation
- Enables near-normal cognitive development and improved social integration

SMA treatment in Kerala represents a shift from palliative care to functional survival.

2.3.2. Lysosomal Storage Disorders (LSDs)

(Including Gaucher disease, Pompe disease, Fabry disease, MPS)

Nature of disease

- Progressive metabolic disorders due to enzyme deficiency
- Lead to organ damage (liver, heart, muscles, bones, brain)
- Untreated disease causes disability, shortened lifespan, and poor quality of life

Treatment provided in Kerala

- Enzyme Replacement Therapy (ERT) for selected conditions
- Regular intravenous infusions administered at tertiary hospitals
- Symptom-specific management (cardiac, respiratory, orthopaedic care)

Impact on quality of life

- Slows or halts disease progression
- Improves mobility, endurance, and organ function
- Reduces pain, fatigue, and frequency of hospital admissions
- Allows children to attend school and adults to maintain daily activities

While not curative, ERT converts a rapidly disabling disease into a manageable chronic condition.

2.3.3. Growth Hormone therapy for selected genetic conditions with GH Deficiency

Nature of disease

- Endocrine and chromosomal disorders affecting growth and development
- Without treatment, children have short stature and associated psychosocial challenges

Treatment provided in Kerala

- Free growth hormone therapy through government programmes
- Long-term supervised treatment at paediatric endocrine clinics

Impact on quality of life

- Improved final adult height
- Better physical development and self-esteem
- Reduced long-term health complications
- Improved educational and social participation

These treatments have a strong psychosocial and societal impact despite not being lifesaving.

2.3.4. Inherited Metabolic Disorders Detected Early

(e.g., select amino acid, organic acid, and fatty acid metabolism disorders)

Nature of disease

- Often present in newborns or early infancy
- Can cause seizures, developmental delay, coma, or death if untreated

Treatment provided in Kerala

- Dietary modification
- Vitamin or cofactor supplementation
- Supportive metabolic care
- Early detection through targeted screening and referral

Impact on quality of life

- Prevention of irreversible brain damage
- Normal or near-normal development if treated early
- Reduced long-term disability and dependency

Early diagnosis is critical; treatment is low-cost compared to lifelong disability care.

2.3.5. Haematological Rare Disorders

(e.g., severe haemophilia, select bone marrow failure syndromes)

Nature of disease

- Chronic bleeding or marrow dysfunction
- High risk of disability without continuous care

Treatment provided in Kerala

- Factor replacement therapy
- Support through state health schemes and hospital-based care
- Management of complications

Impact on quality of life

- Reduced bleeding episodes
- Preservation of joint function
- Improved school attendance and productivity

2.3.6. Intravenous Immunoglobulin (IVIG) for primary immunodeficiency Disorders

- IVIG therapy involves the regular intravenous administration of purified human immunoglobulins obtained from healthy donors. The treatment does not correct the underlying genetic defect, but replaces the missing or dysfunctional antibodies, thereby restoring the body's ability to prevent infections.
- As regular, lifelong therapy at defined intervals, usually every 3–4 weeks
- Alongside infection surveillance and supportive care
- Impact on disease course and survival

Before the availability of IVIG, many patients with primary immunodeficiency experienced:

- Frequent life-threatening infections
- Progressive lung damage (bronchiectasis)
- Repeated intensive care admissions
- With regular IVIG therapy:
- The frequency and severity of infections are markedly reduced
- Hospital admissions and antibiotic use decrease substantially
- Long-term complications such as lung damage are slowed or prevented
- Survival improves significantly, approaching that of the general population when treatment is sustained

Impact on quality of life

- The most significant benefit of IVIG therapy is the transformation of daily life for affected children and families:
- Children can attend school regularly instead of repeated hospital stays
- Physical growth and development improve due to reduced illness burden
- Families experience reduced emotional and financial stress
- Adults with immunodeficiency are able to maintain employment and social participation
- IVIG thus converts a previously disabling and life-threatening condition into a stable, manageable chronic disease.

2.4 Supportive and Multidisciplinary Care Across Conditions

Across all rare diseases, Kerala provides:

- Physiotherapy and rehabilitation
- Respiratory support
- Nutritional counselling
- Genetic counselling for families
- Psychological and social support

Quality-of-life impact

- Reduces caregiver burden
- Improves functional independence
- Enhances adherence to long-term therapy
- Improves overall family wellbeing

Key Medical Insight for Policymakers

- Many rare disease treatments do not merely prolong life, but transform severe disability into functional living

Early and sustained treatment significantly reduces:

- Hospital admissions

- Intensive care dependence
- Long-term social care costs
- The greatest gains are seen when treatment is started early and delivered consistently

2.5 Rehabilitation, Palliation, and Long-Term Care for Rare Diseases in Kerala

People living with rare diseases often require ongoing supportive care that goes beyond definitive therapies. This includes rehabilitation to maximise function, palliative care to improve quality of life, and long-term support to manage chronic disability and social participation. Kerala's health system, community services, and social welfare schemes provide a continuum of long-term care, integrated with medical treatment where possible.

2.5.1. Multidisciplinary Rehabilitation Support

Many rare diseases — such as neuromuscular disorders, skeletal anomalies, chronic metabolic conditions, and post-surgical states — lead to functional impairment affecting mobility, breathing, and daily activities.

In Kerala, rehabilitation support is provided through:

- **Physiotherapy and Occupational Therapy**
  Patients receiving care at tertiary centres (such as SAT Hospital) are routinely referred to physiotherapy and rehabilitation teams to improve strength, mobility, respiratory function, and independence in daily activities. These services are integrated with clinical care for conditions like SMA and musculoskeletal complications.
- **Respiratory and Nutritional Support**
  Ongoing support for breathing and nutrition — essential for many rare neuromuscular conditions — is coordinated through hospital outpatient departments and linked district services.
- **Community Neuro-Rehabilitation Initiatives (NGO & Government Linkages)**
  non-governmental programmes, such as community rehabilitation projects based on WHO's Community-Based Rehabilitation (CBR) framework, work with local health systems to provide outpatient therapy, individualized rehabilitation plans, family training, and reintegration support. These are particularly relevant for conditions like cerebral palsy and chronic neurological disorders.

Rehabilitation services help patients:

- Regain or maintain physical function,
- Reduce disability from contractures or muscle loss,
- Enhance participation in school or work,
- Reduce caregiver burden.

2.5.2. Palliative and Supportive Care Networks

For patients with progressive, debilitating, or life-limiting rare conditions, palliative care focusses on symptom relief, comfort, and psychosocial support throughout the disease journey — not only at end-of-life.

In Kerala, palliative care is well-integrated into the health system:

- **Kerala Care – Universal Palliative Service Scheme**
  A state-wide, coordinated palliative care network is being implemented to ensure comprehensive care for bedridden and seriously ill patients across the state. This network combines government health facilities and trained volunteers to deliver regular home-based support.
- **Voluntary and Civil Society Participation**
  Over a thousand institutions and several thousand trained volunteers are registered with the palliative care grid. These volunteers, alongside professionals, provide regular psychosocial, medical, and supportive care at home for patients with chronic needs.
- **NGO-Led Palliative Programs**
  Some registered organizations and community projects provide multidisciplinary home visits — offering pain and symptom management, emotional support, counselling, and assistance with daily living — which benefit rare disease patients with complex care needs.

Palliative care in Kerala:

- reduces suffering,
- supports families and caregivers,
- ensures continuity of care at home,
- and enhances quality of life even when a cure is not possible.

2.5.3. Integrated Long-Term Clinical Follow-Up

Long-term care in Kerala also includes structured **medical follow-up and specialist continuity**, facilitated by:

- **Centres of Excellence and Rare Disease Clinics**
  Tertiary centres such as SAT Hospital provide follow-up care through multidisciplinary teams, including paediatric neurology, orthopaedics, respiratory care, nutrition, and rehabilitation — ensuring continuity of care beyond acute treatment phases.
- **Regional Linkages and Hub-and-Spoke Model**
  Efforts to extend care through a hub-and-spoke model link district centres with specialist

institutions, improving access to long-term monitoring and therapy closer to patients' homes.

- **Psychosocial and Family Support Groups**
  Kerala has encouraged the formation of patient and caregiver support groups, providing peer support, counselling, and shared resources — a vital component of long-term care for conditions requiring ongoing management.

2.6 Financial Protection and Social Support Schemes

KARE (Kerala United Against Rare Diseases) and State Care Schemes

Kerala's health department has instituted a state-level rare disease care programme that provides direct, government-funded treatment support for several high-cost rare conditions (such as SMA, lysosomal storage disorders, growth hormone deficiency, etc.).

Under this programme, expensive therapies and medicines are provided free of cost at designated centres such as the SAT Hospital, Thiruvananthapuram, with multidisciplinary care support. This reduces out-of-pocket expense on costly lifelong treatments.

Vishu Kaineettam Project (Public Donation Support for Rare Diseases)

- Launched to supplement government financing for rare disease treatment through public donations and contributions, recognising that many therapies are prohibitively expensive and may exceed state budgets.
- A designated fund accepts contributions that can be used to support individual patients' treatment costs, extending coverage beyond what the state budget alone can provide.

2.6.1. Major Health Coverage and Financial Protection Schemes in Kerala

These broader health financing schemes are **not specific to rare diseases** but significantly help reduce financial burden, especially for long-term and serious health needs:

Karunya Arogya Suraksha Padhathi (KASP)

- Provides free cashless treatment up to ₹5 lakh per family per year for inpatient care covering pre-hospitalisation to post-hospitalisation services.
- Covers pre-existing diseases and chronic conditions, which can include some aspects of rare disease management depending on hospitalisation needs.
- Delivery through empanelled public and private hospitals across the state strengthens access for families with rare and chronic health needs.

Karunya Benevolent Fund (KBF)

- Offers one-time financial aid (up to around ₹2 lakh) to lower-income families for serious health treatments.
- Funds are raised through the Kerala State Lottery and can be used toward substantial health expenses when other coverage is limited. Though not disease-specific, it can help rare disease families with acute treatment costs.

Arogya Kiranam

- Free treatment for children under 18 years in government hospitals for serious and chronic conditions, regardless of economic status.
- This scheme can provide important inpatient and follow-up services for children with rare diseases that require hospital care.
- CHIS Plus and other health coverage options
- Comprehensive Health Insurance Scheme (CHIS) Plus and related coverage through the state health insurance authority offer assistance up to set limits (e.g., ₹70,000) for tertiary care delivered through government hospitals — a supplementary protection layer beyond the Karunya schemes.

2.6.2. Social Support and Caregiver Assistance Schemes

Aswasakiranam Scheme

- Provides monthly financial assistance (~₹600) to caregivers of persons with severe physical or mental disabilities or bedridden patients, administered by the Kerala Social Security Mission.
- This support indirectly benefits rare disease families where long-term caregiving is necessary, helping offset household financial strain related to caregiving duties.

Other Social Security Supports

- While not specific to rare disease per se, broader social security schemes (e.g., disability pensions, educational support for children with special needs, and targeted welfare allowances) may be accessed by rare disease families through departments of Social Justice and Health Services, depending on eligibility criteria.

2.6.3. Central Government and Voluntary Support Platforms (Complementary to State Schemes)

Central Rare Disease Support Platforms

- The Union Government operates a national digital platform for voluntary crowd-funding and corporate donations for rare disease treatment costs. Individuals and institutions can contribute directly to specified patients' treatment funds, which can be useful when state and insurance coverage fall short.

Umbrella Schemes and National Assistance

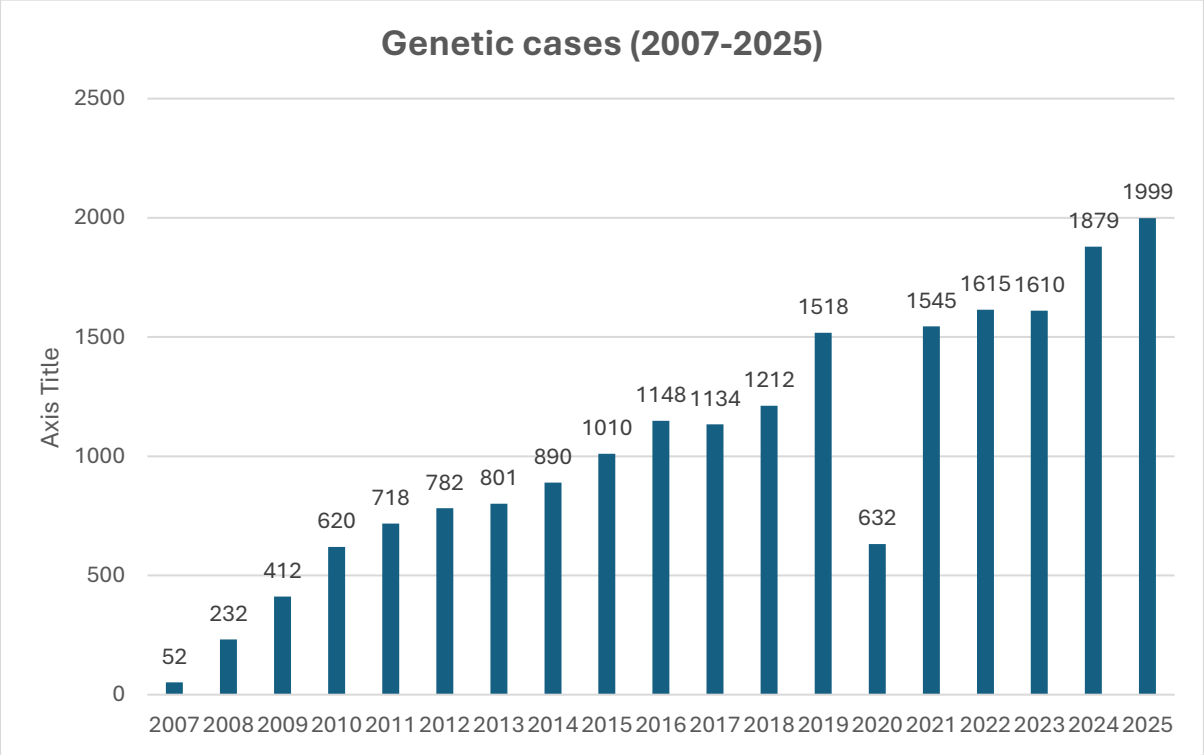
- National programmes such as the Umbrella Scheme of Rashtriya Arogya Nidhi (RAN) may provide financial support for rare diseases that fit defined criteria, offering up to tens of lakhs of rupees in eligible cases. Although utilisation varies, such national funds can complement state financing.

Chapter 3. Achievements in the field of RARE DISEASE in SAT hospital

3.1 Genetic Clinic (RARE DISEASE Out patient service)

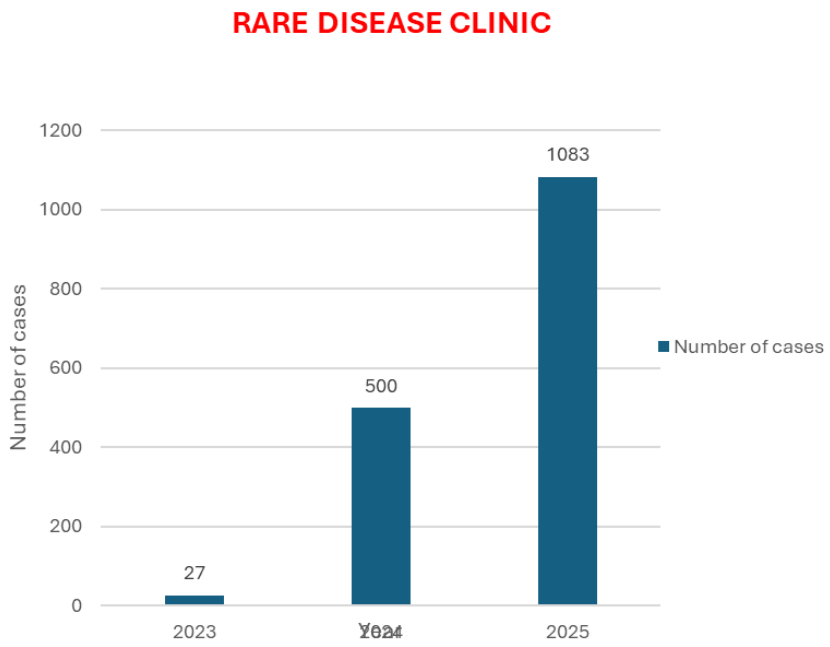
Genetic Clinic (Rare Disease) attached to Department of Paediatrics, SAT hospital, Government Medical College, Thiruvananthapuram, Kerala is unique clinic in the State. This Hospital is the apex institute in the state for paediatric care where 10,000 deliveries are occurring every year. We are having the following department in SAT Hospital for managing children with various diseases Department of Paediatrics (5 Units), Department of Paediatric surgery (3 Units), Department of neonatology, Department of Paediatric Neurology, Department of Paediatric cardiology, Department of paediatric Nephrology, and Department of Medical genetics. Patients in Genetic Clinic are managed by a fully qualified and trained Medical Geneticist. Genetic Clinic started in July 2007 and the number of patients and affected families are increasing every year. In the clinic, we are providing diagnosis of genetic disorders and genetic counselling services. This includes pretest counselling, post-test counselling and antenatal counselling to the affected families. The number of OPD status from 2007 is given below.

Figure 1: Genetic Cases (2007-2025)



As a part of expansion of the Outpatient services, one more day OPD started on Fridays as RARE disease clinic in 2023. The number of OPDs in rare disease clinic from 2023 onwards is depicted below.

Figure 2: Rare Disease Clinic



3.1.1 Clinical genetic services provided by the Genetic clinic of SAT hospital, Govt. Medical College:

- Complete clinical genetic evaluation, proper diagnosis and management of the disease and its associated complications and appropriate referral for multidisciplinary care.
- Genetic counselling of the patient and/ or family members regarding the pattern of inheritance,
- implications to the family and the risk of recurrence of the disease in future pregnancies / generation of the family.
- Long term follows up for preventing or managing evolving complications known to be associated with each disorder.
- Provision of prenatal diagnosis in at risk pregnancies –molecular genetics/ cytogenetic/ biochemical genetic tests as applicable - for families with previously affected members with chromosomal/genetic disorders and in pregnancies which test positive for fetal aneuploidy screening or have anomalies detected in antenatal sonograms.
- Determination of diagnosis to ascertain the risk of recurrence in subsequent pregnancies and initiation of appropriate preventive/ prenatal diagnostic strategies for future pregnancies.

3.1.2 Genetic & Metabolic laboratory, Child Development Centre, Thiruvananthapuram

The Genetic and Metabolic Unit of the Child Development Centre (CDC), an autonomous institution located within the SAT Hospital campus, Thiruvananthapuram, has evolved into a state-of-the-art facility offering comprehensive diagnostic services for genetic and metabolic disorders in children. Over the years, the centre has achieved several significant milestones in the establishment and expansion of genetic clinical services, cytogenetics, and molecular diagnostics. The major milestones are outlined below.

A. 2013 – Establishment of the Cytogenetics Laboratory (Karyotyping Facility)

In 2013, the Cytogenetics Laboratory was initiated with karyotyping as the primary diagnostic service. This was a major leap forward in in-house genetic diagnostics, enabling the detection of numerical and structural chromosomal abnormalities such as Down syndrome, Turner syndrome, and other chromosomal disorders. This facility significantly reduced the dependency on external laboratories and improved turnaround time for critical diagnoses.

B. 2015 – ICMR Multicentric Research Project

In 2015, the Genetic and Metabolic Unit achieved national recognition by participating in an Indian Council of Medical Research (ICMR) funded multicentric project focusing on rare genetic disorders such as Gaucher disease, Achondroplasia, and Apert syndrome. This project strengthened the research component of the laboratory and enhanced expertise in the diagnosis and management of skeletal dysplasia's and lysosomal storage disorders.

C. 2017 – Establishment of the Molecular Genetics Laboratory

In 2017, the Molecular Genetics Laboratory was established, expanding the diagnostic scope of the centre beyond cytogenetics. Molecular diagnostic techniques were introduced for the detection of single-gene disorders. This marked a significant technological advancement, enabling precise mutation-based diagnosis and facilitating carrier detection and prenatal diagnosis in selected conditions.

D. 2019 – Installation of Genetic Sequencer Facility

In 2019, the laboratory further strengthened its molecular diagnostic capabilities with the installation of a Genetic sequencer 3500. This facility enabled DNA sequencing for mutation analysis, significantly improving the accuracy and depth of genetic testing. It laid the foundation for advanced diagnostics and research activities and prepared the laboratory for next-generation technologies.

E. 2021 – Introduction of SMA Diagnosis by MLPA

In 2021, Spinal Muscular Atrophy (SMA) diagnosis using MLPA (Multiplex Ligation-dependent Probe Amplification) was introduced. This was a major milestone as SMA is a critical childhood neuromuscular disorder requiring early diagnosis for effective management. The availability of MLPA testing at CDC greatly benefited patients from across the state by providing rapid, reliable, and cost-effective diagnosis. National Health mission (NHM) has given financial support for establishing this test.

F. 2023 – NABL Accreditation for Cytogenetics and Biochemistry

In 2023, the Cytogenetics and Biochemistry sections of the laboratory achieved NABL accreditation as per ISO 15189 standards. This accreditation established the laboratory's compliance with international quality standards for medical laboratories and reinforced its commitment to accuracy, reliability, and patient safety in genetic testing.

G. 2023 – Designation as Centre of Excellence (CoE) for Rare Diseases

In the same year, the Centre received recognition as a Centre of Excellence (CoE) for Rare Diseases for SAT Hospital. The Genetic Laboratory at the Child Development Centre serves as the core laboratory facility for this CoE. This milestone strengthened the role of CDC as a referral hub for rare disease diagnosis and management in the state.

In addition to routine karyotyping, FISH, and molecular diagnostics, the laboratory has continuously expanded its diagnostic portfolio to include advanced and specialized tests. These include:

- Haemophilia diagnosis (Inversion 22 mutation detection)
- FISH testing for DiGeorge syndrome (22q11.2 deletion)
- FISH for sex chromosome analysis (XX/XY)
- SRY gene deletion analysis
- Other targeted molecular tests for inherited disorders

The laboratory currently offers cytogenetics and molecular diagnostic services in-house, with advanced technologies such as microarray and next-generation sequencing (NGS) being performed through collaborative arrangements with other reputed centers.

From its modest beginning as a genetic clinic in 2007 to becoming a NABL-accredited laboratory and Centre of Excellence for Rare Diseases in 2023, the Genetic and Metabolic Unit of the Child Development Centre has made remarkable progress. The continuous upgrading of infrastructure, technologies, and test menu reflects its strong commitment to excellence in patient care, diagnostics, teaching, and research in medical genetics.

Figure 3:

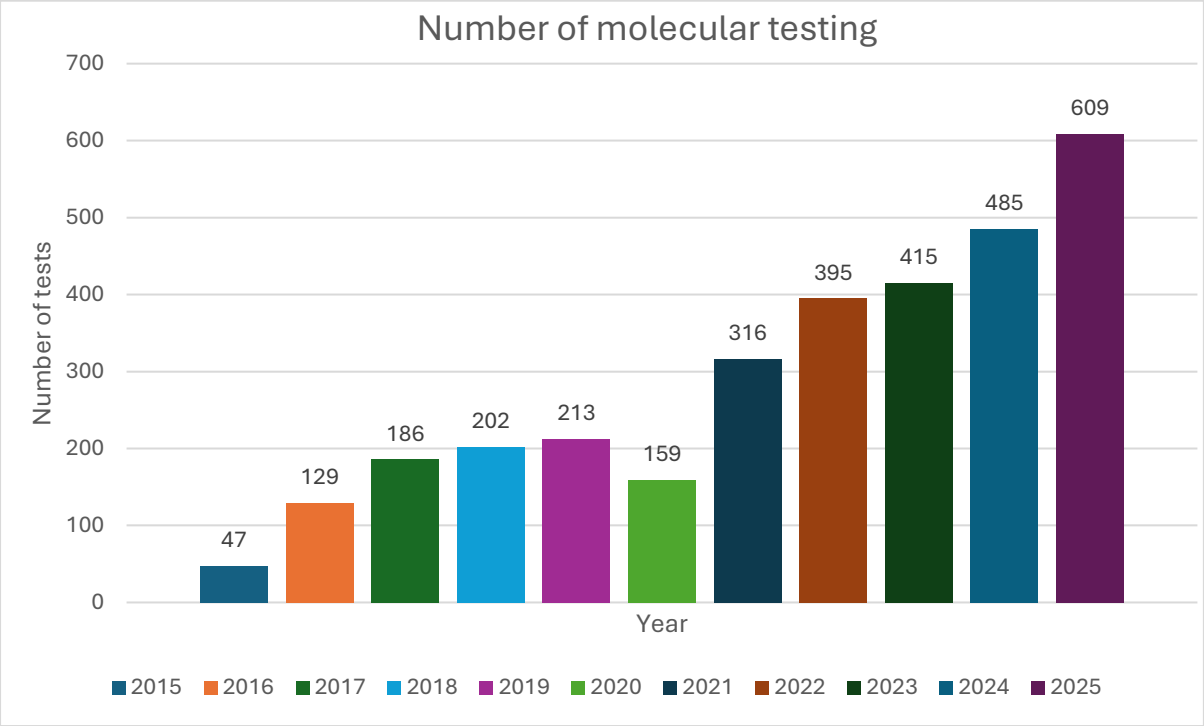
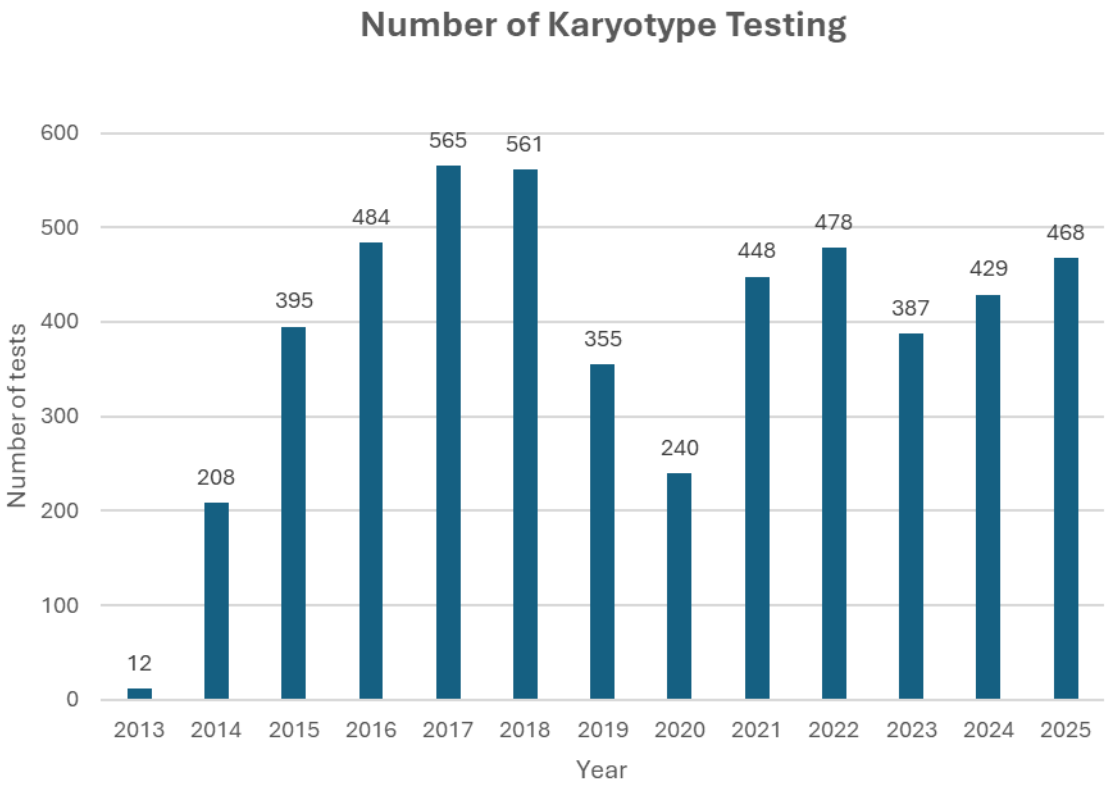


Figure 4:



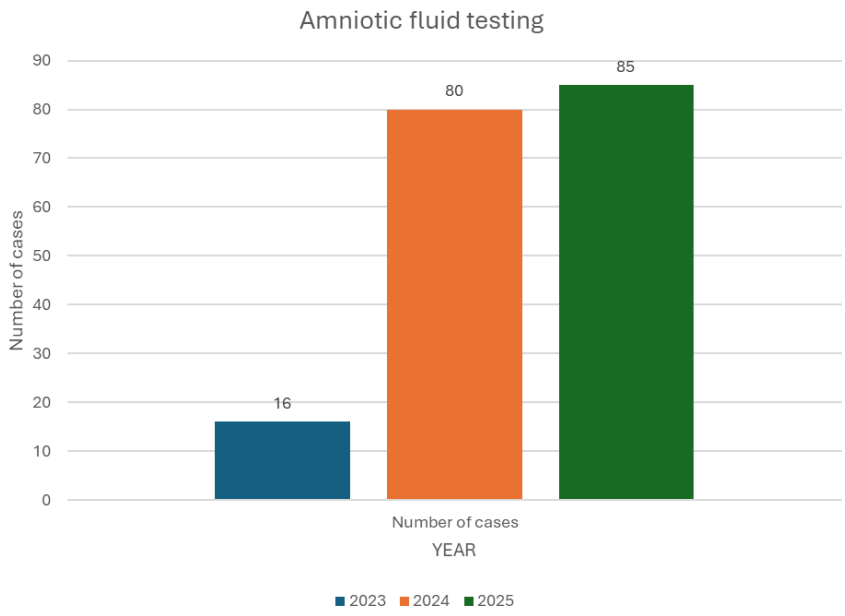
3.2 Prenatal Diagnosis facility (SHRDHA Clinic)

Prenatal diagnostic facility is now made available at Child Development Centre (CDC) nearby Genetic Clinic of SAT. As part of the Reduction of childhood disability initiatives of CDC a project titled “SRADHA project was started during the year 2020. The “Sradha project” aims at reduction of childhood disability through various antenatal intervention including anomaly scanning using the 4D Ultrasonography machine and advanced equipment available at Genetic & Metabolic unit of CDC. The major services offered are First trimester scan (11-14 weeks), Early Anomaly Scan – 16 weeks), Target Anomaly Scan (18 to 27 weeks), Target Anomaly scan with fetal ECHO, Growth scan with fetal Doppler. Antenatal Ultrasound examination is done in the SAT Hospital by USG by Radiologist in Department of Radio diagnosis.

Both facilities are registered under PNDT Act.

All patients with antenatal diagnosed anomalies and high-risk pregnancies for genetic disorders is counselled in the genetic clinic for the option of the prenatal diagnosis. Facility for the procedure and laboratory testing is available in our centre. We are also having a faculty with training in fetal Medicine in our team for antenatal ultrasound and invasive procedure. The family is provided the post-test counselling after the prenatal diagnosis result.

Figure 5:



3.3 Spinal Muscular atrophy (SMA) Clinic

SMA Clinic was established at SAT hospital as a commitment of Government of Kerala towards these children with the RARE genetic disorder. Government of Kerala initiated the process in 2021, and the clinic was inaugurated on 28th February 2021. The clinic is operational on first Monday of every month where multidisciplinary team will evaluate these children. The multidisciplinary team comprises of Paediatric Neurologist, Medical geneticist, specialist from pulmonology, orthopaedic specialist and Physical medicine & Rehabilitation specialist. Other specialist will be consulted as per the requirement. The total number of patients registered since 2021 is 206.

Table 3: number of OPD attendance in SMA Clinic

2021	85
2022	182
2023	323
2024	608
2025	753

For Spinal Muscular atrophy there are 3 forms of therapy which can be considered as Disease modifying drugs : One time gene therapy Zolegensma, intrathecal therapy with nusinersan and oral Risdiplam. Mechanism of action and effects are different for three. All are very costly medicines. Both gene therapy molecule are NOT available in India and Not approved by DCGI. The Oral medicine RISDIPLAM is licensed and approved by DCGI in July 2021 and we are giving this drug to patients affected with SMA.

There is a state level technical committee under the Director of Medical Education (DME) to decide on the initiation of expensive disease modifying therapy (Risdiplam) in SMA. State level Technical Committee is identifying the beneficiaries for SMA treatment support based on the specific criteria

- Clinical diagnosis of spinal muscular atrophy
- Genetic testing showing Homozygous deletion of Exon7 and/or Exon 8 in SMN1 gene (confirmatory of SMA)
- Genetic testing showing 3 or less copies in the Exon 7/Exon 8 in SMN2 gene copy suggestive of SMA type I or SMA type II
- Age of the patient (previously less than 5 years on the date of enrolment) and presently less than 12 years on the date of enrolment
- Not received any other recent molecular therapy for SMA (gene therapy like Zolegensma or Anti sense oligonucleotide like Nusinersan) government scheme (KARE).

The total number of patients getting RISDIPLAM under this scheme is 106

Another major milestone in SMA care in our state is facility creation for spinal surgery for scoliosis in Government facility under KARE programme which was benefited to 11 patients.

Multidisciplinary care including physiotherapy and pulmonary therapy is important for all patients with Spinal muscular atrophy. This made available in all district hospitals and medical colleges where physiotherapy facilities are available. A training programme was conducted in Trivandrum to

train PMR specialist and physiotherapist in all district and this facility is mapped for referring these patients.

3.4 Cytogenetic laboratory facility under MDRL

The Government of Kerala has sanctioned a Multi-Disciplinary Research Laboratory (MDRL) at Govt. Medical College Thiruvananthapuram in 2013. The MRU (Multi-Disciplinary Research Units) laboratory funded by ICMR is now functioning in the MDRL with more than 4000 sq. ft laboratory area. Other than MRU the MDRL contain Virus Research and Diagnostics Laboratory (VRDL), Medical Genetics, biochemistry, analytical chemistry, drug designing, physiology, and community medicine laboratories.

The Multidisciplinary Research Laboratory [MDRL] is having a designated space for diagnostic Genetic laboratory where the cytogenetic facility started. This lab is provided with culture room, space for harvesting and reporting area. The instrumentation for cytogenetic facility to the tune of 1 CRORE was supported by Multidisciplinary Research Unit and made functional in 2024. Since there was no manpower support from MRU, the facility will be operated with the help of SAT health education society (SATHEES). They are supporting the manpower and consumables for the cytogenetic testing. The cytogenetic facility started operational since September 2025. This laboratory will act as a diagnostic facility as services, research facility in cytogenetics as a part of MRU, and as a part of academic/training facility for students in medical college, Thiruvananthapuram.

3.5 Centre of Excellence FOR Rare Disease

Under the rare disease policy formulated by the government of India there should be a Centre of excellence in every state for managing the families with rare disease. The most important step in the management is the confirmation of diagnosis in rare disease. There should be the state-of-the-art genetic laboratory for coordinating this diagnostic workup. More over these rare diseases and its genetic basis is also having a good research potential.

Considering the facilities in Government Medical College, Thiruvananthapuram, Ministry of Health, Government of India, gave the status of Centre of Excellence for RARE disease to SAT hospital, government Medical College, Trivandrum as per OM . There was some minimal facility gap identified by the inspection team which was rectified within first 6 months.

The responsibilities and activities of COE would be as follows:

1. Education & Training at all levels
2. Screening – Antenatal, neonatal (specified disorders), High risk screening
3. Diagnostics- Cytogenetic, molecular, Metabolic
4. Prevention by prenatal screening &diagnosis
5. Research in the area of low-cost diagnostics & therapeutics.
6. Treatment of rare diseases

Financial support up to Rs. 50 lakhs under the Umbrella Scheme of Rashtriya Arogya Nidhi shall be provided by the Central Government for treatment, of those rare diseases identified by the central technical committee. Beneficiaries for such financial assistance would not be limited to BPL families, but extended to about 40% of the population, who are eligible as per norms of Pradhan Mantri Jan Arogya Yojana, for their treatment in Government tertiary hospitals only.

Registration to the RARE disease clinic under NPRD 2021 was started on January 2023.

Each case will be evaluated in detail by the technical committee formulated by the institute and beneficiaries were identified based on strict entry criteria. The procurement of drugs will be supervised by the core committee (purchase) in the institute.

Table 4: The beneficiaries given treatment through this scheme from 2023-2025 (3 Years)

Sl. no	Condition	Number patients
1	ERT for Gaucher Disease (GROUP III)	8
2	ERT for Pompe Disease (GROUP III)	3
3	RISDIPLAM for SMA type II (GROUP III) Under Court Direction	1
4	Growth Hormone Therapy for GH Deficiency, Turner Syndrome, Noona Syndrome and Prader Willi syndrome (GROUP II)	66
5	Intravenous gamma Globulin (IVIG) therapy for prima Immunodeficiency disorders	6
	TOTAL fund utilized for the management of RARE Diseases till December 2025	**6.15 CR**

In Group 1 few patients are identified for Haemopoietic stem cell transplantation on detailed pre transplant work up in Malabar cancer centre, Tellicherry.

With the introduction of Centre of Excellence for rare disease and separate fund for management (up to 50 LAKHS) changed the landscape of treatment for rare diseases.

3.6 ICMR Registry

This is a hospital based national registry for rare and inherited disorders. SAT hospital, Government Medical College, Thiruvananthapuram is a participating centre in this ICMR registry since 2025. This registry with clinical trials initiated by ICMR will help to have new treatments for our patients with rare diseases.

3.7 NIDAN KENDRA

Nidan Kendras have been set up by Department of Biotechnology (DBT) under Unique Methods of Management and treatment of Inherited Disorders (UMMID) project for genetic testing and counselling services. These Nidan Kendra's will be performing screening, genetic testing and counselling for rare diseases. Nidan Kendra's possessing the facility for treatment may do so under the guidance and supervision of a CoE.

Establishment of DBT NIDAN Kendra and training centre in our hospital would help us to achieve complete clinical genetic evaluation, proper diagnosis and management of the rare genetic disorders and its associated complications. Under this DBT-NIDAN Kendra we will be able to provide comprehensive services for the patient and their families affected with the rare diseases.

The DBT-NIDAN Kendra began functioning at the Government Medical College, Thiruvananthapuram, from December 2024 onwards. Molecular diagnostic facility under NIDAN KENDRA is established in the Genetic laboratory in the multi-disciplinary research laboratory (MDRL) building. Along with cytogenetic facility established under MRU/DHR fund, this will be a one stop diagnostic facility for all genetic disorders.

All the required equipment were purchased and installed in the Medical Genetics lab, Medical College TVM as proposed in the original proposal. The proposed manpower support for three years is recruited and standardisation procedure started. Some of the test like karyotype and Y microdeletion already standardised and other genetic tests are under standardisation. With fully functional NIDAN KENDRA laboratory, molecular diagnostic facility for all common genetic disorders will be available under one laboratory.

3.8 Advanced Genetic Laboratory facility under Centre of Excellence

The proposed COEs shall be given one-time financial support up to a ceiling of Rs 5 crore for procurement of equipment as per individual centres need for strengthening patient care services for screening, diagnosis and prevention (prenatal diagnosis) of rare diseases based on a gap analysis. The list of equipment which are likely to be useful for these activities is annexed.

The major equipment planned under this funding is as follows

1. Microarray platform (advanced tests to evaluate copy number variants)
2. Bioinformatic analysis station (for analysis of Exome data)
3. Antenatal screening equipment
4. Cytogenetic workstation
5. Digital PCR

3.9 Department of Medical Genetics

As per the NPRD policy 2021, State Governments decided to create Department of Medical Genetics at least in Medical College, Thiruvananthapuram for imparting education for strengthening the manpower. Government of Kerala has taken this as a priority and two faculty post (one professor and one assistant professor in medical genetics) was created to develop the medical genetics department in 2024. With presence of two faculty and other facilities, DM programme in medical genetics will be started soon for strengthening the manpower.

Chapter 4. Research and Development

A fundamental challenge in research and development for the majority of rare diseases is that there is relatively little known about the pathophysiology or the natural history of these diseases. Rare diseases are difficult to research upon as the patient pool is very small and it often results in inadequate clinical experience. Therefore, the clinical explanation of rare diseases may be skewed or partial. The challenge becomes even greater as rare diseases are chronic in nature, where long term follow-up is particularly important. As a result, rare diseases lack published data on long-term treatment outcomes and are often incompletely characterised.

This makes it necessary to explore international and regional collaborations for research, collaborations with the physicians who work on any rare disease and with patient groups and families dealing with the consequences of these disorders. This will help gain a better understanding of the pathophysiology of these diseases, and the therapeutic effects that would have a meaningful impact on the lives of patients.

4.1 Priority Areas of Research

- Clinical and Molecular characterisation of various genetic disorders which will help to delineate the common genetic variants, any geographical location, clinical symptoms and complications and prognosis . this will help the policy makers to identify the core diseases where we need to concentrate.
- Screening in populations to identify the carrier status of common genetic disorders to plan the preventive strategies
- Identification of biomarkers for early diagnosis and monitoring in specific rare diseases. This will help to formulate bed side point of care diagnostic tests to identify the rare genetic disorders
- Better cost-effective genetic tests for confirmation of various genetic disorders through newer molecular techniques
- Identification of newer therapeutic molecules and repurpose of known drugs in the management of rare genetic disorders
- PHASE 2 and PHASE 3 clinical drug trail and bioequivalence trails of the newer drugs in the management of rare genetic disorders
- Newer strategies for chronic care of patients and families affected with rare genetic disorders
- Quality of life and real-world problems (qualitative studies) in patients and families affected with rare diseases to identify the challenges faced by them for effective intervention by the policy makers

4.2 Our work in last 15 Years in the areas of RARE Diseases

We are collaborating with various national organisations like ICMR/DBT and industry for various research activities and drug trails related to RARE diseases

4.2.1 Multi centric study on Clinical, Biochemical and Molecular characterisation of Lysosomal storage disorders (ICMR study) (2015-2018).

In 2015, the Genetic and Metabolic Unit achieved national recognition by participating in an Indian Council of Medical Research (ICMR) funded multicentric project on Lysosomal Storage disorders focusing on rare genetic disorders such as Gaucher disease. This project strengthened the research component of the laboratory and enhanced expertise in the diagnosis and management of skeletal dysplasia and lysosomal storage disorders.

4.2.2 Publications from this Multicentric Project

1. Bidchol AM, Dalal A, Shah H, S S, Nampoothiri S, Kabra M, Gupta N, Danda S, Gowrishankar K, Phadke SR, Kapoor S, Kamate M, Verma IC, Puri RD, Sankar VH, Devi AR, Patil SJ, Ranganath P, Jain SJ, Agarwal M, Singh A, Mishra P, Tamhankar PM, Gopinath PM, Nagarajaram HA, Satyamoorthy K, Girisha KM. GALNS mutations in Indian patients with mucopolysaccharidosis IVA. Am J Med Genet A. 2014 Nov;164A(11):2793-801.
2. Uttarilli A, Ranganath P, Matta D, Md Nurul Jain J, Prasad C K, Babu A S, Girisha KM, Verma IC, Phadke SR, Mandal K, Puri RD, Aggarwal S, Danda S, Sankar V H, Kapoor S, Bhat M, Gowrishankar K, Hasan AQ, Nair M, Nampoothiri S, Dalal A. Identification and Characterization of 20 Novel Pathogenic Variants in 60 unrelated Indian patients with Mucopolysaccharidoses (MPS) type I and type II. Clin Genet. 2016 May 5.
3. Ranganath P, Matta D, Bhavani GS, Wangnekar S, Jain JM, Verma IC, Kabra M, Puri RD, Danda S, Gupta N, Girisha KM, Sankar VH, Patil SJ, Ramadevi AR, Bhat M, Gowrishankar K, Mandal K, Aggarwal S, Tamhankar PM, Tilak P, Phadke SR, Dalal A. Spectrum of SMPD1 mutations in Asian-Indian patients with acid sphingomyelinase (ASM)-deficient Niemann-Pick disease. Am J Med Genet A. 2016 Oct;170(10):2719-30.
4. Mistri M, Mehta S, Solanki D, Kamate M, Gupta N, Kabra M, Puri R, Girisha K, Hariharan S, Nampoothiri S, Sheth F. Identification of novel variants in a large cohort of children with Tay–Sachs disease: An initiative of a multicentric task force on lysosomal storage disorders by Government of India. Journal of human genetics. 2019 Oct;64(10):985-94.
5. Pasumarthi D, Gupta N, Sheth J, Jain SJ, Rungsung I, Kabra M, Ranganath P, Aggarwal S, Phadke SR, Girisha KM, Shukla A. Identification and characterization of 30 novel pathogenic variations in 69 unrelated Indian patients with mucolipidosis type II and type III. Journal of Human Genetics. 2020 Nov;65(11):971-84.
6. Agrawal N, Verma G, Saxena D, Kabra M, Gupta N, Mandal K, Moirangthem A, Sheth J, Puri RD, Bijarnia-Mahay S, Kapoor S,Hariharan SV . Genotype-phenotype spectrum of 130 unrelated Indian families with Mucopolysaccharidosis type II. European Journal of Medical Genetics. 2022 Mar 1; 65(3):104447.

4.3 Intramural Projects (completed)

4.3.1 Establishment of a birth defect registry in a tertiary hospital (2013-2016) SAT Endowment Project

Sujatha Thankappan Lakshmi, Uma Thankam, PreethaJagadhamma, AnujaUshakumari , Nirmala Chellamma, SankarVaikamHariharan. Risk factors for still birth: a hospital-based case control study. Int J Reprod Contracept Obstet Gynecol. 2017 Mar; 6(3):970-974.

Vaikom Hariharan Sankar, Thankam Uma, Sabu George, Anu K Vasu, Sobha Kumar, A Santhoshkumar, Nirmala Chellamma. Pattern of congenital abnormalities in a tertiary hospital and its impact on neonatal mortality. Indian J Child Health. 2017 Oct – Dec; 4 (4): 599-602.

4.3.1 Genetic evaluation in patients with disorders of Sex development (2015-2018) – Multidisciplinary research unit (MRU) project

Sreejith PS, Balakrishnan S, Sankar VH, et al. Patient with Disorders of Sex Development(DSD): A Case Report from a Tertiary Care Hospital in Thiruvananthapuram, India. J ReprodInfertil. 2019;20(3):191-194.

4.3.2 COVID related research done (2019-2021)

Hariharan SV, Muthusamy S, Asokan SK. Persistent viral shedding after SARS-CoV-2 infection in an infant with severe combined immunodeficiency. Indian Journal of Paediatrics. 2022 Jan;89:94-.

Sasidharan B, Sugunan S, Monica K, Chinchilu RV, Niyas HR, Sankar VH. A hospital based comparative study of the first and second waves of Covid-19 related multi-system inflammatory syndrome in children. Sri Lanka Journal of Child Health. 2022 Sep 5;51(3).

Anand V, Vinitha A, Joseph S, Sankar V, Yadev I. Comparing the Clinical Spectrum of Paediatric In-patients in pre-COVID-19, during COVID-19 and post-COVID-19 Pandemic Periods in a Tertiary Level Teaching Centre. Journal of Clinical & Diagnostic Research. 2024 Jan 1;18(1).

4.4 Cytogenetic abnormality in primary amenorrhoea (2021-2022)

THANKAM U, HARIHARAN SV, SAROJAM S, SYAMALA R, ALEX ST, RATNAMMA NV, JACOB S. Proportion and Pattern of Chromosomal Abnormalities in Primary Amenorrhea in Kerala-A Retrospective Study. Journal of Clinical & Diagnostic Research. 2022 Nov 1;16(11).

4.4.1 Genetic Evaluation of SMN1 Gene in Paediatric Patient with Hypotonia. (SBMR funded)(2021-2023).

Geetha AC, Sankar VH, Alex ST, Santhi S, Dasaradh H. Prevalence of exon 7/exon 8 deletion in patients with hypotonia and spinal muscular atrophy: SMN1 exon 7/exon 8 deletion in spinal muscular atrophy. Indian Journal of Experimental Biology (IJEB). 2024 Sep 30;62(10):810-4.

4.4.2 Clinical Trial in Hunter syndrome (2023-2024)

A prospective, Multicenter, single-arm, open-label, Interventional phase IV study to evaluate the safety and efficacy of Idursulfase (r-DNA origin) (Elaprase TM) in Indian Pediatric and adult population with Hunter Syndrome (Mucopolysaccharidosis II) [Clinical trial study] (2023-2024)

4.5 Ongoing Projects

1. Establishment of DBT NIDAN-Kendra (DBT funded) (2024-2027)
2. Application of expanded newborn screening by integration of Metabolomics and Genomics for second tier DNA analysis (ICMR funded Multicentric project) (2024-2027)
3. National Registry for rare and inherited disorders (ICMR study) (2024-2026).

4. Respiratory Syncytial Virus (Rsv): Burden Estimation and the Development of a Monoclonal Antibody-Based Point of Care Diagnostic in collaboration with Institute of Advanced Virology, Thonakkal, TVPM. (ICMR study) (2025- 2028).

4.6 Way Forward

- Multicentric collaborative research and academic clinical trials under various central funding agency will help our research opportunities.
- Partnership with various other NGO and patient support groups will improve the visibility of our facility to patients and accessibility for the patients.
- We are planning research activities in collaboration with various central funding agencies like ICMR, DBT and also panning collaborative research with central institutes like AIIMS-New Delhi and CDFD- Hyderabad.
- Also actively participating in the academic drug trails by ICMR through INTENT network and regulatory drug trails of newer molecules for RARE diseases.
- We should plan and encourage multicentric study in our state collaborating all health units for a state wide data for intervention strategies

Chapter 5. KARE Program

5.1 Background and Rationale

Rare diseases pose significant public health challenges due to their low prevalence, delayed diagnosis, limited availability of specialised care, and extremely high cost of treatment. Individuals affected by rare diseases often experience lifelong morbidity, disability, psychosocial stress, and financial hardship. In India, access to timely diagnosis and advanced therapies remains limited, particularly within the public health system, leading to inequities in care.

Recognising these challenges, the Government of Kerala launched the KARE (Kerala United Against Rare Diseases) Programme as a comprehensive state-led initiative to address unmet needs of persons affected by rare diseases. The programme aims to ensure equitable access to diagnosis, treatment, long-term care, and social protection, particularly for children from economically vulnerable families. The programme is anchored at SAT Hospital, Thiruvananthapuram, designated as the Centre of Excellence, and follows a hub-and-spoke model for referral, treatment, and follow-up across the state.

5.2 Objectives and Scope

The primary objective of the KARE programme is to reduce morbidity, mortality, and financial hardship associated with select rare diseases by strengthening public-sector capacity for diagnosis, treatment, and long-term care. The programme focuses on diseases with high disease burden, proven therapeutic benefit, and substantial treatment costs that are otherwise unaffordable for most families.

The scope of KARE includes early identification, access to high-cost medicines and advanced therapies, multidisciplinary clinical management, rehabilitation, psychosocial support, and financial assistance. The programme also aims to build state-level capacity for rare disease registries, research, and policy planning, in alignment with the National Policy for Rare Diseases (NPRD).

5.3 Case Definition and Classification

Under the KARE programme, rare diseases are defined in accordance with national and international standards, primarily as conditions affecting a small proportion of the population and requiring specialised medical care. The programme currently prioritises genetically inherited, chronic, and life-threatening conditions with significant impact on child health.

The diseases covered include:

- Plexiform Neurofibromatosis (PN)
- Spinal Muscular Atrophy (SMA)
- Selected Lysosomal Storage Disorders (LSDs)
- Turner Syndrome
- Growth Hormone Deficiency

These conditions are classified based on genetic origin, system involvement (neuromuscular, metabolic, endocrine), disease severity, and availability of evidence-based treatment options.

5.4 Burden of Cases – Kerala & India

Although individual rare diseases have low prevalence, their cumulative burden is substantial. India is estimated to have millions of individuals affected by rare diseases, with a significant proportion being children. In Kerala, improved health-seeking behaviour and tertiary care access have led to increased identification of rare diseases, particularly neurogenetic and metabolic disorders.

Conditions such as SMA, PN, and LSDs are associated with high childhood morbidity and mortality if untreated, while endocrine disorders like Turner Syndrome and Growth Hormone Deficiency significantly affect growth, development, and quality of life. The financial burden of treatment for these conditions often exceeds ₹10–20 lakh per child annually, necessitating state-supported intervention.

5.5 Rare Diseases Management

5.5.1 Early Identification and Diagnosis

Early identification is a core pillar of the KARE programme. Children presenting with developmental delay, neuromuscular weakness, growth failure, dysmorphism, or unexplained systemic involvement are prioritised for specialist evaluation. Diagnostic pathways include clinical assessment, advanced imaging, biochemical testing, and genetic confirmation where indicated.

SAT Hospital functions as the nodal centre for confirmatory diagnosis, supported by referral linkages with district and medical college hospitals to enable early case detection.

5.5.2 Clinical Management and Treatment

The KARE programme provides comprehensive, multidisciplinary clinical management tailored to each disease category. This includes access to high-cost targeted therapies for Plexiform Neurofibromatosis, advanced disease-modifying treatments for SMA, enzyme replacement therapy for select Lysosomal Storage Disorders, and long-term hormone therapy for Turner Syndrome and Growth Hormone Deficiency.

Kerala has emerged as the first state in India to provide free treatment for Plexiform Neurofibromatosis through the government health system, with medicines worth approximately ₹10 lakh provided to an initial beneficiary. Treatment protocols emphasise regular monitoring, specialist follow-up, and management of complications through coordinated care teams.

5.6 Prevention and Risk Reduction

While primary prevention of genetic rare diseases is limited, the KARE programme emphasises secondary prevention through early diagnosis and timely treatment to prevent disease progression and irreversible complications. Genetic counselling is integrated into service delivery, particularly for families affected by inherited metabolic and neuromuscular disorders, to support informed reproductive decisions and recurrence prevention.

5.7 Rehabilitation, Palliation, and Long-Term Care

Given the chronic and progressive nature of many rare diseases, KARE places strong emphasis on long-term care. Rehabilitation services including physiotherapy, occupational therapy, nutritional support, and respiratory care are integrated into treatment plans, particularly for SMA and LSDs.

Psychosocial support, counselling, and palliative care services are provided to improve quality of life for affected children and their families, ensuring continuity of care across childhood and adolescence.

5.8 Financial Protection and Social Support

The high cost of rare disease treatment often leads to catastrophic out-of-pocket expenditure. The KARE programme addresses this gap by providing medicines, diagnostics, and specialist care free of cost through public facilities. Financial assistance mechanisms, counselling, and linkage with social welfare schemes are incorporated to support families beyond clinical care, particularly those not covered under national rare disease funding mechanisms.

5.9 Partnership and Collaboration

The KARE programme operates through strong partnerships between the Health Department, tertiary care institutions, medical colleges, and specialist departments. Collaboration with academic institutions, genetic laboratories, and national agencies strengthens diagnostic capacity and treatment planning. The programme also engages patient families and caregiver groups to improve adherence, follow-up, and community awareness.

5.10 Research and Recent Developments

KARE provides a platform for strengthening rare disease research in Kerala through systematic data collection, clinical registries, and documentation of treatment outcomes. The programme supports evidence generation on disease patterns, therapeutic effectiveness, and cost implications, contributing to national and global knowledge on rare diseases. Ongoing developments include expansion of diagnostic services, improved access to genetic testing, and exploration of sustainable financing models.

5.11 Achievements, Challenges, and Way Forward

The KARE programme represents a pioneering model for state-led rare disease management in India. Key achievements include free treatment initiation for high-cost conditions such as Plexiform Neurofibromatosis, structured care for SMA and LSDs, and equitable access to growth hormone therapy for endocrine disorders.

Challenges remain in terms of expanding disease coverage, ensuring sustainable financing, strengthening genetic diagnostics, and scaling services statewide. The way forward involves phased inclusion of additional rare diseases, enhanced registry systems, strengthened research partnerships, and long-term policy integration to ensure sustainability and equity in rare disease care.

CHAPTER 6. Challenges and Way Forward

Even though we achieved a lot of advancement in the field of rare disease , diagnosis & management, there are a large number of challenges in this field. We are here with discussing some of the challenges and way forward.

1. Preventive aspects in the community should be encouraged by Information, education and communication (IEC) activities which will reduce the burden of genetic disorder in the community. The option of carrier screening for common genetic disorders like thalassemia, spinal muscular atrophy and sensorineural hearing loss should be encouraged for identification of carrier couple and genetic counselling with option of prenatal diagnosis. The community should be educated about the increased risk among consanguineous couple and measures to be taken for prevention. Other important health intervention like periconceptional folic acid, rubella vaccination and avoidance of teratogenic drugs also should highlighted for reduction of birth defects in the community.
2. The diagnostic gap from the onset of disease to diagnosis should be reduced significantly for early management initiation for better management. This can be significantly reduced by better awareness creation among health care practitioners. There should be workshops, CMEs and other educational programmes to increase the awareness about the early diagnosis and management.
3. Availability and affordability of genetic tests for the confirmation of diagnosis should be increased. With the introduction of DBT -NIDAN KENDRA, improvement in the availability has happened in the major medical colleges. However, infrastructure development should be encouraged to have genetic laboratory in all major medical colleges and high advanced genetic tests like NGS/Microarray in at least two major medical college.
4. The definitive disease modifying therapy is available for some of the rare diseases like enzyme replacement therapy (ERT) in Gaucher Disease and gene therapy in spinal muscular atrophy. The availability and affordability of theses advance treatment is one of the major challenges. With the introduction of NPRD policy with financial support of 50 LAKHS for the treatment of an individual affected with few (63) rare diseases, we were able to manage some of these conditions with this advanced therapy. However, after exhausting 50 LAKHS continuation and sustainable therapy is big challenge. There should be other mechanisms like state budget provision or crowdfunding platform for continuation of therapy.
5. Some of the drugs like Cystagon for Cystinosis is NOT licenced by DCGI and NOT available in India. This drug needs to import for the patient. Even though this condition is included in the

NPRD list, there is challenges in importing the drug in the government system. Government should take initiatives for this better availability.

6. Since a lot of new drugs are identifying for rare diseases, clinical trials should be initiated in tertiary care hospitals to get this benefit for our patients.
7. Along with this definitive therapy, some of the diseases may require supportive therapy like physiotherapy and surgical management which also should be supported through some mechanisms. Multidisciplinary care pathways should be created for all these conditions where comprehensive management options are available.
8. All families affected with rare diseases should undergo genetic counselling and option of prenatal diagnosis. Prenatal screening facility and prenatal diagnosis facility should be created in all medical colleges with counselling facility which will help the families affected with genetic disorder.
9. Monitoring indicators like time to diagnose the condition, time to start the treatment, survival advantage, quality adjusted life years (QALY), disability adjusted life year (DALY), should be used to evaluate the rare disease management programme.
10. Our pharma industry should take the initiatives to manufacture these drugs and biological products in our country to reduce the cost of these newer medicines. Recent announcements of BIO PHARM in the central budget is a good direction to promote theses biological products in our country at reduced cost
11. Support system should be developed for the patients affected with rare diseases like travel concession and psychological support
12. Formation of Department of Medical genetics with sufficient faculty position will help us to start the academic programme like DM in Medical genetics and training programme for clinicians which will increase the manpower in the field of Medical Genetics.