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NATIONAL RARE DISEASES POLICY- INDIA-2021- AN OVERVIEW

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BACKGROUND:

The government has finalized National Policy for Rare Diseases, 2021 and put in the public domain. The policy aims to reduce the incidence and prevalence of rare diseases through an integrated and comprehensive preventive strategy that includes awareness generation, premarital, post-marital, pre-conception, and post-conception screening and counselling programmes to prevent the birth of children with rare diseases, and, given resource constraints and competing health care priorities, enable access to affordable health care to patients of rare diseases[1].

The policy establishes a National Consortium for Research and Development on Therapeutics for Rare Diseases, with an expanded mandate that includes research and development, technology transfer, and therapeutic indigenization for rare diseases. The Department of Health Research (DHR) will convene it, and the ICMR will be a member[2].

Under the Policy, the central government will provide financial support up to Rs 20 lakhs under the Umbrella Scheme of Rashtriya Arogaya Nidhi for treatment of those rare diseases that require a one-time treatment listed in Group 1. Beneficiaries for such financial assistance would not be limited to BPL families, but would be extended to approximately 40% of the population who are eligible under the Pradhan Mantri Jan Arogya Yojana for treatment only in government tertiary hospitals[3].

State governments may also consider providing assistance to patients suffering from rare diseases that can be managed with special diets, hormonal supplements, or other relatively low-cost interventions listed in Group 2[3].

With regard to resource constraints and the compelling need to prioritise available resources in order to achieve maximum health gains for the community or population, the government will attempt to create an alternate funding mechanism by establishing a digital platform for voluntary individual and corporate donors to contribute to the treatment costs of patients with rare diseases.

Given the government's limited resources and competing health priorities, it will be difficult for the government to fully fund the treatment of high-cost rare diseases. The gap can be filled, however, by developing a digital platform that connects notified hospitals where such patients are receiving treatment or have come for treatment, on the one hand, and prospective individual or corporate patients, on the other.

Through the online system, the notified hospitals will share information about the patients, the diseases from which they are suffering, the estimated cost of treatment, and the details of bank accounts for donation or contribution. Donors will be able to view patient information and donate funds to a specific hospital[4].

This will allow donors from all walks of life to contribute funds to the treatment of patients suffering from rare diseases, particularly those classified as Group 3. Conferences will be held with corporate sector companies to encourage them to make generous donations via digital platforms. The Ministry of Corporate Affairs will be asked to encourage PSUs and corporate houses to contribute in accordance with the Companies Act and the Companies (Corporate Social Responsibility Policy) Rules, 2014. (CSR Rules). Promoting health care, including preventive health care, is on the list of CSR activities. The patient's treatment costs will be the first charge on this fund. Any funds left over after covering treatment costs can also be used for research[4].

Under the Umb, financial assistance is currently provided to poor patients living below the poverty line, as well as to the population who are eligible under the Pradhan Mantri Jan Arogya Yojana under Ayushman Bharat, suffering from

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specified rare diseases for treatment at Government Hospitals or Institutes with super speciality facilities or government tertiary hospitals. The budget allocation for rare diseases for the current fiscal year 2021-2022 is Rs 25 crore.

In July 2017, the Ministry of Health and Family Welfare of the Government of India issued a National Policy for the Treatment of Rare Diseases (NPTRD). However, the policy's implementation was fraught with difficulties. One constraint in its implementation was bringing states on board and a lack of clarity on how much government support there could be in the context of tertiary care. Public health and hospitals are primarily the responsibility of the state. Stakeholder consultation with state governments could not be carried out in a detailed manner at the draught stage of policy formulation. When the policy was shared with state governments, some of them raised concerns about the cost effectiveness of interventions for rare diseases in comparison to other health priorities, the sharing of expenditure between the central and state governments, and the flexibility given to state governments to accept or change the policy based on their circumstances.

Aim of the policy[5]:

1. Increased emphasis on indigenous research and medicine production on a local scale.
2. To reduce the cost of treating rare diseases.
3. To screen for and detect rare diseases in their early stages, which will aid in their prevention.

1. Rare Diseases: Issues & Challenges

The field of rare diseases is diverse and complex. The landscape of rare diseases is constantly changing, as new rare diseases and conditions are identified and reported in medical literature on a regular basis. With the exception of a few rare diseases, where significant progress has been made, the field is still in its infancy. For a long time, doctors, researchers, and policymakers were unaware of rare diseases, and there was no real research or public health policy addressing issues in the field until recently. This presents significant challenges in developing a comprehensive policy on rare diseases. Nonetheless, it is critical to take steps, both short and long term, with the goal of addressing[6].

1.1 Different definitions of rare diseases

The World Health Organization defines rare disease as a debilitating lifelong disease or disorder with a prevalence of 1 or less per 1000 population. Different countries, however, have their own definitions to suit their specific needs and in the context of their own population, health care system, and resources. In the United States, a rare disease is defined as one that affects fewer than 200,000 people in the country (6.4 in 10,000 people).

The European Union defines rare diseases as those that are life-threatening or chronically debilitating and affect no more than 5 people out of every 10,000. In Japan, rare diseases are defined as those with fewer than 50,000 prevalent cases (0.04 percent) in the country.

Table 1: Definitions of Rare Disease in different countries

S.No	Country	Prevalence less than per 10,000 population
1	USA	6.4
2	Europe	5.0
3	Canada	5.0
4	Japan	4.0
5	South Korea	4.0
6	Australia	1.0
7	Taiwan	1.0

Source: The I.C. Verma Sub-Committee Report ‘Guidelinesfor Therapy and Management

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The use of different definitions and terminology can lead to confusion and inconsistencies, which has implications for treatment access as well as research and development. According to a study1 that reviewed and analysed definitions from various jurisdictions, most definitions, as discussed above, appear to take disease into account.

Although prevalence is important, other factors, such as disease severity and whether or not the disease is curable, may also be considered. Whether or not the disease is life-threatening, and whether or not alternative treatment options are available, and whether it is inherited. The study discovered that only a few definitions included qualifiers relating to disease severity and/or a lack of available treatments, whereas the majority of definitions included a prevalence threshold. The average prevalence thresholds used to define rare diseases vary by jurisdiction, ranging from 1 to 6 cases/10,000 people, with WHO recommending a prevalence of less than 10/10,000 population for defiant diseases. The study concluded that efforts to harmonise the various definitions should focus on standardising objective criteria such as prevalence thresholds and avoid qualitative descriptors such as disease severity.

However, it has been argued that disease prevalence alone may not be an accurate basis for defining rare diseases because it does not account for population changes over time. As a result, some have proposed that a more reliable approach to arriving at a definition could be based on – a) location – a disease that is uncommon in one country may be quite common in another. b) Rarity levels - some diseases may be much more rare than other diseases that are also rare. uncommon; and c) study-ability - whether a disease's prevalence lends itself to research clinical trials and research[7].

This highlights the need for additional research to better understand the extent of the existing diversity of definitions for rare diseases and to investigate the scope of arriving at a definition that is best suited to the conditions in India. As soon as sufficient data is available, it will be completed on a priority basis. Already, steps have been taken to establish a hospital-based National Registry for rare diseases in India by ICMR.

1.2 Diagnosis of rare diseases

Early diagnosis of rare diseases is difficult due to a variety of factors, including a lack of awareness among primary care physicians and a lack of adequate screening and diagnostic facilities.

Traditional genetic testing includes tests that can only address a small number of diseases. As a result, physicians frequently provide their best guess as to which tests should be performed. If the test is negative, additional testing will be required using next generation sequencing-based tests or chromosomal microarrays, both of which are applicable but costly and time-consuming processes requiring interpretation and counseling[8].

There is a lack of awareness about rare diseases in both the general public and the medical community. Many doctors lack the necessary training and awareness to be able to diagnose and treat these conditions in a timely and accurate manner. According to a recent report, it takes an average of 7.6 years for patients in the United States (US) and 5.6 years for patients in the United Kingdom (UK) to receive an accurate diagnosis, with as many as eight physicians involved (four primary care and four specialists). Furthermore, two to three misdiagnoses are common before arriving at a final diagnosis[9].

Patients' suffering is multiplied exponentially by a delay in diagnosis or a wrong diagnosis. There is an urgent need to raise awareness among the general public, patients and their families, and doctors, as well as train doctors to make early and accurate diagnoses, standardize diagnostic modalities, and develop newer diagnostic and therapeutic tools.

2. Research and development challenges

A fundamental challenge in research and development for the majority of rare diseases is that little is known about their pathophysiology or natural history. Rare diseases are difficult to research because the patient pool is so small, resulting in insufficient clinical experience. As a result, the clinical explanation for rare diseases may be skewed or incomplete. The challenge is exacerbated by the fact that rare diseases are chronic in nature, necessitating long-term follow-up. As a result, rare diseases frequently lack published data on long-term treatment outcomes and are often understudied[10].

This necessitates the exploration of international and regional research collaborations, collaborations with physicians who work on any rare disease, and collaborations with patient groups and families dealing with the consequences of these disorders. This will aid in gaining a better understanding of the pathophysiology of these diseases, as well as the therapeutic effects that would have a significant impact on the lives of patients. There is also a need to review and, if possible, modify clinical trial norms while keeping the specific challenges in rare diseases, without jeopardising the safety and quality of the medications or diagnostic tools.

2.1 Challenges in treatment

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2.1.1 Unavailability of treatment

Medicine availability and access are critical for reducing morbidity and mortality associated with rare diseases. Despite recent advances, effective or safe treatment for the majority of rare diseases is still unavailable. As a result, even if a correct diagnosis is made, there may not be a treatment available to treat the rare disease. There are between 7000 and 8000 rare diseases, but only about 5% of them have therapies available to treat them. Approximately 95 percent of rare diseases have no approved treatment3, and less than one out of every ten patients receive disease-specific treatment. Where drugs are available, they are prohibitively expensive, putting a huge strain on available resources[11].

2.1.2 Prohibitive cost of treatment

Because the number of people suffering from individual rare diseases is small, drug manufacturers do not see a significant market for developing and bringing drugs for them to market. As a result, rare diseases are also referred to as "orphan diseases," and the drugs used to treat them are referred to as "orphan drugs."

Where drugs for rare diseases are produced, the prices are exorbitantly high, presumably to recoup the cost of research and development. At the moment, only a few pharmaceutical companies in the world manufacture drugs for rare diseases, and India has no domestic manufacturers except for Food for Special Medical Purposes (FSMP) for small molecule inborn errors of metabolism. Because most therapies are expensive, the government has been unable to provide them for free. The annual cost of treatment for some rare diseases for a child weighing 10 kg is estimated to range between Rs. 10 lakh and Rs. 1 crore per year, with treatment lasting a lifetime and drug dose and cost increasing with age and weight[12].

Countries have dealt with this one-of-a-kind problem of high cost through a variety of methods tailored to their specific needs. Instruments such as the Orphan Drug Act (ODA) in the United States and Canada provide incentives to drug manufacturers to encourage them to develop drugs for rare diseases. The Act's economic incentives and safeguards ensure that local patients benefit. However, the exorbitant prices of drugs for rare diseases have raised concerns even in developed countries about the long-term viability of rare disease funding/reimbursement programmes. The exorbitant prices have prompted calls for transparency in drug pricing and price control, as well as scrutiny and congressional inquiries[12].

3. The Indian scenario

In India, there is a lack of data on how many people suffer from various diseases that are considered rare globally. So far, all cases have been diagnosed at tertiary hospitals. a scarcity of epidemiological data on the occurrence and prevalence of rare diseases obstructs understanding of the scope of the burden of rare diseases and the development of a definition. It also impedes efforts to accurately estimate the number of people affected by these diseases and describe their morbidity and mortality. In such a scenario, the economic burden of the majority of rare diseases is unknown and cannot be adequately estimated using existing data sets.

Despite the fact that it is extremely difficult, given the complexity of various diseases and the difficulty in diagnosis, there is a clear need to conduct systematic epidemiological studies to determine the number of people suffering from rare diseases in India. So far, only a small number of diseases from tertiary care hospitals in India have been recorded, despite the fact that the scope may include 7000 to 8000 disorders[13].

Primary immunodeficiency disorders, Lysosomal storage disorders (Gaucher's disease, Mucopolysaccharidoses, Pompe disease, Fabry disease, and others) are among the most commonly reported diseases. Small molecule inborn metabolic errors (Maple Syrup urine disease, organic acidemias, and so on), Cystic Fibrosis, osteogenesis imperfecta, certain forms of muscular dystrophy, and spinal muscular atrophy, among others.

3.1 Experiences from other countries

While India was developing a policy for rare diseases, policies from other countries were reviewed. The Orphan Drugs Act in the United States of America seeks to encourage the development of drugs for rare diseases by incentivizing industry through market exclusivity, grants to researchers, and tax breaks on expenditure incurred during drug evaluation for therapeutic efficacy. However, critics claim that pharmaceutical companies have exploited this arrangement and "gamed the system" in order to maximise profits. The European Joint Programme on Rare Diseases is primarily concerned with on investigation.

The National Health Service (NHS) England, for example, states that Biogen (the pharmaceutical company that manufactures treatment for SMA) will make the treatment for Spinal Muscular Atrophy (SMA) available to the youngest and most severely affected (SMA Type 1) patients immediately, with NHS England offering funding on National Institute for Health and Care Excellence (NICE) publication of final guidance[15].

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In Singapore, a fund called the Rare Disease Fund was established to fund five medicines to treat rare diseases. Three uncommon disease conditions Access is subsidised in Malaysia and Australia for those who qualify Patients are reimbursed for costly and life-saving drugs.

4. In resource-constrained settings, it is necessary to balance competing public health priorities.

Rare diseases impose a significant economic burden on any country, particularly those with limited resources. With regard to treatment for rare diseases, the financial capacity to support exorbitant treatment costs is an important consideration in public health policy development.

In resource-constrained settings, it is critical to balance competing public health interests in order to achieve the best possible outcome for the resources available. Because resources are limited and have multiple uses, policymakers must prioritise certain sets of interventions over others; the appropriate choice is then to support those interventions that provide the greatest number of healthy life years for given sum of money while simultaneously looking at the equity i.e., interventions that benefit poor who cannot afford healthcare are prioritized[16].

Thus, interventions that address the health problems of a much larger number of people with a relatively smaller budget are prioritised over others, such as funding. treatment of rare diseases, which will necessitate significantly more resources a much smaller number of people have health problems.

As a result, any policy on rare diseases must be considered in the context of available scarce resources and the need for their most judicious utilisation in order to maximise overall health outcomes for the entire society as measured by an increase in healthy life years.

5. Definition of Rare Diseases

There is no such thing as a universal or standard definition of rare disease. A rare disease is one that occurs infrequently, and it has been defined by different countries in terms of prevalence – either in absolute terms or in terms of prevalence per 10,000 population. A country defines a rare disease based on its own population, health-care system, and resources[17].

As previously stated, India faces the limitation of a lack of epidemiological data to define rare diseases in terms of prevalence or prevalence rate, as other countries have done. To address this, a hospital-based National Registry for Rare Diseases was established Diseases was started by ICMR by involving centres all over the country involved in the diagnosis and treatment of rare diseases. This will provide critical epidemiological data for rare diseases. In the absence of epidemiological data on diseases considered rare in other countries, prescribing threshold prevalence rates to define a disease condition as rare is impossible[17].

Until such data is available and the country arrives at a definition of a rare disease based on prevalence data, the term rare diseases shall refer to the following groups of disorders identified and classified by experts based on their clinical experience:

Group 1: Disorders amenable to a single-time cure:

a) Disorders treatable with Hematopoietic Stem Cell Transplantation (HSCT) – Lysosomal Storage Disorders (LSDs) for which Enzyme Replacement Therapy (ERT) is currently unavailable, and severe form of Mucopolysaccharoidosis (MPS) type I within the first two years of life.

i) ioiAdrenoleukodystrophy (early stages), prior to the onset of severe neurological symptoms.

ii) Immune deficiency disorders such as Severe Combined Immunodeficiency (SCID), Chronic Granulomatous Disease, Wiskot Aldrich Syndrome, and others.

iii) Osteopetrosis

iv) Fanconi Anemia

b) Disorders amenable to organ transplantation

i) Liver Transplantation -Metabolic Liver diseases:

a. Tyrosinemia,

b. Glycogen storage disorders (GSD) I, III and IV due to poor metabolic control, multiple liver adenomas, or high risk for Hepatocellualr carcinoma or evidence of substantial cirrhosis or liver dysfunction or progressive liver failure,

c. MSUD (Maple Syrup Urine Disease),

d. Urea cycle disorders,

e. Organic acidemias.

ii) Renal Transplantationa. Fabry disease b. Autosomal recessive Polycystic Kidney Disease (ARPKD), c. Autosomal dominant Polycystic Kidney Disease (ADPKD) etc.

iii. Patients requiring combined liver and kidney transplants can also be considered if the same ceiling of funds is maintained. (Rarely Methyl Malonicaciduria may require combined liver & Kidney transplant) etc.

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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:

a) Disorders managed with special dietary formulae or Food for special medical purposes (FSMP)
i) Phenylketonuria (PKU)
ii) Non-PKU hyperphenylalaninemia conditions
iii) Maple Syrup Urine Disease (MSUD)
iv) Tyrosinemia type 1 and 2
v) Homocystinuria
vi) Urea Cycle Enzyme defects
vii) Glutaric Aciduria type 1 and 2
viii) Methyl Malonic Acidemia
ix) Propionic Acidemia
x) Isovaleric Acidemia
xi) Leucine sensitive hypoglycemia
xii) Galactosemia
xiii) Glucose galactose malabsorbtion
xiv) Severe Food protein allergy
b) Disorders that are amenable to other forms of therapy (hormone/ specific drugs)
i) NTBC for Tyrosinemia Type 1
ii) Osteogenes isImperfecta – Bisphosphonates therapy i
iii) Growth Hormone therapy for proven GH deficiency, Prader Willi Syndrome, Turner syndrome and Noonan syndrome.
iv) Cystic Fibrosis- Pancreatic enzyme supplement
v) Primary Immune deficiency disorders -Intravenous immunoglobulin and sub cutaneous therapy (IVIG) replacement eg. X-linked agammablobulinemia etc.
vi) Sodium Benzoate, arginine, citrulline, phenylacetate (Urea Cycle disorders), carbaglu, Megavitamin therapy (Organic acidemias, mitochondrial disorders) Others
vii) Hemin (Panhematin) for Acute Intermittent Porphyria, High dose Hydroxocobalamin injections (30mg/ml formulation – not available in India and hence expensive if imported)
viii) Large neutral aminoacids, mitochondrial cocktail therapy, Sapropterin and other such molecules of proven clinical management in a subset of disorders

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.

3a) Based on the literature sufficient evidence for good long-term outcomes exists for the following disorders
1. Gaucher Disease (Type I & III {without significant neurological impairment})
2. Hurler Syndrome [Mucopolysaccharisosis (MPS) Type I] (attenuated forms)
3. Hunter syndrome (MPS II) (attenuated form)
4. Pompe Disease (Both infantile & late onsetdiagnosed early before development of complications)
5. Fabry Disease diagnosed before significant end organ damage.
6. MPS IVA before development of disease complications.
7. MPS VI before development of disease complications.
8. DNAase for Cystic Fibrosis.

3b) For the following disorders for which the cost of treatment is very high and either long term follow up literature is awaited or has been done on small number of patients
1. Cystic Fibrosis (Potentiators) 16
2. Duchenne Muscular Dystrophy (Antesensce oligoneucletides, PTC)
3. Spinal Muscular Atrophy (Antisense oligonucleotides both intravenous & oral & gene therapy)
4. Wolman Disease
5. Hypophosphatasia
6. Neuronal ceroid lipofuschinosis

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The list of diseases under Group 1, Group 2 and Group 3 are not exhaustive and will be reviewed periodically based on updated scientific data by the Technical Committee[18].

6. Policy Direction

The policy aims to reduce the incidence and prevalence of rare diseases through an integrated and comprehensive preventive strategy that includes awareness generation, premarital, post-marital, pre-conception, and post-conception screening and counselling programmes to prevent the birth of children with rare diseases, and enable access to affordable health care to patients of rare diseases which are amenable to one-time treatment or relatively low cost therapy.

Given the scarcity of data on rare diseases and competing health priorities, the focus would be on prevention of rare diseases as a priority for all three groups of rare diseases identified by Experts. Because public health and hospitals are a state responsibility, the Central Government would encourage and support states in their efforts to screen for and prevent rare diseases through Centres of Excellence under the Rare Disease Policy and Nidan Kendras under the Department of Biotechnology[19].

7. Prevention & Control of Rare Diseases:

7.1 Capacity building of health professionals

The Central Government will collaborate with state governments to increase the capacity of health professionals at all levels. The content of such capacity building would be based on various health professionals' roles. The Centres of Excellence would create Standard Operating Protocols that would be used at various levels of care for patients with rare diseases in order to improve early diagnosis and care coordination[20].

7.2 Prevention at different levels

Though, thanks to technological advancements, understanding of the pathophysiological mechanisms of rare genetic disorders has improved in the last two decades, treatment options are limited, and available therapies may not result in "cure." More importantly, they are prohibitively expensive and not widely available and accessible. As a result, prevention must be the primary focus for all genetic disorders. Preventing genetic disorders can be accomplished on several levels. In order to use these, the first step in developing strategies is to increase the capacity of health professionals. The general public is becoming more aware of the prevalence of such diseases, and Preventative measures[20].

Frontline workers will be adequately trained to screen for rare diseases. Adequate IEC material will be designed and made available at multiple levels of the health care pyramid, as this is a fundamental pillar in addressing the issue of low awareness.

7.3 Primary Prevention:

This aims to prevent the disease from occurring, i.e., to prevent the birth of an affected child. Though not always feasible, this strategy yields the greatest long-term returns in terms of decreasing the incidence and prevalence of rare disorders in the population. Some of the strategies that can be used are as follows:

→Avoiding pregnancy at an advanced age or any other rare monogenic disorder by not marrying a carrier, carrier couples not reproducing, and so on are examples, but these are not realistic options in the real world.

➔ As a result, in the majority of cases, the most viable preventive 18 strategy is secondary prevention. A simple checklist, however, will be made available to primary health care providers in health and wellness clinics to identify a couple at risk based on disease in a previous sibling or a family history of that disorder.

7.4 Secondary prevention:

This strategy focuses on preventing the birth of an affected foetus (prenatal screening and diagnosis), early detection of the disorders, and appropriate medical intervention to alleviate or minimise the manifestations (newborn screening).

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a) Prenatal screening:

Biochemical screening and ultrasonography for chromosomal disorders such as Down syndrome, as well as ultrasonography for other structural defects, are currently recommended for all pregnancies. The goal of prenatal screening and diagnosis in the context of rare diseases is to identify high-risk mothers for having an affected foetus with a rare disease. The goal of prenatal screening and diagnosis in the context of rare diseases is to identify high-risk mothers for having an affected child. A foetus suffering from a rare disease Based on the family tree, these mothers can be identified (previously affected child or affected relative with a known or suspected condition) a genetic condition).

Based on the suspected disease, a targeted screening of the affected child or couple for a specific disorder or carrier testing for monogenic disorders using next generation sequencing techniques, the latter of which is currently expensive, can be provided[21].

b) Prenatal diagnosis by invasive testing (e.g., chorionic villus sampling and amniocentesis):

It is possible for any single-gene disorder and any chromosomal abnormality if the disease-causing variant in the gene/enzyme defect is known.

The most common causes are known single-gene disorders or chromosomal abnormalities in a previous affected child in the family.

These tests can also be provided if the married couple is found to be carriers for any single gene disorder and mutations in the couple have been identified. Prenatal diagnosis for the aforementioned disorders is now widely available in India at many institutions. Obstetricians and foetal medicine specialists perform the invasive procedures.

However, these procedures carry a small risk of foetal loss, which is very low if performed by experienced specialists. This must be communicated to the family prior to the procedure. The cost would be determined primarily by the type of test to be performed on the sample. If the foetus is found to be abnormal, the couple has the option of terminating the pregnancy, the legal age of which has been raised in India.

c) Newborn screening (NBS):

This is the best example of secondary prevention because babies are screened within a few days of birth before symptoms of the disease appear. Symptoms appear, and treatment is initiated, preventing morbidity and mortality. In the case of the developed world, NBS is available for a variety of rare disorders, most notably the Apart from the common disorders, there are treatable ones (e.g., LSDs, SCID).

d) Early postnatal diagnosis and treatment:

Prior to the development of severe manifestations/complications that are irreversible is also included in secondary prevention for disorders amenable to therapy, which would necessitate increased awareness and improved diagnostic availability. The key is to refer suspected patients and their families to appropriate facilities that are equipped to make a correct diagnosis and, if necessary, initiate treatment. Genetic testing will also be supplemented by laboratories affiliated with the National Genomics Core, which is supported by the Department of Biotechnology, the Institute of Genomics and Integrative Biology (IGIB), and the Centre for Cellular and Molecular Biology[22].

7.5 Tertiary prevention refers to providing better care and medical rehabilitation to patients with rare diseases who have reached an advanced stage of the disease. It includes providing the best supportive care to patients suffering from a variety of rare diseases. Disorders, including those for which there is no specific treatment. This would be beneficial and enhance the quality of life for affected individuals and families.

Developmental assessment and intervention, including early stimulation and behavioural intervention, physical therapy and rehabilitation, the provision of visual and hearing aids, and, most importantly, emotional and psychological support to affected individuals and families, are all part of supportive care.

7.6 Optimal screening and diagnosis strategy:

Given competing priorities and limited resources, universal screening for all pregnancies and/or newborns in the country for all rare disorders is not feasible. The policy recommends a screening and diagnostic strategy in which pregnant women with a history of a child born with a rare disease and that child's diagnosis are screened.

This strategy is consistent with the policy goal of lowering the prevalence of rare diseases in the population. In cases where the diagnosis could not be determined during the examination.

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During the prenatal period, it is essential to offer to the newborn or infant as the case may be It is possible and would include newborn screening for:
(a) small molecule Inborn Metabolic Errors (IM) by liquid chromatography – tandem mass spectrometry (LC-MS/MS),
(b) SCID diagnosis by T cell receptor excision circles (TREC), and
(c) lysosomal storage disorders (LSDs) diagnosis by microfluids / LC-MS/ MS.
(d) the diagnosis of disorders using newer but less expensive molecular diagnostic platforms.

8. Centres of Excellence (COE) and Nidan Kendras

The government will announce the names of selected Centres of Excellence, which will be premier government tertiary hospitals equipped with diagnostic, prevention, and treatment facilities for rare diseases. To begin, the institutes listed below would be designated as Centers of Excellence for Rare Diseases:
a) All India Institute of Medical Sciences, New Delhi
b) Maulana Azad Medical College, New Delhi
c) Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow
d) Post Graduate Institute of Medical Education and Research, Chandigarh
e) Centre for DNA Fingerprinting & Diagnostics with Nizam's Institute of Medical Sciences, Hyderabad
f) King Edward Medical Hospital, Mumbai
g) Institute of Post-Graduate Medical Education and Research, Kolkata
h) Center for Human Genetics (CHG) with Indira Gandhi Hospital, Bengaluru

More Centres of Excellence, however, can be added for regional outreach if they are found to be suitable in terms of infrastructure and human resources based on technical committee recommendations.

8.1 The following are the COEs' responsibilities and activities:

- Education & Training at all levels
- Screening – Antenatal, neonatal (specified disorders), High risk screening (Both antenatal & in newborns and children)
- Diagnostics- Cytogenetic, molecular, Metabolic
- Prevention by prenatalscreening &diagnosis
- Research in the area of low cost diagnostics & therapeutics.
- Treatment of rare diseases.

Based on a gap analysis, the proposed COEs will be given one-time financial support up to a maximum of Rs 5 crore for the procurement of equipment as needed by individual centres for strengthening patient care services for screening, diagnosis, and prevention (prenatal diagnosis) of rare diseases[23].
These Centers of Excellence will make the necessary treatment and funding decisions on rare disease cases within two weeks of receiving a new application.

8.2 Nidan Kendras: The Department of Biotechnology (DBT) established Nidan Kendras for genetic testing and counselling services as part of the Unique Methods of Management and Treatment of Inherited Disorders (UMMID) project. These Nidan Kendras will provide rare disease screening, genetic testing, and counselling. Nidan Kendras with treatment facilities may do so under the supervision of an expert[23].

List of Nidan Kendras is given below:

- Lady Hardinge Medical College (LHMC), Delhi
- Nizam's Institute of Medical Sciences (NIMS), Hyderabad, Telangana
- All India Institute of Medical Sciences (AIIMS), Jodhpur
- Army Hospital Research & Referral, Delhi
- Nil Ratan Sircar (NRS) Medical College and Hospital, Kolkata

Currently Nidan Kendras/Mentor Institutes are supporting aspirational districts for screening of rare diseases. List of aspirational districts covered under the programme is given below:

Table 2: List of mentor institutes and states

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Name of the Mentor Institute	Aspirational District	State
LHMC, New Delhi	Mewat	Haryana
CDFD, Hyderabad	Yadgir	Karnataka
AIIMS, New Delhi	Haridwar	Uttarakhand
CMC, Vellore	Washim	Maharashtra
MAMC, New Delhi	Ranchi / Bokaro	Jharkhand
SGPGIMS, Lucknow	Shrawasti	Uttarpradesh
NIIH (KEM hospital campus), Mumbai	Nandurbar	Maharashtra

More aspirational districts will be covered in the future, either by establishing more Nidan Kendras or by existing Nidan Kendras adopting more than one aspirational district.

9. Government of India support in treatment:

The following initiatives will be implemented for patients suffering from rare diseases:
1. The Central Government will provide financial support up to Rs. 20 lakh under the Rashtriya Arogaya Nidhi Umbrella Scheme for treatment of those rare diseases that require a one-time treatment (diseases listed in Group 1). Beneficiaries for such financial assistance would not be limited to BPL families, but would be extended to approximately 40% of the population who are eligible under the Pradhan Mantri Jan Arogya Yojana for treatment only in Government tertiary hospitals.
2. State governments may consider assisting patients with rare diseases that can be managed with special diets, hormonal supplements, or other low-cost interventions (Diseases listed under Group 2)
3. With regard to resource constraints and the compelling need to prioritise available resources in order to achieve maximum health gains for the community/population, the government will endeavour to create an alternate funding mechanism by establishing a digital platform for voluntary individual and corporate donors to contribute to the treatment costs of patients with rare diseases.

10. Voluntary crowd-funding for treatment

Given the government's limited resources and competing health priorities, it will be difficult for the government to fully fund the treatment of high-cost rare diseases. The gap can be filled, however, by developing a digital platform that connects notified hospitals where such patients are receiving treatment or have come for treatment, on the one hand, and prospective individual or corporate donors, on the other.
The notified hospitals will share information about the patients, the diseases they are suffering from, the estimated cost of treatment, and the details of bank accounts for donation/contribution via an online system. Donors will be able to view patient information and donate funds to a specific hospital.
This will allow donors from all walks of life to contribute funds for the treatment of patients suffering from rare diseases, particularly those classified as Group 3. Conferences will be held with corporate sector companies to encourage them to make generous donations via the digital platform.
The Ministry of Corporate Affairs will be asked to encourage PSUs and corporate houses to contribute in accordance with the Companies Act and the Companies (Corporate Social Responsibility Policy) Rules, 2014. (CSR Rules). Promoting health care, including preventive health care, is on the list of CSR activities in the Schedule[23].

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Treatment cost of the patient will be first charge on this fund. Any leftover fund after meeting treatment cost can be utilized for research purpose also.

10.1 Development of manpower

The following initiatives will be implemented to strengthen manpower: State governments will be asked to establish a Department of Medical Genetics at at least one medical college in their state for the purpose of imparting education and raising awareness among health care professionals.

The services of Nidan Kendras established under the Department of Biotechnology will also be used for medical practitioner training.

10.2 Constitution of Consortium

(a) **Consortium of Centres of Excellence** so created will synchronize prevention and treatment efforts. AIIMS, Delhi will be the nodal hospital to coordinate with other Centres of Excellence for various activities relating to prevention and treatment of rare disease.

(b) **National Consortium for Research and Development on Therapeutics for Rare Diseases:** The mandate of the National Consortium for Research and Development on Therapeutics for Rare Diseases can be expanded to include research and development, technology transfer, and indigenization of therapeutics for rare diseases. It will be hosted by the Department of Health Research (DHR), with the ICMR as a participant.

10.3 Increasing the affordability of drugs for rare diseases

(a) Research & Development activities on rare diseases

The Indian Council of Medical Research (ICMR), the Department of Biotechnology, the Department of Pharmaceuticals, the Department of Science and Technology, and the Council of Scientific and Industrial Research will be asked to promote rare disease research and development for diagnosis and treatment.

Creation of an integrated research pipeline to begin the development of new drugs, in which pharmaceutical companies, research organisations, and funding agencies would be encouraged to participate. The use of biosimilars and drug repurposing research would be encouraged. New drug approval and trial decision-making will continue to be provided.

(b) The Ministry of Finance will be asked to reduce customs duties on the import of medicines for rare diseases.

(c) In consultation with the Ministry of Health and Family Welfare, the Ministry of Chemicals and Fertilizers, the Department of Pharmaceutical (DoP), and the National Pharmaceutical Pricing Authority (NPPA) shall take measures to document and make publicly available the prices of drugs for rare diseases, as well as work toward drug affordability for rare diseases.

(d) Measures for creating conducive environment for indigenous manufacturing of drugs for rare diseases would be taken. Department of Pharmaceuticals, Department for Promotion of Industry and Internal Trade (DPIIT) will be requested to promote local development and manufacture of drugs for rare diseases at affordable prices and take legal/legislative measures for creating conducive environment for indigenous manufacturing of drugs for rare diseases at affordable prices. PSUs would be encouraged for local manufacturing of drugs for rare diseases.

11. Implementation strategy

Given the scarcity of epidemiological data on rare diseases, resource constraints, and competing health priorities, the government will prioritise the following:

1) The government will establish a hospital-based National Registry for Rare Diseases at ICMR with the goal of compiling a database of rare diseases. ICMR has already taken steps in this direction. The registry is expected to produce information on hospital-based data and disease burden over time.
2) The government will take steps to raise awareness of rare diseases among all levels of health care personnel as well as the general public. This will encourage people to seek pre-marital genetic counselling, identify high-risk couples and families, and result in birth prevention and early detection of cases of rare diseases.
3) Because public health and hospitals are a state responsibility, the Central Government must encourage and support state governments in implementing a targeted preventive strategy.

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4) The government will provide financial assistance up to Rs. 20.00 lakh (under the Rashtriya Arogya Nidhi Umbrella Scheme) to the entitled population, in accordance with PMJAY norms, for treatment in a government tertiary hospital for rare diseases amenable to one-time treatment (identified under Group 1).
5) State governments may treat disorders managed with special dietary formulae or food for special medical purposes (FSMP) as well as disorders amenable to other forms of therapy (hormone/specific drugs)- diseases covered under Group 2.
6) The government will notify designated Centers of Excellence at premier government hospitals for the comprehensive management of rare diseases. If such infrastructure is not available, the Centres of Excellence will be given a one-time grant of up to Rs. 5 crore each for the development of screening, testing, and treatment infrastructure.
7) The government will establish a digital platform to connect notified Centers of Excellence where patients with rare diseases can receive treatment or come for treatment, on the one hand, and prospective voluntary individual or corporate donors willing to support such patients' treatment, on the other. The funds raised through this mechanism will be used to treat patients suffering from rare diseases.
8) To ensure transaction transparency in the provision of funding under RAN/crowd funding, etc., the Centres of Excellence receiving the funds should be linked to the ICMR registry.
9) The government will help to create an enabling environment in the country that promotes research and development of diagnostic and therapeutic modalities. A Consortium of Centres of Excellence will be established in order to coordinate research efforts. AIIMS, Delhi, will serve as the nodal hospital for coordinating various activities with other Centers of Excellence.
10) State governments will be asked to establish a Department of Medical Genetics at at least one medical college in their state in order to educate and raise awareness among health care professionals. This will strengthen the country's manpower base for managing Rare Diseases.
11) The Department of Pharmaceuticals and the Department for Promotion of Industry and Internal Trade (DPIIT) will be asked to promote local development and manufacturing of drugs for rare diseases by public and private sector pharmaceutical companies at affordable prices, as well as to take legal/legislative steps to create a conducive environment for indigenous manufacturing of drugs for rare diseases at affordable prices.
12) The Ministry of Finance will be asked to reduce customs duties on the import of medicines for rare diseases.

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References:

1. https://www.drishtiias.com/daily-updates/daily-news-analysis/national-rare-disease-policy-2021
2. https://main.mohfw.gov.in/sites/default/files/Final%20NPRD%2C%202021.pdf
3. https://pib.gov.in/PressReleaseIframePage.aspx?PRID=1709369
4. https://www.thehindu.com/news/national/disquiet-over-govts-new-policy-for-rare-diseases/article34225606.ece
5. http://www.indiaenvironmentportal.org.in/files/file/Final%20NPRD%202021.pdf
6. https://main.mohfw.gov.in/sites/default/files/Final%20NPRD%2C%202021.pdf
   Google Scholar
7. Imranullah, M.S. (2020, February 11) *Draft national policy on rare diseases published, Centre tells Madras HC*.
8. India Filings. (n.d.) . *Corporate social responsibility under companies act*. India Filings.
9. Kyle, M. K. (2007). Pharmaceutical price controls and entry strategies. *The Review of Economics and Statistics*, 89(1), 88–99.
10. National Institutes of Health (n.d.) *Rare diseases*
11. https://ordindia.in/about-rd/rare-disease-in-india/
12. https://health.economictimes.indiatimes.com/news/industry/rare-diseases-in-india-the-jouney-ahead/84191154
13. Jha P, Sinha S, Kanchan K, Qidwai T, Narang A, Singh PK, et al. Deletion of the APOBEC3B gene strongly impacts susceptibility to falciparum malaria. Infect Genet Evol. 2012;12(1):142–8.
14. Kanchan K, Pati SS, Mohanty S, Mishra SK, Sharma SK, Awasthi S, et al. Polymorphisms in host genes encoding NOSII, C-reactive protein, and adhesion molecules thrombospondin and E-selectin are risk factors for Plasmodium falciparum malaria in India. Eur J Clin Microbiol Infect Dis. 2015;34(10):2029–39.
15. Venugopal A, Chandran M, Eruppakotte N, Kizhakkillach S, Breezevilla SC, Vellingiri B. Monogenic diseases in India. Mutat Res. 2018;776:23–31.

ISSN:0975-3583,0976-2833 VOL12,ISSUE05,2021

16. Sachdeva K, Saxena R, Puri R, Bijarnia S, Kohli S, Verma IC. Mutation analysis of the CFTR gene in 225 children: identification of five novel severe and seven reported severe mutations. Genet Test Mol Biomarkers. 2012;16(7):798–801.
17. Ankala, A., Kohn, J. N., Dastur, R., Gaitonde, P., Khadilkar, S. V., and Hegde, M. R. (2013). Ancestral founder mutations in calpain-3 in the Indian Agarwal community: historical, clinical, and molecular perspective. Muscle Nerve 47, 931–937. doi: 10.1002/mus.23763
18.
19. Ankala, A., Tamhankar, P. M., Valencia, C. A., Rayam, K. K., Kumar, M. M., and Hegde, M. R. (2015). Clinical applications and implications of common and founder mutations in Indian subpopulations. Hum. Mutat. 36, 1–10. doi: 10.1002/humu.22704
20. Ara, A., Kumar, D., Dewan, D., and Digra, N. (2018). Incidence of congenital anomalies in a rural population of Jammu - A prospective study. Indian J. Public Health 62, 188–192. doi: 10.4103/ijph.IJPH_77_17
21. Auvin, S., Irwin, J., Abi-Aad, P., and Battersby, A. (2018). The problem of rarity: estimation of prevalence in rare disease. Value Health 21, 501–507. doi: 10.1016/j.jval.2018.03.002
22. Ayme, S., Urbero, B., Oziel, D., Lecouturier, E., and Biscarat, A. C. (1998). Information on rare diseases: the Orphanet project. Rev. Med. Interne 19(Suppl. 3), 376S–377S.
23. Basu, A., Sarkar-Roy, N., and Majumder, P. P. (2016). Genomic reconstruction of the history of extant populations of India reveals five distinct ancestral components and a complex structure. *Proc. Natl. Acad. Sci. U.S.A.* 113, 1594–1599. doi: 10.1073/pnas.1513197113