

Rare diseases in India: time for cure-driven policy initiatives and action

Anjali Taneja*, L. S. Shashidhara and Alok Bhattacharya

India is estimated to have a large number of patients suffering from rare diseases (RDs). More than 95% of such diseases are incurable. In many cases, the available treatments are expensive and often have to be provided lifelong to the patients. As a result, the direct and indirect costs of these diseases are significantly high, adding to the country's socio-economic burden. It is time for India to implement healthcare policies that are focused on encouraging domestic production of drugs against RDs and finding innovative cures for them. This article delineates the existing social, economic and policy scenario governing RDs in India. It also examines some of the global policy approaches in this field. Taking a cue from such international practices, this article advocates the need for a comprehensive regulatory framework for RDs in India with the ultimate goal of ensuring 'cure for all patients'.

Keywords: Diagnosis and treatment, health policy initiatives, orphan drugs, rare diseases.

RARE diseases (RDs), as the name suggests, afflict a relatively small number of patients worldwide. There is no uniform definition of such diseases globally, and differential cut-offs have been used to qualify a disease as rare. For example, in USA, the number of patients must be fewer than 200,000 in order to be categorized under RDs¹. According to the World Health Organization (WHO), a disease is considered rare if its occurrence is 1 or less in 10,000 in the population².

In India, the Central Drugs Standard Control Organization (CDSCO)'s definition of RDs is considered as the national standard benchmark. In the new clinical trial guidelines, RD is one that afflicts fewer than 500,000 patients in the country³. About 80% of RDs are genetic disorders and nearly 50% of the patients are children. A large number do not survive beyond the age of 20 (ref. 4). According to various Government of India (GoI) estimates, 35% of deaths take place before the age of 1, 10% between the ages of 1 and 5, and 12% between 5 and 15 (refs 4, 5). Most of these diseases are chronic and degenerative causing extreme disability, which progresses with age. As a result, the patients suffering from RDs often require specialized supportive care.

The direct and indirect costs of RDs are high in comparison to other diseases. The high costs are primarily attributed to delayed diagnosis, lack of adequate treat-

ment facilities and large dependency on imported drugs in the country. While over 95% of RDs are incurable, the available treatments are also expensive, partly because they have to be administered lifelong to the patients. Moreover, most of such treatments involve the procurement of expensive drugs (note 1), be they biological or non-biological. This could further increase the financial burden of patients^{6,7}.

For instance, it has been reported that the international price of Spinraza (Nusinersen), a drug that is used in the treatment of spinal muscular atrophy (SMA), is somewhere around US\$ 375,000 per patient⁸. Similarly, chemical chaperone Migalastat, which is used to treat Fabry's disease, could cost annually around US\$ 310,000 in the international market⁹. This is almost equal to the cost of undergoing a biological enzyme replacement therapy. Since these drugs are not produced in India, the imports of such medicines add to the price of procurement, thereby aggravating the overall cost of local treatments.

Therefore, it is imperative to develop sustainable regulatory mechanisms that could mitigate and eventually eliminate such costs. Such enablers should be able to ensure equitable access to timely diagnosis, clinical management, supportive therapies and treatments for all patients. The need of the hour is to have in place a well-defined national policy framework with the ultimate goal of curing RDs. The policy should define concrete measures in promoting scientific innovation, advanced research, domestic production of drugs and enable active engagement of patients in the overall process of growth and development. This article discusses such policy options in the context of the Indian economy, emphasizing the need for implementing an outcome-driven health

Anjali Taneja is in the Science Policy Cell and L. S. Shashidhara and Alok Bhattacharya are in the Department of Biology, Ashoka University, Sonapat 131 029, India; L. S. Shashidhara is also in the Department of Biology, Indian Institute of Science Education and Research, Pune 411 008, India.

*For correspondence. (e-mail: anjali.taneja@ashoka.edu.in)

policy or a focused legislation on RDs, one which is directed towards finding a cure for all patients, nationwide.

The problem: nature and extent

Global figures report the existence of nearly 7000 RDs worldwide¹. About 80% are caused due to genetic alterations⁵. In India, about 450 RDs have been reported so far¹⁰. Although each of these diseases may impact a relatively small number of patients, together they affect the lives of millions. Between 72 and 96 million of India's population is likely to be suffering from RDs¹⁰. This figure, though under-reported, is based on the global population prevalence of RDs estimated in the range 3.5–5.9% or between 263 and 446 million affected persons globally at any point in time¹¹.

Actual numbers may be higher for India, evident from a study conducted on GNE myopathy, an autosomal recessive muscle disease. About 150 cases of this disease have been reported in India so far. On the contrary, based on the frequency of pathogenic founder mutation (V727M), about 40,000 cases of GNE myopathy could be estimated¹². Therefore, it is clear that this disease is highly under-reported in the country. This scenario could be plausible for other RDs as well.

Diagnosis of rare diseases

Diagnosis of RDs requires a dedicated team of trained clinicians, clinical geneticists and specialized diagnostic and imaging facilities. India, however, faces some challenges on this front.

For instance, it might take years to get a correct diagnosis of a RD. According to the Organization for Rare Diseases in India (ORDI), the average diagnosis period of a genetic disorder is around seven years owing to the lack of specialized clinics with diagnostic facilities¹³. For example, there are only two main diagnostic centres for myopathies in India, namely the National Institute of Mental Health and Neurosciences, Bengaluru and Bombay Hospital, Mumbai. Moreover, a specialized diagnosis could be expensive¹⁴.

Concerning the number of clinical geneticists, estimates suggest that there may be roughly about 100 of them in 30 centres nationwide, and only about half-a-dozen training programmes running in India⁶. Therefore, running specialized clinics and programmes to train specialists could significantly reduce the delay in diagnosis. These centres could also run clinical trials for new therapies and carry out advanced studies on RDs.

Few public and private sector initiatives are in place. For instance, GoI has inaugurated a chain of clinical diagnostic and testing centres, namely the National Inherited Diseases Administration Kendras. They are established at Delhi's Lady Hardinge Medical College and Army Hospital Research and Referral, Telangana's

Nizam's Institute of Medical Sciences-Hyderabad, Jodhpur's All India Institute of Medical Sciences and Kolkata's Nil Ratan Sircar Medical College and Hospital¹⁵. Similarly, the private sector has set up DNA sequencing service companies in metropolitan cities. However, the accessibility of such facilities in remote areas or for poor patients still needs to be evaluated.

Treatment of rare diseases

As previously mentioned, a large number of RDs are life-threatening and treatments have to be taken lifelong. This may not help patients to lead a healthy life for a reasonably long period. For example, in the case of Duchene muscular dystrophy, the average lifespan of patients is 18–26 years due to degeneration and weakness of the muscles, affecting the heart and lungs and leading to death⁵. Similarly, patients suffering from Gaucher disease need regular infusion of medicines throughout their lives. In such cases, continuous visits to hospitals and clinics could also be time-consuming and exhausting for them.

Moreover, the available treatments are expensive, largely because the drugs or medicines used in such treatments are not locally produced in the country. Therefore, they are out of financial reach for many Indian patients. Estimates suggest that the treatment cost of most genetic disorders may vary between INR 18 lakhs and INR 1.7 crores a year^{4,5}. Specifically, the annual cost of enzyme replacement therapy for six lysosomal storage disorders, for example, could range somewhere between INR 39 lakhs and INR 1.33 crores⁵. Similarly, 'Spinraza' (Nusinersen), which is used to treat SMA has to be imported as it is not produced locally. As a result, the treatment cost is estimated somewhere around INR 5 crores annually⁶. Besides, the absence of health insurance facilities to cover such costs aggravates the financial burden of such patients and their families in the country.

Economic and social burden of rare diseases

The socio-economic burden could be examined in terms of direct and indirect costs. The former includes excessive financial burden on the patients and their families due to the high cost of diagnosis, treatments, therapies, drugs and hospitalizations, whenever required. On the other hand, lack of access to timely and corrective treatments for patients besides regular hospital visits could lead to further disabilities in completing one's education, finding employment and accessing physical space in the society. Moreover, problems in social acceptance might lead to despondency, physical and psychological stress, emotional distress and disillusionment among the patients⁶.

A study (note 2) has reported the instances of absenteeism from school and work by patients suffering from haemophilia. Without access to treatment, physical activity gets limited as a result of extreme pain and

discomfort¹⁶. The percentage of school dropouts or inability to attend schools, on account of bleeding in haemophilia-affected patients, was almost 36.5 (ref. 17). This is high compared to the average annual dropout rate which ranges between 4% and 18% at various levels of school education¹⁸. Similarly, another study has estimated the annual number of school days lost due to haemorrhagic episodes as 19.2 (ref. 19). Ultimately, the consequence of illness and poor education could be witnessed in the high proportion of unemployed patients aged over 18 years, which was 51% (ref. 17).

The indirect costs in terms of high mortality and morbidity rates among RD patients have also been reported in some studies. Global studies have indicated the instances of mortality and morbidity in such patients²⁰. For India, while infant mortality rates have gone down to 30 per 1000, genetic diseases have caused high levels of morbidity and mortality due to the lack of therapies for majority of these diseases^{2,6}. However, in the absence of adequate data that can predict the prevalence of RDs, and associated morbidity and mortality levels of the patients, the socio-economic burden of most of these diseases cannot be correctly estimated.

Initiatives in India vis-à-vis rest of the world: an update

Global picture

Internationally, several countries have implemented domestic Acts and Laws on RDs. For example, Taiwan has implemented RD Control and Orphan Drugs Act since 2000 under the umbrella of which a special counseling window on RDs has been established besides centres of drug distribution, food supply, nutrients, etc. Similarly, the RDs Act (2016) of the Philippines focuses on the diagnosis, clinical and genetic counselling, drug research development, data registry and new-born screening. USA's RD Act (2002) is a public law that allows the establishment of an Office of RDs at its National Institute of Health. Brazil has also joined the league of such countries after approving its RDs policy in 2018, which allows access to treatment of such diseases as a part of its national unified health system^{1,10,21,22}.

Various countries have also introduced legislation governing the production of local drugs for the treatment of RDs. For example, China's New Drug Approval Regulation (1999), Drug Registration Regulation (2007) and Special Review and Approval Procedures for Drug Registration (2009) underline criteria for registration and approval of 'orphan drugs'. Japan has introduced its revised 'orphan drug' regulations in 1993 by amending the Pharmaceutical Affairs Act and Drug Fund for Adverse Reaction Relief and Research Promotion. Countries like Singapore and South Korea have specific guidelines on the production of such medicines governed by Medicines

Act (1991) and Orphan Drug Guidelines (2003), respectively^{1,10,21,22}.

The India scenario

Unlike such economies, India does not have a comprehensive policy or separate legislation on RDs. Efforts towards addressing this issue gathered momentum in 2014 and subsequently in 2017, a policy document titled 'National policy on treatment of rare diseases' was introduced by GoI. The document delineated measures to deal with the treatment of RDs in the country. It also underlined the need to create a dedicated corpus fund at the Centre and States with initial funding of INR 100 crores towards treatment⁵.

While some noteworthy suggestions could be read in the policy document, there was no mention of measures to improve the diagnosis of patients suffering from RDs, especially those belonging to marginalized sections or finding a suitable cure in the country. There was also no indication of research efforts for finding cures for RDs in the country.

In 2018, GoI decided to review the 2017 policy and a 10-member Committee was constituted to review the same, define RDs in India and draft a new national policy (note 3) on RDs (ref. 23).

Incidentally, the Committee did not comprise of representatives from the academic community or patient groups. The existing literature suggests that engagement of patients and patient groups in policy-making processes enables equitable access and inclusive participation in the country. Highly organized patient groups on some RDs elsewhere in the world have been effective as lobbyists in policy formulation, research, generating resources and keeping track of new technologies for treatments²⁴. In Argentina, Canada and Taiwan, for example, patients' advocacy has helped implement legislative changes²⁵. In USA, parent project muscular dystrophy has demonstrated that the best interests of patients could be ensured through organized efforts of their families²⁶. The Indian Organization for RDs and ORDI are some of the known RD patient organizations, among others²⁷.

Therefore, the lack of holistic involvement of all stakeholders in the formulation of a comprehensive national policy on RDs in India, though in the right direction, may not be a fair and balanced approach.

Karnataka was among the first States to commit some funding towards the treatment of RDs; most of which had to be disbursed through different legal proceedings⁶. Moreover, the funding allocated for treatments, in the new draft policy, is a small fraction of the total money which is required on the ground. Also, there is no mention of a separate fund allocation towards research, development and local production of drugs⁴. Therefore, the lack of adequate budgetary support could be a hindrance in the implementation of the new policy.

In February 2019, GoI introduced a Financial Assistance Scheme for RD-affected poor patients under the umbrella of Rashtriya Arogya Nidhi²⁸. However, there is no clarity on its implementation, fund allocation and disbursement.

Research, innovation, funding, data generation and awareness: India vis-à-vis the world

The R&D on RDs has not been given the attention that it deserves in India. Traditionally, it has been neglected in favour of more common diseases, causing fragmented research and knowledge scarcity on RDs. Lack of research has hindered the development of evidence-based clinical guidelines to inform best practices²⁹. This is largely due to inadequate government funding in this field³⁰.

In several economies, government funds RD-driven research initiatives. Japan, for instance, conducts programmes to promote local research on RDs under the Specified Disease Treatment Research Programme, supported by its Ministry of Health, Labour and Welfare. The country also offers tax credits to institutions, to the tune of almost 15% of research costs. South Korea's Research Centre for RDs was established with the help of its Ministry of Family Affairs, Health and Welfare to oversee RD-centric collaborative research projects and clinical research networks. Such countries also offer strategic funding in the form of financial subsidies and grants to universities and research institutions for undertaking clinical and non-clinical R&D activities^{1,10,21,22}.

Similarly, in the context of local production of drugs, there is a need for schemes providing financial, economic and regulatory incentives to promote domestic innovation and discovery of therapies. These could include: (i) marketing exclusivity for the drug, whereby drug sponsors are granted a period of market exclusivity during which no other drug will be approved to treat the disease in question and (ii) simplification of procedure and preference in drug authorization, fast-track approval, fee waivers and protocol assistance³¹.

Globally, countries offer various incentives to their domestic manufacturers. For example, in Japan, exclusive marketing rights for 10 years, up to 14% reduction in corporate tax priority review, fast-track approval, free protocol assistance and user-fee waivers are offered to companies producing local drugs for treating RDs¹⁰. Taiwan, South Korea, Brazil and the Philippines have also enacted specific legislation to ensure the domestic discovery of drugs^{1,21,22}.

Evidence confirms that such incentives have encouraged innovations and drug discoveries resulting in an increased number of licensed drugs³². Therefore, with specific incentives and provision of suitable export opportunities, GoI can also pave the way for pharmaceutical companies to invest in R&D to manufacture these drugs at a much lower cost, without compromising on quality.

Accessibility and outreach could also be ensured through various insurance covers, reimbursement schemes and infrastructure facilities for RD-affected patients, especially those from remote areas or marginalized sections.

For instance, in Asian economies like Taiwan, Orphan Drug Distribution and Special Nutritional Supplement Supply Centres facilitate the distribution of drugs and reimbursements of up to 70–100% of costs incurred by RD patients on treatments, depending upon the income levels of households²¹. The country also has several genetic counselling centres besides neonatal screening programmes to enable proper care and basic diagnosis²⁵. Similarly, Japan's National Health Insurance negotiates prices with the local pharmaceutical companies, offering reimbursement facilities for almost 56 RDs, with the expenses of patients covered through insurance and its government²². Such initiatives reduce the financial burden on patients and enable their participation in national development.

Several countries have also encouraged the generation of funding through industry's Corporate Social Responsibility spending and philanthropy contributions. France's Genethon is an example of one such initiative. Genethon was set up for the design and development of gene therapy treatments, mainly funded through charity funds raised at events of the Muscular Dystrophy Association³³. In countries like the Philippines, Singapore, Malaysia and Thailand, industry funding is quite common besides public charity initiatives³⁴.

Besides establishing sustainable funding mechanisms, India also needs to update epidemiological data. A functioning national registry is the first step in this direction as it can provide readily available information on patients and RDs as well as accurately estimate their prevalence across the country. To enable such record-keeping, standardized algorithms for diagnosis, accurate reporting of RDs and extensive awareness campaigns are needed. Advanced economies like USA, UK, Germany, Denmark and emerging economies like Taiwan, Singapore, and South Korea already have a structured national registry in place¹⁰.

In 2017, the Indian Council of Medical Research (ICMR) announced the launch of a national registry during the National Initiative for Rare Diseases. The registry aims to cover a set of rare and ultra-rare disorders prevailing in the country³⁵. However, the process of nationwide data collection is yet to be initiated.

Moreover, a greater number of efforts towards the sequencing of populations and ethnic groups across India is essential. Such data would be useful in generating estimates of pathogenic allele frequency in the population and examining the overall burden of RDs in India. Some existing initiatives include the launch of GenomeIndia by the Indian Institute of Science, Bengaluru³⁶ and Whole Genome Sequencing of the Council of Scientific and Industrial Research under the IndiGen initiative³⁷.

Finally, public awareness and information dissemination on RDs, patients, patient groups and experts are pertinent in the policy formulation process. Various countries have actively popularized online awareness platforms. For example, in South Korea, the RD Information Database and Korean Organization provides information on RD patients, researchers, pharmaceutical companies, etc. Similarly, Taiwan's Foundation for Rare Disorders provides general information and support to RD patients concerning medication, education, employment and long-term care. Malaysia's RD Society and other patient groups host awareness campaigns through social media and other offline channels^{1,21,34}.

In India, public forums and workshops have also been conducted to reinforce the need for creating a sustainable policy ecosystem surrounding the treatment for RDs. Over the last couple of years, nearly 12–15 discussion meetings have been conducted in different parts of the country to examine various issues concerning RDs. Many experts have reiterated constantly the need for a structured regulatory framework in place. In the absence of this, RDs continue to pose significant challenges to patients, public health systems and perhaps hinder the economic growth and development.

Way forward: policy suggestions

The policy uncertainty concerning RDs that is looming in India calls for a proactive and collaborative approach on the part of all stakeholders from government, academia, healthcare service providers, industry, patients and patient groups.

The national health policy should be focused on the long-term objective of finding a cure for RDs, one which is accessible to every patient in India and from any part of the country. In other words, 'cure for all' should be the cornerstone of the policy or legislative framework governing such diseases.

The policy should also enlist concrete measures to ensure an effective RECIPE for the cure and timely diagnosis of patients, clinical management, supportive therapies, care giving and suitable healthcare insurance support. It should encourage:

- Advanced research (R) and knowledge exchange (E) in this field.
- Capacity (C) building and skills development.
- Innovation and economic incentives (I) for discovery and domestic production of drugs in the country.
- Public (P) awareness and information dissemination.
- Engagement (E) of patients and patient groups in mainstream economic activity and policy formulation processes.

Any suitable policy formulation must ensure active engagement and cooperation of all stakeholders. In this respect, some specific suggestions are listed below.

(1) The RD patients in India could be given a separate status of 'medical disability' with special benefits. GoI could consider the inclusion of RDs (due to the progressive nature of such diseases) and associated medical disability of patients in the Rights of Persons with Disabilities Act, 2016.

(2) Setting up of a nodal point of contact on RDs within the Central Ministry. For example, GoI has set up a Central Tuberculosis Division. Perhaps, a central RDs Division could also be considered, along similar lines.

(3) Formulation of a concrete plan with sufficient budgetary support to set up diagnostic centres, possibly in every district of India. The regulators could perhaps examine the model being undertaken by private pathology laboratories. These laboratories offer services even in remote areas by setting up sample collection centres that seamlessly integrate with their main facilities. Alternately, public-private partnership (PPP) initiatives could also be explored to increase their outreach, especially in remote locations¹².

(4) Efforts should be undertaken to maintain a national registry which is active and constantly updated, besides sequencing data of populations. Considering the diverse population and low frequency of pathogenic alleles, such activities could be undertaken in a PPP model with long-term funding commitment. This could improve the efficiency of data collection and enable meaningful analysis from the gathered datasets.

(5) Fostering advanced research and capacity building through specialized Centres of Excellence or Research Centres. The Centres could focus on translational genetic research, studies on human genetics, drug discovery, innovative therapies and treatments. They could also promote interdisciplinary studies. For example, examining the socio-economic impact of these diseases. Existing studies have analysed the economic evaluation of RDs in the global context^{38,39}. However, there is hardly any study that specifically examines the impact on India. In this regard, such a Centre could become the focal point for cross-disciplinary research. GoI could also consider disbursement of focused grants and subsidies for facilitating clinical research on RDs.

(6) Targeted studies through population surveys and access to inexpensive screening tools can be specifically helpful in identifying the burden of RDs in India, especially in remote areas. For example, a simple blood coagulation test for sickle cell anaemia has helped in the diagnosis of a large number of patients⁴⁰.

(7) Promoting university-industry collaboration to advance research and elevate the relevance of the issue in mainstream nation-building processes. Such an engagement contributes positively to address innovation market failures and helps realize the full social returns of R&D investments⁴¹. Formation of Research Alliance Networks and Knowledge Exchange Consortia on RDs in association with international institutions such as International

Rare Diseases Research Consortium. India's higher education universities could facilitate some of the initiatives listed above. Suitable funding avenues for running such networks or centres could be explored through GoI or with the help of international multilateral agencies such as World Bank, Asian Development Bank, etc. and public philanthropy efforts.

(8) GoI could also consider setting up research resource centres on RDs in partnership with international organizations to promote the exchange of patented research works needed for the development of therapies. These centres could serve as molecular libraries and also act as preserves for genes, disease models, vectors and compounds. They can be accessed by researchers and scientists working on drug discoveries and advanced research.

(9) Provision of economic incentives to local industry for production and manufacture of cost-effective drugs and therapies. National legislation is the need of the hour to encourage innovation and domestic production. At present, the Indian pharma industry finds it non-profitable to invest in such drugs since the market share is small. It may also be worthwhile for India to invest or procure futuristic technology platforms, such as patent-protected gene therapy and stem cells, to develop 'one-shot cure' drugs.

(10) Enabling an investment-friendly environment to encourage local manufacturing of nutritional diets for patients. For example, patients suffering from Inborn Errors of Metabolism are instructed to consume prescribed diets with specific nutrient supplements. They generally spend on an average between INR 40,000–400,000 a year on these supplements. This is primarily because of the scarcity of such local products with a handful of producers enjoying a monopoly in the domestic market. Therefore, economic incentives backed up with investor-centric policies could drive investments in the economy and competition in the domestic market, lowering the market prices of such products.

(11) Ensuring adequate public awareness of RDs through funded digital platforms. While public forums are conducted regularly, e-learning should also be promoted extensively in this field. India is taking some online awareness measures through organizations like ICMR and ORDI in disseminating information. More important is to have in place a digital platform that serves as the national e-focal point in India for RDs. Such an initiative could enable prompt interactions and patient-to-healthcare provider connects, thereby mitigating the delays in finding the right service providers for diagnosis and treatment.

The suggestions listed above could be useful insights in formulating necessary policies and legislation governing RDs in India.

Conclusion

The field of RDs is complex, heterogeneous, constantly evolving and requires scientific knowledge. Considering

their genetic or congenital origin, such diseases have a serious impact on patients, caregivers, physicians, health-care providers, and society. They also constitute a significant economic burden, independent of a country's size and demographics, arising from increased healthcare spending and paramedical support.

In India, this field has not been given the priority that it deserves, unlike some other economies. Many developing countries besides those of the West, have been actively pursuing national policies and programmes to encourage knowledge-sharing, R&D, interdisciplinary studies, drug discoveries and innovative therapies.

Therefore, the need of the hour is to have in place a comprehensive national policy framework, strategies and legislation directed towards finding a cure for RDs as well as addressing the needs of the patients, irrespective of their geographical location or income status in India.

This could perhaps be ensured by devising measures to implement RECIPE, i.e. advancing interdisciplinary research and knowledge exchange through research centres and consortia, especially in higher-education institutions; enabling capacity building of geneticists and clinicians for timely diagnosis especially in remote areas; provision of incentives for innovation of cost-effective treatments, therapies and domestic production of drugs backed up with health insurance schemes and finally, enabling public awareness and engagements of patients and patient groups for effective policy formulation.

To conclude, concerted efforts are required on the part of all stakeholders from the government, academia, industry, civil society and patient groups to work collaboratively towards achieving the common goal of 'cure for all' from RDs in India.

Notes

1. Generally, biological and non-biological drugs for treating RDs are expensive.
2. This is a reported impact of one RD. The lack of India centric studies for other RDs limits the evidence. The percentage of school dropouts and unemployment rates are likely to be high among patients suffering from RDs. Focused studies should be conducted to examine such data and their impact in the Indian context.
3. In January 2020, GoI has proposed a new draft policy on RDs that is undergoing discussions currently. The policy is yet to be finalized.

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