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Rare Disease Policies in Asia-Pacific

GLOBAL BENCHMARKING AND FUTURE DIRECTIONS

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Table 1.Summary of rare disease policies, regulations, laws and initiatives in countries across globe

Country	Orphan drug legislation	National plan/ strategy for RD orRD act	Neonatal screening	Market Exclusivity	Financial incentive	Non- financial incentive	Reimbursement	Public advocacy groups	Highlights
us [154, 292]	Orphan drug act (1983)	Rare disease act (2002)	Yes	7 years	50% tax credits, FDA fee waivers, grants	Scientific advice, protocol assistance, pre-licensing access	95% covered underMedicare -prior authorization needed after a co-payment of USD $4350	NORD, Genetic alliance	Center of excellence: CNRDI; Registry: RaDaR program; **NIH** funded research programs
Canada [154, 273, 292]	No	Proposed National Strategy launched with Rare Alliance Canada	Yes	No	Tax incentive, marketing authorization fee reduction	Protocol assistance, regulatory assistance	Covered under Public Service Health Care Plan, increased from 80% to 100% after patient copayment reaches threshold of Can$3000	CORD, Rare Alliance Canada	Health Canada special access program; Centers of Expertise; Canadian Institutes for Health; Formal inclusion of RD in CIHR is proposed
UK [153, 154, 293]	Yes (as in EU)	UK strategy for rare diseases. Plan adopted for all 4 UK countries; ongoing implementa--tion	Yes(asin EU)	10 years	No	Ongoing debate on pre-licensing access	Given for approved ODs given they meet ICER criterion of £20,000-30,000 per QALY (it can be higher than ODs)	Rare disease UK and specialized healthcare alliance	UK IOK project on RD genetics to build RD registry; specialist centers
EU [154]	1:2000	Regulation (EC) No. 141/2000 (1999)		10 years	Different in participating countries; Centralized drug approval				
France [154,293, 294,295, 296]	As in EU	First **NP** (2005-08), Second **NP** (2011-14), Third NP (2018-22)	Yes	10 years	Tax exemptions	Scientific advice, protocol assistance, pre-licensing access	65-100% reimbursement for ODs. Additional, co-payments are covered by health insurance	Alliance Maladies Rares, French Foundation for Rare Diseases	Early access program; Hospital clinical research programmes;131 reference centers and 501 centers of competence; Launch of Maladies Rares national database

Germany [154,293, 294,297]	As in EU	NAMSE	Yes	10 years	No	Pre-licensing access	Fully reimbursed based on benefit analyses by IQWiG. Fixed co-payment of €10/drug, annual threshold cut-off at 2% of individual annual income	ACHSE	RD expert centers; Genetic diagnosis act, proposal for disease specific registries of RDs; cross-border healthcare
Greece [154,293, 294,298]	As in EU	National plan for RDs (2008-12) proposed; not implemented yet	Yes	10 years	No	Pre-licensing access (granted compassio--nate use)	Listed ODs reimbursed via public insurance system, fixed co-payment of 50% of the reference drug price	PESPA	No official RD expert centers but specialized services are provided for some conditions; proposed creation of national registry
Italy [154,293, 294,299]	As in EU	National plan for RDs under Ministerial Decree n. 279/2001 (2013-16)	Yes	10 years	Specific cost exemption	Off-label, compassio--nate procedure (Law 648/96)	Reimburseme--nt for licensed drug under different categories, special service support	UNIAMO FIMR	Volpi amendment for neonatal screening will include more conditions; National register for RDs; no renewal of NRDP; dedicated funding for research regional service networks
Portugal [154,293, 300]	As in EU	National strategy (2008-15)	Yes	10 years	No	Early access programs, specializat--ion authori--zation of use	Drugs reimbursed through National programmes for RDs; National Health Services	The Portuguese National Alliance	6 centres of expertise; personal card for RD patients for better care and continuity of treatment
Spain [154,293, 301]	As in EU	National plan (2010)	Yes	10 years	Reduced rebates (4% instead of 5% and 7.5%)	Pre-licensing access (compassio--nate use and temporary authorizat--ion of use)	100% reimbursement for approved drugs. Covered in National Health System coverage	FEDER	SpainRDR (registry); Spain UDP; Royal Decree 1015/ 2009 improved procedure for faster access to drugs for compassionate use or temporary authorization

Bulgaria [154,293, 302]	As in EU	National plan for RDs (2009-13); second plan to be officialized by 2014	Yes	10 years	No	Pre-licensing access	ODs are reimbursed by NHIF	NAPRD	National registries for 10 conditions are active; no integrated national registry so far; no expert centres for RDs
Czech Republic [154,293, 303]	As in EU	Czech National Strategy (2010-20); National plan (NAP) for RDs: NAPI- 2012 -14 via Decree 633 and NAP2- 2015-17	Yes	10 years	No administrat- -ive fees for application	Compassion- -ate use, individual patient reimburse- -ment scheme	In-patient case drugs are fully reimbursed, variable for out-patients based on negotiation between market authorization holders and payers (insurance funds) along with healthcare professional	CAVO	In process of establishing national registry; The Act on social services for people with disabilities (2007)
Lithuania [154,293, 304]	As in EU	National plan for RDs (Order No V-938) (2012)	Yes	10 years	No	Patient basis	Reimbursed from the Compulsory Health Insurance Fund budget	No alliance for RDs; Council of representa- -tives of Lithuanian patient organizations	No official centres of expertise and national registry; implementation of E-Health project (2013-15); Lithuanian R&D priorities (2007 -10) and several other academic research projecton genetic diseases
Slovenia [154,293, 305,306]	As in EU	Nation plan for RDs	Yes (limited)	10 years	Reduced fees for marketing authorization	No	Reimbursed by compulsory health insura- -nee and partly by complemen- -tary health insurance	Slovenian rare disease association	Planning for national registry for RDs
Slovakia [154,293, 307]	As in EU	National strategy for RD (2012)	Yes	10 years	No	Pre-licensing access, individual basis	Authorized ODs are reimbursed with a co-payment ranging between 1.51% to 20.61%of the total drug price	Slovak rare disease alliance	No national registry or centres of expertise

Cyprus [154,293, 308]	As in EU	CNSPRD (2012)	Yes (limited)	10 years	No	Several ODs available on patient name basis	No	CARD	No national registry or centres of expertise; no dedicated research funds for RDs
Latvia [154,293, 309]	As in EU	National plan (2013)	Yes (limited)	10 years	Fee exemption or reduction	Scientific advice and free protocol assistance	Some ODs covered under "Medical treatment of RDs for children", reimbursement for drugs in positive reimbursement list, 2% reimbursement budget for every patient	Latvian rare disease organization Caldrius	Planning for national plan (2017-20) ongoing; no official centres of expertise and national registry; funding available for RD projects but not specific for RD research
Nether lands [154,293, 310]	As in EU	Nation plan for RDs (2013)	Yes	10 years	Registration fee waiver	No obligation for pharma--coe conomic data in case of no alternative treatment	100% reimbursement for approved ODs. Addition rules for "too expensive" ODs	VSOP	No national registry; planning for centres of expertise; several research programmes (eg. ZonMw with a funding of €13.4m; €22.5m funds for national biobanking infrastructure); tax reductions forR&D
Belgium [154,293, 311]	As in EU	Belgian plan for RDs	Yes	10 years	Tax exemptions	Compassion--ate use programs, Medical Need programs,	Fully reimburs--ed (for some may require specialist prescription from recogniz--ed centre), Special Solidarity Fund for some non-reimbursed drugs	RaDiOrg	Centres of expertise with funding; national registry; RD related research funding
Austria [154,293, 312,313]	As in EU	Austrian national action plan for RDs (NAP.se) (2014-18)	Yes	10 years	Fee waiver for marketing authorization, tax exemptions	No	Physicians are entitled to prescribe drugs in the EKO	Pro Rare Austria (Allianz fur seltene Erkrankungen)	No designated centers of expertise; no national registry; genetic testing facility available with reimburse--ment; no dedicated research funds

Sweden [154,293, 314]	As in EU	Strategy exists but not adopted	Yes	10 years	Fee waiver for clinical trial	Scientific advice, Compassio--nate use, Named patient prescription	Full reimburseme--nt by social insurance for ODs positively recommended by the Dental and Pharmace--utical Benefits Agency	Rare Diseases Sweden (Riksforbundet Sallsynta diagnoser)	Centres of exper--tise; National patient registry exists however not dedicated to RD; Parts of national strategy are implemented; decent prerequi--sites for innova--tion in the field of RD
Malta [154,293, 315]	As in EU	No plan or strategy	Yes (limited)	10 years	No	Scientific advice, free protocol assistance, Compassio--nate use programmes	Full reimbursement for ODs via National Health Scheme which are either on national government formulary list or approved via Exceptional Medicines Treatment policy	National Alliance for RDs Support Malta	Planning for Malta RD national register; limited initiatives; No specific research programmes for RD but several projects under--way with funds from University of Malta and EU
Poland [154,293, 316]	As in EU	National plan for RDs- the roadmap completed but not implemented yet	Yes	10 years	No	No	Reimbursem--ent for approved drugs. For some drugs reimbursement via therapeutic programmes	National forum for the therapy of RDs-ORPHAN	No official centres of expertise; no national registry; some training and education initiatives in place; No specific RD research programmes but 10% funding from Polish Ministry allocated for RD research
Hungary [154,293, 317]	As in EU	National plan for RDs-approved	Yes	10 years	No	Off-label use possible but difficult	Reimburseme--nt at different levels under special equity procedure as per law	HUFERDIS	Specific budget for RD national plan; no officially approved centres for expertise but 8 informally recognized centres; initiationof RDs register by NRDC; training and education initiatives; research funds available

Croatia [154,293, 318,319]	As in EU	National programme for RDs (2015-20)	Yes (limited)	10 years	No	Compassio--nate use possible	Available ODs are fully reimbursed by the Croatian health insurance fund ("expensive drug fund")	Croatian Society of Patients with Rare Diseases	3 Referral Centres for RDs; no national registry; 40 projects on genetic diseases funded by Ministry
Estonia [154,293, 320]	As in EU	ERTA or Estonian National Health Plan (2009-20)	Yes	10 years	No	No	100% reimbur--sement for children under 4 years of age; reimbursement from Estonian Health insura--nee funds	ECDP	No national registry; Tartu University Hospital serves asCentres of expertise; special courses for physicians on RDs
Luxem bourg [154,293, 321]	As in EU	National plan (2018-22)	Yes (limited)	10 years	No	Off-label use	Full reimbursement for approved ODs	ALAN absl.	No centres of expertise or national registry
Romania [154,293, 322]	As in EU	PNBR (2013-20)	Yes (limited)	10 years	No	Compassio--nate use and off-label use of ODs	Reimburseme--nt via National Programme for RDs	RONARD	No. of centres exist but no official centres for expertise and registry; training and education provided; no specific RD research funding
Finland [154,293, 323]	As in EU	Finnish National Programmer for RDs (2014-17)	Yes	10 years	No	Free administrat--ive and scientific advice	Basic reimbursement of 35% of purchase price, special reimbursement of 65%-100% available	HARSO	No national registry but 2 legal RD registries: the Finnish register of congenital anomalies and the Finnish register of visual impairment; no specific research funds
Denmark [154, 293, 324]	No official definition; Danish Health and Medicines Authority (500-1000 patients, 1-2/10,000 in the Danish population)	National strategy for RDs (2015-20)	Yes	10 years	No	Free scientific advice, Compassio--nate use of drugs	All ODs dispensed at hospitals are free; on needs-based co-payment when dispensed from pharmacy	RDD	2 centres of expertise; no national registry or specific research funding;2 rare diseases centres to educate healthcare professionals, families and caretakers

Mexico [154,292, 325]	As in EU	Article 224 revision (2012)*	Yes (limited)	**No**	**N/A**	**N/A**	Some reimbursement via Seguro Popular (public health insurance policy)	**N/A**	Few to no national initiativesfor research; academic or private support for research
Argentina [154,292, 325]	As in EU	National legislation- Law No. 26.689 (2011)*	Yes	**No**	**N/A**	**N/A**	**N/A**	**N/A**	Few to no national initiatives for research; academic or private support for research; ongoing legislation projectfor creation of specific funds for RDs
Colombia [154, 292, 325]	1/5000 people	Orphan disease law - Law 1392 (2010)	Yes	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	
Brazil [154, 292, 325]	65/100,000 people	National Policy for RDs (2014)	Yes (limited)	**N/A**	**N/A**	**N/A**	ODs included in SUS are fully reimbursed	**N/A**	Few to no national initiativesfor research; academic or private support for research; no national registry; call for reference treatment centre establishment
Chile [154,292, 325]	As in EU	Ricarte Soto Law (2015)*	Yes	N/A	N/A	N/A	N/A	N/A	The law provides funding for RD patients; allotment of 200 bn pesos grant over 4 years
Peru [154, 292, 325]	Not defined	Law 29698 (2011)*	Yes	N/A	N/A	N/A	N/A	N/A	The law promotes national strategy for RDs

Japan [154,217, 292]	1:2500	Orphan Drug Amendment to the Pharmaceut--ical Affairs Law (1993)	Yes	10 years	Waived consultation fee ($20k USD), up to 50%of development costs, 12% tax exemptions, 14% corpora--te tax, ~25% reduction in review fees	Pre-licensing access, scientific advice and free protocol assistance	Fully reimbursed for approved ODs with 30% contribution from insurance companies and 70% from government	-	Specified disease treatment research program (1972); National registry of designated intractable disea s es
Korea [154,217, 235, 2 g2]	1:2500	Rare Disease Management Act 2015	Yes	6 years	May get 50% price reduction for application fee	No	Reimbursed by NHI with a co-payment of 10%, low income families 100%covered	KORD	Research centres and dedicated research funding for RDs; Korean Biobank Project; MoHW announced 4-year roadmap for national system to tackle RD
Taiwan [154,217, 238,292]	1:10,000	Rare Diseases Control and Orphan Drug Act (2000)	Yes	10 + 2 years	Fee reductions; copay can be waived	Regulatory and protocol assistance	RD patients can get 80% reimbursement, low income patients can get 80-100%	TFRD	Universal health coverage of 99.9% citiz ns e
Australia [154,202, 217,292]	1:2000	Australian orphan drugs program (1997)	Yes	5 years	Fee reduction formarket authorization of ODs	Pre-licensing access, regulatory assistance	Fully reimbursed by LSDP programme	AVA	Western Australia Rare Diseases Strategic Framework 2015-18; dedicated WGS progra me m
New Zealand [153, 154, 217,292]	1:2000	N/A	Yes	No	No	NPPA	Reimbursed for drugs on Pharmaceutical Schedule	NZORD	Universal health coverage; limited research fund ng
China [153, 154, 217, 292]	1:50,000	No	Yes	No	Value added tax reduction on ODs from 16% to 3% (80% reduction)	Can be allowed for smaller CTsor waiver ofCTs if required	Often paid by patients as OOP; ODs on NRDL are 100% reimbur--sed and inclusion based on cost-effectiveness and low pricing	CORD and others	CRDPTA launched national research program (2013); no national registry but planning ongoing;proposal for improvement of drug exclusivity; several initiatives in different provinces; inclusion of 121 drugs in rare disease list

Hong Kong [153, 154, 217, 292]	N/A	N/A	Yes	No	No	No	Several subsidized ODs by Hospital Authority	HKARD	Social support provided to RD patients
Singapore [153, 154, 217, 292]	< 20,000	Orphan Drug Exemption to the Medicines Act (1991)	Yes	10 years	**N/A**	**N/A**	Medishield Life covers congen--ital diseases; decision to reimburse made by CDA	ROSS, RAB	Orphan drug legislation not activated yet; RD funds requested with initial corpusof SGD $200mn
Malaysia [153, 154, 217,292]	1:4000	National Framework for Rare Diseases 2019	Yes	No	N/A	EPP	ODs included in national medicine formulary are free with a co-pay of RMS	MRDS	3 Centres of expertise; EPP status to pharma's
Indonesia [153, 154, 217, 292]	1:2000	No	**No**	**No**	No	Off-label drug use, expedited review	OOP	**N/A**	Launch of BPJS Kesehatan (new healthcare policy) to cover all citizens by 2019; Centre of excelle--nee to support RD patients
India [109, 154, 217]	1:5000	National policy for treatment of RDS+ 2021	No	N/A	N/A	Compassion--ate use or named patient programme	Usually self-funded or via NGO's, pharmaceutical companies	I-ORD and others	No dedicated funds for researchand innovation; RD policy recently revoked
Philippin--es [153, 154, 217,292]	1:20,000	General Appropriations Act (GAA) of 2022 or Republic Act 11639	Yes	N/A	N/A	Expedited review of ODs, Comp--assionate use scheme	N/A	PSOD	Social awareness programs; limited research funds
Vietnam [153, 154, 217, 292]	1:500-1:2000	N/A	Yes	N/A	N/A	Compassio--nate use of drugs possible	**N/A**	NHP RD club	No patient registry; limitedto no research funding; GAP program; Vietnam's New Pharmacy Law

Thailand [153, 154, 217, 292]	1:2500	In planning stage	Yes	N/A	N/A	Treatment for Gaucher disease provided	Few ODs centrally supplied and funded by the GPO;OOP	Genetic LSD foundation	No national registries; Centre of excellence exists; ThaiRDN launched project to develop platform for sharing resources for RD community; some research funding

Abbreviation: RDs = Rare diseases; ODs= Orphan drugs; NAMSE = Nationales Aktionsbundnis fur mit Seltenen Erkankungen; IQwiG = Institute for Quality and Efficiency in Healthcare; ACHSE = Alliance of Chronic Rare Diseases; PESPA = Greek Alliance for Rare Diseases; SpainRDR = Spanish Rare Diseases Registries Research Network; SpainIDP= The Spanish Undiagnosed Rare Diseases Program; FEDER= the Spanish Rare Disease Federation; NHIF = National Health Insurance Fund; NAPRD = The National Alliance of People with Rare Diseases; CAVO = The Czech Association for Rare Diseases; CNSPRD = The Cyprus National Strategic Plan for Rare Diseases; CARD= Cyprus Alliance for Rare Disorders; VSOP = Dutch national alliance of patients organization for rare and genetic disorders; ZonMw = The Netherlands Organization for Health Research and Development; RaDiOrg = Rare Diseases Organization Belgium; EKO = Austrian Reimbursement Code; NRDC = National Rare Diseases Centre; HUFERDIS = Hungarian Federation of People with Rare and Congenital Diseases; ERTA = Eesti Rahvastiku Arengukava; ECDP = Estonian Chamber of Disabled People;ALAN = Luxembourg Association for Neuromuscular and Rare Disorders; PNBR = National Plan for Rare Diseases; RONARD = Romanian National Alliance for Rare Diseases; HARSO = HArvinainen (rare) Sairauksien (diseases) Organisaatio (organization); ROD= Rare Diseases Denmark; SUS= Unified Health System; LSDP = Life-saving drug programme; AVA= Rare Voices Australia; WGS =Wide genomic sequencing; CTs = Clinical trials; NRDL = National ; CORD= Chinese Organization for Rare Disorders; OOP = Out of pocket; NPPA = Named Patient Pharmaceutical Assessment; NZORD = New Zealand Organization for Rare Disorders; ROSS= Rare Disorders Society Singapore; RAB= Rainbows Across Borders; CDA = Centre for Drug Administration; MRDS = Malaysian Rare Disorders Society; EPP= Early Point Project; BPJS Kesehatan = Badan Penyelenggara Jaminan Sosial; I-ORD= Indian Organization for Rare Diseases; PSOD = Philippines Society for Orphan Disorders; HKARD = Hog Kong Alliance for Rare Diseases; TFRD = Taiwan Foundation of Rare Diseases; KORD = Korean Organization for Rare Disease; MoHW = Ministry of Health and Welfare; NHP RD club= National Hospitals of Pediatrics; GAP= Global Alliance for Progress; GPO= Government Pharmaceutical Organization; ThaiRDN = Thailand Rare Disease Network; N/A = Not available; No= Does not exist

(*)=currently are either law or legislation but not national plan or strategy

(+)=temporarily withdrawn

1. RARE DISEASE OVERVIEW

1.1. Introduction

A rare disease (RD), alias orphan diseases, are often characterized by their low prevalence with bulk of them being chronically incapacitating and life threatening. Even for rare diseases with treatments available, the disease is typically a lifetime condition for the patient [1]. As of 2018, the current world population stands at~ 7.4 billion and out of this approximately 4-8 % (296- 592 million) of the population is under the grip of rare diseases. At present more than 6000 rare diseases are known to medical community but stay wary that this number is continuously rising at the rate of about 250 new conditions being added every year [2,3]. Around 80% of rare diseases have genetic origin and roughly 20% are either infectious or auto-immune in nature. To date, the underlying cause of rare diseases remains a mystery. These diseases considered uncommon and affect a reasonably low proportion of the population, whichis a major responsible factor for the negligence towards their diagnosis, available treatment options, awareness and support. Due to the lack of big enough market, heavy cost involved in drug development, clinical trials and low revenue generation potential, pharmaceutical industries have been averse to develop and market drugs for rare diseases. This has led to the classification of drugs for rare diseases as "orphan drugs". When in fact, the total number of rare disease suffering population is astronomical, and the effects of these diseases are agonizingly devastating to warrant particular and timely attention. It was for the first time in 1983 that the development of orphan drugs was given attention when the "Orphan Drug Act" by the US Food and Drug Administration (FDA) was implemented [3,4]. This report will share insights into rare disease policies as adopted or implemented in different countries across Asia, current status of rare disease policies in benchmark countries such as US, Europe, Canada and Japan. Furthermore, we will discuss
the current challenges and gaps in the area of rare disease and make recommendations which could aid in improving the current treatments and support offered to rare disease population.

1.2. Global view on rare diseases

1.2.1. Definition of rare diseases in different countries

A rare disease is known to impact a lesser number of individuals when compared with the other known diseases which affects the mass population. It is further characterized by its rarity, low prevalence, severity and existence of limited number of available treatment options. As of today, there is no single universally recognized definition for rare disease and their classification differs across the globe. However, World Health Organization (WHO), defines rare disease as often debilitating, lifelong disorder with a prevalence of 1 or less per 1000 individuals. Table 1 shows the definition of rare disease as defined or adopted by different countries across the world.

Table 2. Definition of RD defined in different countries as per government agency or other accepted bodies

Country	Definition	Total RD population	Remarks (Reference)
US	1:1500 individuals	25-30 million	[1]
Europe	1:2000 individuals	27-36 million	[1]
Canada	1:2000 individuals	~3 million	
Japan	1:2500 individuals	N/A	[1]
Australia	1:2000 individuals	1.2 million	[5]
Taiwan	1:10,000 individuals	> 2000	[6]
Korea	< 20,000 individuals	500,000	[7]
South Korea	1:2500 individuals	500,000	(7]
New Zealand	1:2000 individuals	377,000	No official definition. Currently based on estimatedprevalence [8]
Hong Kong	N/A	110,000 (1.5%)	Not defined as per HKARD [9]
India	1:5000 individuals	> 70 million	(10]
China	< 1:500,000 or a neonatal morbidity of< 1:10,000	16.8 million	No official definition. A consensus reached by experts of the Genetic Branch of the Chinese Medical Association (11]
Malaysia	1:4000 individuals	1.2 million	No official definition (12,13]
Singapore	< 20,000 individuals	2000-3000	(14]
Philippines	1:20,000 individuals	6500	(15]
Indonesia	1:2000	N/A	(16]
Vietnam	1:500 to 1:2000 individuals	Repalce Reported cases of 9000 (may be more) by 6 million	(17]
Thailand	N/A	3.5-5 million	3.5-5 million

(N/A: Not available; HKARD: Hong Kong Alliance for Rare Diseases)

As mentioned earlier, even when rare diseases affect only a small segment of population in any given country, the cumulative population of rare disease affected individuals worldwide is as high as 296-592 million or approximately 4-8% of the total world population. In other words, individuals suffering with rare diseases constitute a population equivalent to that of a country [2,3]. Collectively rare diseases affect roughly 1 in 15 individuals worldwide. In the United States (US), ~12-25 million individuals and in European Union (EU), ~30 million individuals are affected by one or the other rare disease (18]. In Southeast Asia (SEA), ~45 million (~9%) individuals suffer from rare diseases. To reiterate, currently 6000-8000 rare diseases are recognized but this numberis on the rise with ~250 new rare diseases being discovered every year. Eighty percent (80%) of the known rare diseases have genetic origin whereas other 20% are due to infections (bacterial or viral), environmental causes or unknown reasons (19,20].

Within a single geographical location, a single rare disease may only affect a handful of individuals whilst other may affect up to 50,000 individuals. It is noteworthy and troublesome to know that 75% of these diseases affect children, out of which 35% of the children die within the first year of their life and the other 30% of children are likely to die before their fifth birthday unless they can receive an early intervention (14,21].

GLOBAL VIEW ON RARE DISEASES

2. TYPES OF RARE DISEASES

2.1. Classification of rare disease

The following section describes the diseases included under the rare disease umbrella. The list of rare diseases is exhaustingly long with the inclusion of approximately 6000-8000 diseases, as reported in the literature till date. We are enlisting some of the rare diseases which are commonly known.

Table 3.List of rare diseases based on the part of the body affected

Rare Diseases in Hematology	
Anemia-type red blood cell conditions	Sickle cell disease, Beta thalassemia, Diamond-Blackfan anemia
White blood cell dysfunctions associated with various malignancies	Follicular lymphoma, Mantle cell lymphoma, Chronic myeloid leukemia, Hairy cell leukemia, Multiple myeloma
Immune-disorders	Antiphospholipid syndrome, Evans syndrome, Idiopathic neutropenia
Platelet-based abnormalities that affect coagulation	Thrombotic thrombocytopenic purpura, Bernard-Soulier syndrome, Glanzmann's thrombasthenia, Gray platelet syndrome
Plasma-based issues	Hemophilia A and B, von Willebrand disease
Rare Diseases in Cardiology	
Arrhythmias	Wolff-Parkinson White syndrome, Supraventricular tachycardia
Lipidemias	Familial combined hyperlipidemia, Homozygous familial hypercholesterolemia, Lysosomal acid lipase deficiency
Gene-based congenital heart defects	Arrhythmogenic right ventricular dysplasia, Brugada syndrome, familial hypertrophic cardiomyopathy, Long QT syndrome, Hypertrophic obstructive cardiomyopathy, Holt-Grams syndrome, Marfan syndrome, Tetralogy of Fallot
Benign & cancerous tumors	Atrial myxoma
Others	Hutchinson-Gilford progeria syndrome, Duchenne muscular dystrophy, Fabry disease
Rare Diseases in Endocrine	
Gland-based hormonal imbalances	Acromegaly, Gigantism, Prader-Willi syndrome
Weight regulation issues and physical abnormalities	Addison's disease, Cushing's disease
Autoimmune conditions	Graves' disease
Neurological diseases	Fragile X syndrome
Blood diseases	Sickle-cell disease, Beta thalassemia

Numerous carcinogenic and noncarcinogenic endocrine-related tumor disorders	Neuroendocrine cancer, Multiple endocrine neoplasia, Adrenocortical carcinoma, Papillary thyroid carcinoma, Primary thyroid lymphoma
Rare Diseases of Lysosomal storage	
Lysosomal storage disorder	Tay-Sachs disease
Rare Diseases involving Musculoskeletal conditions	
Genetic	Duchenne muscular dystrophy
Neurological	Charcot-Marie-Tooth disease
Motor neuron	Amyotrophic lateral sclerosis (ALS)
Bones	Osteogenesis imperfecta
Rare Diseases s in Nephrology	
Effect urinary system	Membranous nephropathy, Alport syndrome
Inflammatory & autoimmune diseases	Goodpasture syndrome
Others	Henonch-Schi:inlein purpura nephritis
Rare Diseases in Neurology	
Autoimmune conditions	Transverse myelitis, Optic neuritis, Vascular myelopathy, Acute disseminated encephalomyelitis
Musculoskeletal disorders	Amyotrophic lateral sclerosis (ALS), Duchenne muscular dystrophy, spinal muscle atrophy
Developmental conditions	Batten disease, Charcot-Marie-Tooth disease
Other	Fabry disease
Rare Diseases in Oncology	
Breast	Angiosarcoma of the breast
Gastrinomas	Gastrin-producing small intestine cells
Others	Childhood acute myeloid leukemia (from myeloid blood cells), schwannomas (from the sheath cells covering nerves) retinoblastomas (from retinal cells), or thymomas (from thymus gland cells)

Respiratory Rare Diseases	
Lungs	Idiopathic alveolar proteinosis, Wegener's disease
Autoimmune	Anti-glomerular basement membrane disease
Vasculitis	Takayasu's arteritis
Others	Cystic fibrosis (CF), Pulmonary arterial hypertension (PAH), Idiopathic pulmonary fibrosis (IPF) and hereditary angioedema (HAE)
Other Rare Diseases	
Myeloproliferative disorders	Polycythemia vera, Myelofibrosis, Essential thrombocythemia, Mastocytosis, Eosinophilia
Gene mutations	Noonan syndrome, Imerslund-Grasbeck syndrome, Prolidase deficiency, Von Hippel-Lindau disease

(Note: This is not an exhaustive list of rare diseases. For more updated and extensive list refer https://globalgenes.org/rarelist/ .(22]

2.2. Well-known rare diseases

2.2.1. Phenylketonuria (PKU)

PKU is a genetic disorder which is caused due to a defect in the phenylalanine hydroxylase (PAH) gene. PAH gene produces the enzyme responsible for the breakdown of phenylalanine and its mutation causes buildup of phenylalanine within the body [3]. Increased level of phenylalanine is toxic to brain tissues and if left untreated leads to permanent intellectual disability. Children with PKU tend to have unusually light skin and hair, seizures, development delays, behavioral problems and psychiatric disorders (23,24]. Newborns are screened for PKU within 1-2 days of their birth and diagnosed newborn should receive special infant formula. Currently, Kuvan®(sapropterin dihydrochloride) has been approved by US FDA for PKU but is advised to be used in junction with the PKU diet (24].

2.2.2. Duchenne Muscular Dystrophy (DMD)

DMD is a progressive form of muscular dystrophy (MD), a genetic disorder and is characterized by progressive muscle degeneration and weakness. DMD is caused by mutation of DMD gene that codes for protein dystrophin, responsible for keeping the muscle cells intact. It occurs in about 1:3600-6000 male infants (25]. The disease begins as early as 3-4 years of age and affects the hips, pelvic area, upper legs and shoulders. Most children by the age of 13 years need wheelchair for mobility. No known cure for DMD exists however, the symptoms can be controlled. Given the medical advancement, the life expectancy of patients is increasing. Current treatment option includes glucocorticoids such as prednisone and deflazacort, gene therapy, exon skipping, aminoglycosides, ataluren (PTC124), myostatin, utrophin, vitamin D supplement (3,26,27].

2.2.3. Gaucher Disease (GD)

GD is an inherited lysosomal disorder with the mutation in GBA gene that regulates the synthesis of beta-glucocerebrosidase (G-case), an enzyme responsible for the breakdown of glucocerebroside. Accumulation of fatty chemicals leads to GD which affects different parts of the body (28]. The disease is known to affect 1:40,000 individuals. A standard blood test called a beta-glucosidase leukocyte (BGL) test exists to test for GD. Current treatments help to minimize symptoms and permanent damage to patient body. Two different treatments are used: enzyme replacement therapy (ERT) namely Cerezyme (Imiglucerase), Vpriv (Velaglucerase alfa) and Elelyso (Tagliglucerase alfa) and substrate reduction therapy (SRT) namely Zavesca (Miglustat) and Cerdelga (Eliglustat) (3,29].

2.2.4. Multiple Sclerosis (MS)

MS is a degenerative disease of the central nervous system and is often characterized by episodes of neurological impairment. MS is not an inherited disorder, however clinicians suggest that MS could be a result of either autoimmune effect in genetically susceptible individuals or due to environmental factors [3,30]. MS is not considered as rare disorder in European union (EU).
FDA approved treatment for MS includes orphan drugs which includes Dalfampridine (Ampyra), Avonex (Interferon Beta 1A), Betaseron (Interferon Beta 18), Lioresal (Baclofen), Copaxone®[3,31]. Recently, FDA approved Fingolimod (Gilenya) by Novartis for treatment of relapsing MS in children and adolescents [32].

2.2.5. Narcolepsy

Narcolepsy is a neurological disorder and is characterized by excessive unpredictable sleep-wake cycles. Incidence of narcolepsy is reported to occur in approximately 1:2000 individuals. The onset of narcolepsy generally begins in childhood or as late as age of 50 years. The characteristics of narcolepsy are sudden muscle weakness (cataplexy), hallucination or sleep paralysis [3,33].
Currently, no cure exists for narcolepsy however the disease is managed with life style changes and medications which includes FDA approved orphan drugs such as Provigil (Modafinil) and Xyrem®(Oxybate) [34].

2.2.6. Thalassemia

Thalassemia is an inherited blood disorder which reduces production of functional haemoglobin in human body. This leads to a deficiency of red blood cells (RBCs) and reduced levels of oxygen in the bloodstream, which leads to various health problems. Several types of thalassemia exist but mainly there are two types of thalassemia, alpha thalassemia and beta thalassemia namely. Moderate to severe thalassemia treatment include, frequent blood transfusions, stem cell transplant and/or folic acid supplementation [35,36].

2.2.7. Pompe Disease (PD)

PD or glycogen storage disease type II is an inherited lysosomal disease. Mutation of GAA gene causes PD. GAA is responsible for the production of enzyme acid alpha-glucosidase (aka acid maltase) which breaks down glycogen. Accumulation of glycogen causes impairment of muscles, tissues and organs [37]. This disease affects approximately 1:40,000 births in the US. PD is classified into two types: 1) classic form of infantile-onset PD which presents within a few months of birth, and 2) non-classic form of infantile-onset PD usually appears by age of 1 year. Enzyme replacement therapy (ERT) has shown positive effect in disease treatment. FDA approved drugs: Myozyme© (Alglucosidase alfa) and Lumizyme© (Alglucosidase alfa) for the treatment of PD [38].

2.2.8. Hunter Disease/ Mucopolysaccharidosis II (MPS II)

Hunter disease is inherited lysosomal disease whereby the body is unable to breakdown complex mucopolysaccharides (glycosaminoglycans, GAGs) due to the absence of an enzyme iduronate-2-sulfatase (12S). Mutation of 12S gene leads to accumulation of GAGs. The incidence of MPS is estimated to be 1:100,000 individuals. No signs of disease are evident in babies however, with age most of the organs are affected. Currently, no cure for MPS exists, enzyme replacement therapy (ERT) and haematopoietic stem cell transplant (HSCT) are available for the treatment of hunter's disease. Elaprase (Idursulfase) is US FDA approved ERT [39,40].

2.2.9. Osteogenesis Imperfecta (OI)

01 is a group of rare genetic disease which mainly affect the bones. Patients suffering from 01 have fragile bones that break easily with little or no trauma. The disease is caused by a mutation in gene COL1A1 or COL1A2, which is responsible for the production of collagen, material which strengthens the bones. 01 prevalence is estimated to be 1:20,000 in the U [41]. The disease is currently treated using a combination of physical therapy, surgery and medication. Bisphosphonates such as Aredia®(Pamidronate) and Reclast®/Zometa®(Zoledronate) are used to increase bone mass along with vitamin D and calcium supplement [42].

2.2.10. Huntington Disease {HD)

HD is a genetic, progressive, neurodegenerative disease which leads to the regression of neuromuscular and cognitive abilities. HD is caused by mutation in HTT gene which directs the making of protein, huntingtin. Although the precise function of this protein in human body is unknown, it is suggested as essential for neurons in the brain. HD symptoms normally appear between the age of 30-50 years. Its prevalence is estimated at 1:20,000-1:10,000 in the Caucasian population [43]. At present no cure is available for HD. Two orphan drugs are approved by FDA: Xenazine®(Tetrabenazine) and Austedo®(Deutetrabenazine). Several other treatments are under clinical trials: Pridopidine in phase 3 and phase 2 trials are on-going for VX-15, PEDIOA inhibitor, cysteamine and laquinimod [44].

2.2.11. Cystic Fibrosis (CF)

CF is a genetic disorder, caused by mucus secretion which is abnormally thick and sticky, and affects different body organs especially lungs and pancreas. CF is caused by the mutation of cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTR gene causes alteration in CFTR protein, which leads to changes in the characteristics of exocrine excretions [45]. More than 70,000 individuals are affected by CF worldwide. Standard therapy for CF includes: Cayston (Aztreonam), Kalydeco (Ivacaftor), Orkambi (Lumacaftor), Pulmozyme®(Dornase alfa), Symdeko (Tezacaftor and Ivacaftor combination therapy) and Tobi® (Tobramycin for inhalation) [46].

2.2.12. Hemophilia

Hemophilia is a bleeding disorder which is characterized by the reduction of the blood clotting process. People with this disorder experience prolonged bleeding following an injury, surgery, or sometimes with no trauma [47]. The major types of this disorder are hemophilia A and hemophilia B. Hemophilia A is caused by mutation in the F8 gene (xq28) which encodes for coagulation factor VIII, and hemophilia B by the F9 gene (Xq27) which encodes for coagulation factor IX.

Current treatment of the disease is replacement of missing clotting factor. The FDA has approved recombinant factor VIII for hemophilia A treatment. Eg. Helixate®FS, Recombinate®, Kogenate®FS, ReFacto®, Eloctate®, Xyntha®. Human plasma-derived preparations include Monarc-M, Monoclate-P®, Hemofil Mand Koate-DVI [48,49]. Treatment of hemophilia B includes coagulationfactor IX: Alpha Nine, Alprolix, BeneFix®, Mononine, NovoSeven®RT (recombinant). rIX-FP, Rixubis [50].

2.2.13. Epidermolysis Bullosa (EB)

It is a genetic disorder identified by extremely fragile skin and recurrent blister formation, which can occur even minor mechanical friction or trauma. Normally, human skin has two layers: epidermis and dermis namely. The two layers are maintained by anchors which holds them in place. In EB patients, the two skin layers lack the anchors and as such any action leads to friction between the layers resulting in blisters and painful sores. Over the past two decades, 13 genes have been associated with EB which causes defects in the proteins that adhere the epidermis to the dermis. Mutation in the COL7Al gene causes EB. This mutation leads to disruption of protein Type VII collagen, which gives structure and strength to connective tissues [51].

Children suffering with this condition are also known as "Butterfly children or Cotton wool babies" due to fragile skin. The disease is estimated to be 6.5 per million newborn in the USA. The current treatment for EB is primarily preventive and supportive. Potential future treatments include gene therapy, bone marrow transplantation, protein replacement therapies, cell-based therapies [52].

2.2.14. Hereditary Angioedema {HAE)

HAE is a rare genetic disorder, characterized by recurrent episodes of severe swelling attacks. Three main areas are affected due to accumulation of fluids outside the blood vessels which leads to swelling: skin, gastrointestinal tract and upper respiratory airways. There are several types of HAE: Type I and II, are caused due to mutation in the ClNH (SERPINGI) gene which regulates the level of a complex protein, Cl esterase inhibitor responsible for flow of fluids in and out of cells. Type III is characterized by normal Cl levels. HAE affects both genders equally and its symptoms usually arise during childhood. Prevalence of HAE is 1-9 per 100,000 individuals. Several FDA approved treatments for HAE are currently available: Cinryze, Berinert, Kalbitor, Ruconest, Haegards, Firazyr and Takhzyro [23].

2.3. Burden of rare disease

The economic burden of diagnosing and managing rare diseases is significant for patients, communities and healthcare systems. The expedition from diagnosis to treatment or management of these diseases, comes at a steep price for those suffering with a rare disease. This long odyssey, which includes numerous and expensive diagnostic test along with multiple visits to medical practitioner, can become financially overbearing for those affected [53]. According to a survey report presented by Shire, it takes an average of 7.6 years in the US and 5.6 years in the UK, for patients before they receive a proper diagnosis of their condition [54). Due to lack of local experience, many patients have to travel long distances to see someone with the expertise that is needed to treat them. Being unable to diagnose the rare diseases is only one side of the coin, with other being the inadequate coverage of rare diseases under health insurance and other reimbursements options provided by payors. Shire further reported in this survey, that payors indicated lack of sufficient data available to adequately determine the standards of care to be given to rare diseases. The rising costs of drugs and care for rare disease adds to the snowballing effect of the above factors adding to the ever-increasing burden of rare diseases [54).

One of the cofactors affecting rare diseases that has often received least attention in the past from various stakeholders is social and emotional care for rare disease patients. The pressure of cost, misdiagnosis/no diagnosis and inability to lead a normal life owing to social inadequacies, creates a significant emotional impact on both the patients and their caregivers. This emotional toll isfurther confounded in cases where there are no treatments available. Keeping this in mind the theme for Rare Disease Day 2019, is "bridging health and social care". The increased need for mental health services for rare disease patients and their caregivers is the need of the hour since it adds to the overall expense of the disease. In addition to better understanding the physiology of the underlying cause of rare disease, search for better treatment options and cost and care support, rare disease patients deserve social equality when it comes to education, sports, jobs and leading a normal life s any other normal individual of the society [55).

3. OVERVIEW OF ASIAN ECONOMY & LEGISLATION STATUS OF RARE DISEASES

3.1. The Asian economy

Asia is the largest and most populated continent and had the most rapid economic growth in the world for several decades (see Table 3 below). Over the past few years, the Asian economy has been growing steadily at 6-8% per year and is expected to continue this upward trend. Asia's economic expansion has helped reduce poverty throughout the region and increase living standards [56).

Table 4.Representation of economies in Asia

Country	Population (millions) 2018	Population growth (2018)	GDP (PPP) (2018)	GDP real growth (2018)	Per capita GDP (PPP) (2018)
China	1,415	0.35%	$25.31 trillion	6.9%	$17,936
India	1,354	1.11%	$10.68 trillion	7.3%	$7,783
Indonesia	266	1.06%	$3.49 trillion	5.2%	$13,162
Japan	127	-0.23%	$5.62 trillion	1.0%	$44,549
Philippines	106	1.52%	$960 trillion	6.7%	$8,861
Vietnam	96	0.99%	$728 billion	7.1%	$7,882
Thailand	69	0.21%	$1.3 trillion	4.1%	$18,943
Korea	51	0.36%	$2.13 trillion	2.7%	$41,388
Malaysia	32	1.32%	$999 billion	5.4%	$30,185
Taiwan	23	0.29%	$1.2 trillion	2.7%	$52,960
Hong Kong	7	0.8%	$484 billion	3.7%	$64,794
Singapore	6	1.46%	$554 billion	3.6%	$98,014

PPP= purchasing power parity

According to Dr Timothy Low, Head of Medical Affairs Asia Pacific, Shire, Asia presents a lucrative market for orphan drugs due to lack of treatment options available and with very few activities around to help rare disease patients. Looking at Asia, which constitutes of >2 billion population, >16 trillion in GDP and market worth >230 billion, alone has an estimated population of 100 million inflicted with rare disease. There is a high unmet need in this area, which is pushing governments and regulatory authorities in Asian countries to address the issue with urgency. At present, few Asian countries have orphan drug acts or established national policies to tackle rare diseases. But many others Asian counterparts, are just in the nascent stage of planning or adopting some kind of process to help its rare disease population (57].

3.1.1. International Legislation

The first orphan drug legislation was passed by the FDA named "Orphan Drug Act" (ODA) in the year 1983. This law classifies and regulates orphan drugs independent from other drugs and provides numerous benefits for companies that develop and register drugs with the FDA [3]. Since ODA was passed several other countries have approved orphan drug legislation in several other countries and regions, as follows:

Table 5.State of Asian and other countries with orphan drug acts and/or national policy for rare diseases

Country	Acts or Policy	Year
USA	• Orphan Drug Act • Rare Diseases Act	1983 2002
European Union	Regulation 141/2000 in the Official Journal of the European Communities	2000
GermanyFrance	• National Plan for Rare Diseases • French National Plan for Rare Disease - (First: 2005-2008; Second: 2011-2014; Third: 2018-2022)	2013 2004
Singapore	Orphan Drug Exemption to the Medicines Act	1991
Japan	Orphan Drug Amendment to the Pharmaceutical Affairs Law	1993
Australia	Australian Orphan Drugs Program	1997
South Korea	Orphan Drug Act, Rare Disease Management Act 2015	1998
Taiwan	Rare Diseases Control and Orphan Drug Act	2000
Philippines	• Rare Disease Act (Republic Act No. 10747) • Newborn Screening Act	2016 2004
India	National Policy for Treatment of Rare Diseases, Reframed policy was released in 2021	2017
Canada	NA	
Indonesia	NA	
Thailand	NA	
Vietnam	NA	
Malaysia	In process	
New Zealand	NA	
China	NA	
Hong Kong	NA	

NA= Not available (1,58],
Before the establishment of Orphan Drug Act (1983), 38 orphan drugs were approved. From 1983-2016, 347 drugs designated for 425 indications have been approved.

4. STATUS OF RARE DISEASE IN DIFFERENT COUNTRIES IN ASIA

4.1.1. Introduction

With the largest population in the world, China also has the greatest number of patients ailing with rare diseases which is estimatedto be 17 million. Even with such alarming number of patients affected by rare diseases, China falls behind the USA, Canada, Australia, France, Japan and Brazil in rare disease research, diagnosis, treatment, government support, public policies and social support. No national rare disease policy and regulation exists in China so far (59).

The definition of a rare disease is not officially established due to a lag in legislation. Expert consensus indicates that a rare disease could be identified as an incidence of the disease in adults or neonates is less than 500,000 and 1 in 10,000, respectively (60). Out of 7000 known rare diseases, only about 3-5% have treatment options available. Unfortunately, even these treatments are not available to Chinese population owing to lack of green channel for drug application and arduous approval process. Orphan drugs are often imported in China even then many patient families either cannot afford the treatment or have to illegally import the drugs (grey market) or they have to be prescribed off-label by doctors (61)

China has made tremendous progress in serving the needs of population living with rare disease in the past decade, especially in terms of diagnosis and treatment, access to medicines, and affordability of care.

4.1.2. Update on the rare disease activities in China in last decade

Year 2011 and before

- The Drug Registration Management Measures published in 1999 was the first medical regulation that mentioned about rare diseases in China. However, there was no clear definition of rare diseases. The updated Drug Registration Management Measures in 2007 established two favorable measures for rare disease clinical test and approval, but it still failed to give a clear definition of rare diseases, which presents the first barrier in rare disease research, diagnosis and treatment. Since 2006, several institutes and individuals have made proposals to the government every year for the release of a policy on rare diseases.

- On April 14, 2009, the World Federation of Hemophilia (WFH) officially launched the Global Alliance for Progress (GAP) project in China. This international collaboration with Hemophilia House of China was an intense 4-year effort (2009-12) to identify and diagnose more people with bleeding disorders in China, in order to improve access to safe and affordable treatment, and help develop sustained programs for comprehensive care (62).

- The China-Dolls Centre for Rare Disorders started a voluntary rare disease patient registry in May 2010 and to date it has registered approximately 3,000 patients representing 30 rare diseases. One-third of patients in the registry were reported to have osteogenesis imperfecta (OI) (63).

- At provincial level in 2011, Shanghai covered the treatment of 12 identified rare diseases. This program for rare diseases was similar to a standard medical insurance scheme. The Shanghai government gave 100,000 yuan (USD $16,100) for each child suffering from Gaucher's disease, Pompe disease, Fabry disease and mucopolysaccharidosis (MPS). In 2012, this cover was raisedto 200,000 yuan (USD $32,200). However, as per a newspaper it was reported that treatment of rare disease patients costs an average of 2 million yuan annually (USD $322,200). Additionally, a rare disease specialist branch was set up at the Shanghai medical association in 2011 by the Shanghai Rare Disease Society (64].

- In the same year in Qingdao province, the Shandong Academy of Medical Sciences established a rare disease lab to conduct relevant studies. The Shandong government planned to set up a provincial rare disease foundation to help rare disease patients (63,64).

- In October 2011, Tangling city of Anhui province announced rare disease medical insurance methods which gave special care to patients in outpatient services, drugs and hospital transfer (64).

Year2012

- In 2012, Baxter International Inc, announced the approval of ADVATE (Recombinant human coagulation factor VIII for injection) for hemophilia treatment. This therapy offered new treatment options for hemophilia patients in China and advanced hemophilia care in the country as per Professor Yang Renchi, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, the leading professional hematological institution providing basic medical research with clinical services in China.

  In previous efforts in year 2010, Baxter supported the Ministry of Health to set up a "Hemophila Disease Management System", which was China's first nationwide hemophilia patient registration and management system to integrate diagnosis and treatment information. Over the years, Baxter also donated more than 5 million IUs of hemophilia products to Chinese patients and has provided a number of resources to raise awareness of the disease (65).

  Amongst rare diseases in China, Hemophilia has received most medical support policies. Most Eastern and Central Chinese province, have formulated support policies for hemophilia treatment and established provincial diagnosis, treatment and registration centers (59).

- In July 2012, Qingdao city of Shandong province, issued opinions on establishing an urban medical system and dynamically explored policies on social security on major and rare disease drug use. In the same year, Qingdao government approved a proposal that covered the treatment cost of all disease including rare diseases for up to 400,000 yuan (USD$ 58,000) in the national medical insurance (66).

Year 2013

- In Jinan province of China, Rare Disease Day 2013 marked the launch of the China Rare Disease Prevention and Treatment Alliance (CRDPTA). This alliance implemented one ofthe largest pilot project called the Chinese Pilot Project on Rare Diseases Prevention and Treatment (2013BI07B02), with the aim to provide better resources for 20 focal rare diseases (see list below Table 5).
  This project involved an estimated population of 0.7 billion which includes 17 medical institutions from 13 provinces in China. The goals may be summarized as follows:

1. Establishing experienced medical centres with specialization in the 20 focal rare diseases and building their capacity to develop and use guidelines and pathways. This will be achieved by:

   - Developing medical guidelines and clinical pathways and piloting them in approximately 100 provincial or municipal medical centres within the national collaborative network. The revised guidelines will then be submitted to committees of experts fromthe MOH and Chinese Medical Association for review and will be applied in hospitals nationwide.

2. Establishing a patient registry and data repository for 20 example rare diseases through the national rare diseases network
   - Retrospective review of inpatient medical records from the medical centres of the network dating from 2003-12 to identify cases of the 20 example rare diseases.
   - Prospective case registration (2013-16) of new diagnosed patients with 20 rare diseases.
   - A data repository of de-identified patient data will be created, using Common Data Elements (CDEs) and standardized terminology.
   - Additionally, a web-based open-source patient registry system will be released to the public, as a service to the patient organizations and others, to allow and encourage them to establish additional rare disease patient registries.
3. Establishing a molecular genetic testing centre for rare diseases. Initially, nine single gene and seven Next-Generation Sequencing (NGS) based panel analyses covering 15 example rare diseases will be developed to support molecular genetic diagnostic services [67].

Table 6.List of rare diseases focused in the Chinese Pilot Project on Rare Diseases Prevention and Treatment {20138107802)

No.	Diseases	No.	Diseases
1	Arrhythmogenic Right Ventricular Cardiomyopathy	**11**	Myotonic Dystrophy
2	Congenital Myotonia	12	Neurofibromatosis
3	Congenital Pyriform sinus Fistula	13	Osteogenesis Imperfecta
4	Duchenne and Becker Muscular Dystrophy	**14**	Primary Tethered Spinal Cord Syndrome
5	Epidermolysis Bullosa	15	Primary Cardiac Sarcomas
6	Fahr Syndrome	16	Pseudoxanthoma Elasticum
7	Familial Aortic Aneurysm	17	Sturge-Weber Syndrome
8	Hereditary Spastic Paraplegia	**18**	Thoracic Aortic Aneurysm and Dissection
9	Left Ventricular Noncompaction	19	Tuberous Sclerosis Complex
10	Marfan Syndrome	20	Wilson Disease

Source: [9]

- In 2013, China-doll Center for Rare Disorders, a non-profit organization specializing in fields of rare diseases especially osteogenesis imperfecta (01) was founded by Chinese Organization for Rare Disorders (CORD).
- Chinese health-care system underwent overhauling for the first time since 2009 with the expansion of National Reimbursable Drug List (NRDL), though the system is still governed by cheaper and essential medicines. In addition, groundwork to speed up "orphan drug approval" was flagged by government given the huge regulatory backlog and even clinical trial wavers [61].

- On September 14, 2013, Chinese Rare Disease Research Consortium (CRDRC) was launched during the 1st Chinese Rare Disease Symposium and was seen as an important step towards rare disease policy development. Currently, more than 20 universities, colleges and institutes and 50 specialists are members of this consortium. Following are the goals of the CRDRC:

1. Fund of around 30 million yuan (USD $4 million) was pledged for the creation of a national registry for rare diseases in China.
2. Provision to provide access to harmonized data and samples.
3. Supplement identification of 5-30 rare diseases genes/year followed by making genetic testing based on these genes available to rare disease patients.
4. Facilitating development of therapeutic strategies based on identified rare disease genes.
5. Provision to support funds for rare disease research in China by forming an alliance with the China Natural Science Foundation, the Ministry of Science and Technology, and the MOH.
6. Seeking to launch a Rare Disease Research Institute in China to centralize the rare disease research efforts [68].

Year2014

- In contrast to other positive initiatives for rare diseases, in 2014 China's Food and Drug Administration (CDFA) imposed regulatory constraints on the provision of clinical genetic testing. The extent of this ban is unclear but there is a blanket ban on prenatal DNA testing. According to a known newspaper, Beijing Genome Institute (BGI) with its headquarters in Shenzhen, it was estimated that this ban on prenatal testing would result in the birth of some 11,000 babies with congenital disorders, based on a total of 210,000 babies born past year in the city with a national birth defect rate of 5.6%. This means that the number of individuals with rare diseases will increase adding to the already high burden of the disease [69].

- On 7-9th November 2014, China hosted the 2nd International Rare Diseases Consortium (IRDiRC) conference in Shenzhen. The event was organized by IRDiRC in partnership with BGI, and brought together rare disease stakeholders from all over the world to discuss their experiences and expertise. This international conference witnessed the presence of more than 600 participants representing EU, North America, Australia and Asia.

- On December 26, 2014, China's Social Assistance Foundation (CSAF) launched the 'China Child Rare Disease Aid Fund'. This was a special fund for children and young people with rare diseases and was designed to help them cope with their illness and at the same time establish a support system around them. DeExpo donated 5,000,000 yuan (USD $804,531) for the cause [70).

- China's basic-research spending has historically been extremely low- about 4.8% in 2012 and 2013, compared with 10-25% in developed nations. But in 2014, the allotment for basic research was increased by 12.5% to $6.6 billion - of which the National Natural Science Foundation of China (NSFC) was announced to receive USD $3.1 billion, according its president, Yang Wei.
  The major areas that the foundation funds included studies of biodiversity, air pollution, supercomputers, neurodegenerativediseases and scientific equipment [71).

Year 2015

- At the National People's Congress, motions for legislation on rare diseases were raised by deputies. A motion was raised by Liu Gexin of the Sichuan Kelun Pharmaceutical Company, to support medication for rare disease patients while encouraging independent development of related medicines by domestic companies.

Due to lack of incentives by government Pharma companies in China are not keen to develop drugs for rare diseases. In a bid to tackle the situation where Chinese pharma's are not interested in developing orphan drugs, the motion by Liu of Sichuan Kelun Pharmaceutical Company included setting aside special funding to develop original orphan drugs, offer incentives to producers, fast-track approval and establish a medical insurance system specifically for rare diseases [72]. The National Research Foundation Singapore and the National Natural Science Foundation of China (NSFC) signed a five-year Memorandum of Understanding (MoU) in November 2015 to explore collaboration through joint grant calls. Funding support for each project was SGDS00,000, inclusive of overheads and equipment [73]. On February 28, 2015, a Rare Disease Treatment Centre was formally established in Shanghai Children's Medical Center (SCMC). This centre aims to focus on congenital blood disorders, immune deficiencies, inherited metabolic disorders, cardiovascular diseases and other rare diseases to further improve the diagnosis and treatment of rare disease and related health policies. At the meeting, SCMC donated 120,000 yuan (USO$ 17,500) to the Shanghai Rare Disease Prevention Foundation [74].

Year 2016

- In 2016, Zhejiang province medical insurance started to cover Gaucher's disease, amyotrophic lateral sclerosis (ALS), and phenylketonuria (PKU) [75].

- The China Social Welfare Foundation (CSWF) and the China-Dolls Center for Rare Disorders jointly launched a press conference to mark the occasion of the World Rare Disease Day 2016 and the opening ceremony of the Year of Spreading Philanthropy on February 29th. On this occasion CSWF announced a funding of 1 million yuan (USO $144,015) for establishing Working Commissionon Rare Diseases, to support the development of care for rare diseases in China. This body will support CSWF in the field of rare diseases by providing research, giving policy advice and promoting international communication and cooperation [76].

- Shanghai Health and Family Planning Commission released its first local list of rare diseases in China titled "The list of major rare diseases in Shanghai (edition 2016)". This list included 56 rare diseases and 50 of them are a part of the Chinese Rare Disease List (CRDL).

- In 2016, several articles were published, concerning rare disease policies in China. These articles demonstrated increasing concerns over the availability of orphan medicinal products (OMPs) in China [77].

- Asper another article, "orphan drugs approved in the USA, EU and Japan had 37.8%, 24.6% and 52.4% market availability in China, respectively." It is concerning that the available rare disease drugs in China are not reimbursed and most of them are unaffordable for most Chinese patients. This presses for the need of social security and specific payment options for orphan drugs for RD patients [78, 79].
- The Chinese central government has included rare diseases in major health planning and strategy, including five-year plan on public healthcare (2016-2020) [80] and "Healthy China 2030" planning outline [81].

- Another special research program on rare diseases called the "Rare Diseases Clinical Cohort Study" was launched in December 2016 by the Chinese government. According to their research plan, the unified National Rare Diseases Registry System of China (NRDRS) will be established by 2020, and a large-scale cohort study will be conducted from 2016 to 2020. The project plans to develop 109 technical standards, to establish and improve 2 national databases of rare diseases - a multi-centre clinical database and a biological sample library, and to conduct studies on more than 50,000 registered cases of 50 different rare diseases. More so, this study will be combined with the concept of precision medicine. Chinese population-specific basic information on rare diseases, clinical information, and genomic information will be integrated to create a comprehensive predictive model with a follow-up database system and a model to evaluate prognosis. The collected information will be an evidence for accurate classification, diagnosis, treatment, and estimation of prognosis for rare diseases in China [82]. The allocated budget for this project is 40,000,000 RMB.

- Many academic institutions and major hospitals in China have been playing an important role in translational medicine for the treatment of rare diseases, and particularly in the area of cutting-edge technologies. One such example is, the Shanghai Institute of Materia Medica (SIMM) of the Chinese Academy of Sciences which announced the CFDA approval of one of their orphan drug programs targeting pulmonary arterial hypertension (PAH) to conduct human clinical trials [83]. With respect to cutting-edge technologies, Sichuan University's West China Hospital in Chengdu announced their preparation to conduct the world's first human trial using CRISPR gene editing technology [84].

  In addition, a team of scientists from Tongji Medical College, in collaboration with FivePlus Molecular Medicine Institute in Beijing, successfully conducted a long-term trial of gene therapy in human patients with a rare genetic disorder known as Leber's hereditary optic neuropathy (LHON), more than 10 years after the world's first gene therapy was approved in China [85,86].

Year 2017

- In Shanghai, a fund with starting money of 3 million yuan (USD $435,000) was jointly raised by rare disease prevention and treatment institutions and drug industries such as Sanofi. The fund will primarily be used for enhancing medical treatment for lysosomal storage disorders (LSDs) (87].

- China established a committee to formulate medical strategies for rare diseases to improve its national efforts towards the cause. An official definition of rare disease will presumably be discussed and proposed in the near future (88].

- On May 11, 2017, the CFDA published proposed ground-breaking orphan drug policies (circular no. 52) for public comment. The CFDA proposes that drugs and devices that treat designated rare diseases may apply for a clinical trial waiver. Orphan drugs and devices that have already been approved overseas may be granted a conditional approval without any domestic clinical studies. Follow-up studies as directed by the CFDA must be completed in China after approval.

  The Chinese government will work to help make new drugs available to patients by encouraging hospitals to procure new drug products. The government will work to include more innovative drugs in the national health insurance scheme and more frequently update the reimbursable drugs list in order to make the products more affordable for the public (89].

- On May 19, 2017, Chinese officials announced that they are currently compiling a draft list of rare diseases that may be released by the end of the year. Li Dingguo, chairman of the Shanghai Rare Disease Prevention and Treatment Fund, said China's draft list covers more than 100 diseases.

Year 2018

- As per a report published in March 2018, China launched a program which aims to help patients with rare diseases in diagnosis and treatment and offers financial support to those in need. This program will be sponsored by the Illness Challenge and China Social Assistance foundations and will help with the diagnosis and treatment of up to 100 diseases. The programs purpose is to bridge the gaps between individual patients, medical resources and insurance (90]. In March 2018, China launched its first major project which aims at diagnosing rare children's diseases. The country's pediatric experts will use a technique known as whole genome sequencing (WGS) which will help to create a database of rare and undiagnosed conditions, including mental disorders and physical deformities. WGS, or mapping the entire human genome, has garnered attention of Chinese investors in recent years. In 2017, China's gene-sequencing industry raised over 6.8 billion yuan (USD $1.08 billion) (91].

- On May 22, 2018, the Chinese Government officially released its first list of rare diseases entitled Chinese Rare Diseases List (CRDL; see list below in **Appendix Table 2).** This list aims to facilitate the medical practitioners to treat RDs, to introduce incentives for R&D of orphan drugs and to increase the availability and accessibility of medicinal products for RD patients [92].

- As per a report in China Daily on 26 June 2018, a State Council executive meeting, presided over by Premier Li Keqiang, decided to further simplify approval procedures for imported drugs, reduce prices for anti-cancer drugs and strengthen work to secure the supply of desperately-needed medicines. Approval procedures should be completed in three months for rare-disease medicines and six months for those to help combat life-threatening illnesses.

Meanwhile, prices for anti-cancer medicines will be reduced following the zero-tariff policy adopted this year. An alert system for precautions against supply shortages will be further enhanced, and drug reserves will be substantially expanded. The following decision will allow new drugs that are already sold in overseas markets to be used on the Chinese mainland. The meeting was the latest *move* following the zero-tariff policy for anti-cancer drugs and the central government's encouragement of medical innovation (89, 93].

- National Natural Science Fund guide to programs 2018 by National Natural Science Foundation of China (NSFC) details funding for R&D to research institutes in China. NSFC's funding portfolio consists of 4 categories of programs, namely, Exploration, Talent, Instrument and Convergence, with respective preferential focuses, constituting an integrated funding instrument of the National Natural Science Fund (94].

Figure 2. Timeline indicating the progress on rare disease in China between the period of 2011-2018

(RD= Rare disease, GD= Gaucher's disease, PD= Pompe disease, MPS= Mucopolysaccharidosis, ALS = Amyotrophic lateral sclerosis, CRDPTA = China rare disease prevention and treatment alliance, CORD= Chinese organization for rare disorders, CCRD = China-doll centre for rare disorders, CRDRC = Chinese rare disease research consortium, CFDA = China food & drug administration, IRDiRC = International rare diseases consortium, BGI = Beijing genomics institute, CSAF = China's social assistance foundation, NSFC = National Natural Science Foundation of China, NRFS = National Research Foundation Singapore, SCMC = Shanghai children's medical centre, CSWF = China social welfare foundation, LSD= Lysosomal storage disorder, WGS = Whole genome sequencing, CRDL = Chinese rare disease list)

4.1.3. Market access & pricing of orphan drugs in China

Orphan drug accessibility in China involves many challenges, which includes the absence of official legislation for orphan diseases; the lack of impactful incentives for manufacturers such as tax rebate, registration and drug approval to develop orphan drugs;and limited resources to fund high-cost orphan drugs. As opposed to several other countries such as Japan, in China there are no financial incentives or special pricing policies for orphan drugs.

The market authorization approval process in China is generally quite lengthy. After the application is submitted by manufacturers, it can take up to a year to get an approval from the China Food and Drug Administration (CFDA) and the Center for Drug Evaluation (CDE) for clinical trial to start. Even after the trial, it can take another year or more for CFDA/CDE to approve the registration of the drug. In code, a fast track regulatory approval channel exists for certain new drugs, however, in practice, the approval time for orphan drugs takes as long as for a non-orphan drug to be approved (63). In a recent development, China has approved a prioritizeddrug approval process (duration 3-6 months). Additionally, in a welcoming step Prime minister Li Keqiang, announced value-added tax reduction for orphan drugs from 16% to 3%, which is 80% reduction. This change will take effect from March 1, 2019 (64).

Due to limited clinical expertise in orphan diseases and lack of special diagnostic or treatment centers, the rate of misdiagnosis is quite high (48%) in China. Therefore, even when orphan drugs are approved and available on the market in China, they may not reach the right patients and makes it difficult for meaningful real-world evidence to be gathered. High-cost orphan drugs are often excluded from national reimbursement drug lists (NRDLs) and this results in high out-of-pocket payment (OOP) for patients.
According to the Medical Insurance Directory, China currently has 119 orphan drugs that are at various stages of licensing and registrations. Of these, 49 (41%) are covered by national medical insurance. Some ofthem are 100% reimbursed but most of them are partially reimbursed. Three main sources of funding exist for orphan drugs in mainland China: (1) funding through government (national, regional or local level), (2) funding through charity, (3) funding by patient's OOP payment (77).

After CFDA approval it may take several years for orphan drug to be included in NRDL and their inclusion is driven by two key factors namely cost and efficacy. Drugs for orphan diseases that are reimbursed at 100% on the NRDL are often low-cost and generally produced by local manufacturers. Higher costing drugs are either partially reimbursed or not covered at all. Drugs not included in NRDL can be reimbursed in some provinces or cities through inclusion on the provincial/local RDL. Depending on the budget and local needs and ability to pay, some provinces/cities may include some high cost drugs in their RDL (see Table 7 below) (63).

Table 7.Examples of high-cost drugs for orphan diseases that are included on Chinese province/local RDLs, but not the NRDL {63}

Disease name	Drug name	Reimbursement level	Price (yuan)	Manufacturer
Non-Hodgkin's lymphoma	Rituximab	Partial in some provinces	3,980 (IO0mg/10 ml)	Roche
Neonatal respiratory distress syndrome	Poractant Alfa injection	Partial in some provinces	8,084 (3ml;0.24g)	Chiesi Farmaceutici S.p.A
Chronic myelogenous leukemia & gastrointestinal stromal tumors	Imatinib	Partial in some provinces	25,500 (100mgx120)	Novartis
Advanced non-small cell lung cancer	Gefitinib	Partial in Guang Zhou city	5,000 (0.25gx10)	AstraZeneca

Some high-cost orphan drugs that are not reimbursed are provided by manufacturers free of charge to patients through charitable organizations such as China Charity Federation (CCF). For example, high-cost orphan drugs were donated (valued at USD ~32 million) by manufacturers through CCF, included Cerezyme®by Genzyme for Gaucher's diseases in 2009, Gleevec®by Novartis for chronic myeloid leukemia and Exjade®(deferasirox) by Novartis for beta-thalassemia assistant project in 2010. In 2011, the Qingdao Municipal Charity Foundation and Bayer launched a charity fund to support children with hemophilia who required Kogenate®FS (recombinant coagulation factor VIII) [63, 77]. Charity donations by manufacturers can help in raising awareness of the orphan disease and the drug of interest among key stakeholders, which could lead to reimbursement in the future, as is seen in Cerezyme case study:

Over 10 years ago, Genzyme began donating Cerezyme free of charge to patients with severe Gaucher's disease in China, first through the World Health Foundation, and then through the CCF beginning in 2008. As well as donating drugs for free, the manufacturer worked closely with the CCF to increase public awareness of the disease and promote research into policy and insurance coverage for orphan diseases. As a result of these efforts, Cerezyme has recently been reimbursed in the city of Qingdao. Another way for funding is raising funds via charity. This was seen with a success of the ice bucket challenge for amyotrophic lateral sclerosis (ALS), introduced in China in August 2014 [63].

Out-of-pocket (OOP) payments for orphan drugs is significant and almost 80% of patients with rare disease have< 10% of their total treatment costs reimbursed, and only approximately 10% of patients have> 50% of the total treatment cost reimbursed. Approximately more than 70% of families with rare disease are unable to afford their treatment due to high OOP payment.

The city of Qingdao has been leading the way for orphan drug funding in China, with the local government actively providing coverage for orphan diseases. In 2012, the local government issued a policy to cover two orphan diseases together with other major diseases, and provided direct funding for these diseases. In 2014, the coverage was expanded to include six additional orphan diseases, with several high-cost orphan drugs reimbursed (see Table 8). The diseases covered includes hemophilia, tetrahydrobiopterin deficiency (BH4 deficiency), Gaucher's disease and acromegaly. With the funding from the Qingdao local government and charitable donations, the treatment cost to patients with orphan diseases can be as low as 10 to 15% [63].

Table 8. Examples of orphan diseases and high-cost orphan drugs that are covered by the Qingdao government {63}

Disease name	Drug name	Price (yuan)	Manufacturer
Hemophilia	BeneFIX (recombinant human coagulation factor IV)	6800 (lO0OlU)	Pfizer
Tetrahydrobiopterin deficiency (BH4 deficiency)	Kuvan (saprotein dihydrochloride tablets)	**NA**	Merck
Multiple sclerosis	Betaferon, recombinant human interferon beta - lb	13,000 (8001U)	Schering
Primary pulmonary hypertension	Bosentan tablets	31,630 (125mg*56)	Actelion
Acromegaly	Somatuline	4,260 (40mg)	Ipsen
Gaucher's disease	Cerezyme (imiglucerase)	29,741 (400 units/bottle)	Genzyme

Note: A list of orphan drugs available in China and their affordability is presented in Appendix Table 6 [95]

Currently, there are only a handful of local drug companies in China with in-house R&D programs which are dedicated to rare diseases, although this number is anticipated to multiply in future at a fast pace owing to the increased public awareness and improvement in policy framework for rare diseases. Below **Table 9** shows a list of such companies.

Table 9./nternal Orphan drug programs run by Chinese drug companies [96]

Company	Drug name	Indication/Rare disease condition	Stage of development
Chipscreen	Chidamide	PTCL	Launched in China
Shanghai Genomics	Aisi Rui, Etuary	IPF	Launched in China
Hua Medicine	HMEOl	PD-LID, FXS	Preclinical
Beijing Prosit Sole Biotechnology	Multiple products	Chronic norovirus infection, articular cartilage injury, refractory gout, lupus renal failure and uremia	Preclinical

(PTCL = peripheral T-cell lymphoma; IPF = Idiopathic pulmonary fibrosis; PD-LID= Parkinson's disease - L-dopa-induced dyskinesia; FXS = Fragile X syndrome)

4.1.4. Key stakeholders involved in improving rare disease status in China

Different stakeholders which includes policy makers, clinicians, research institutes, patient groups and advocacy groups play a crucial role to bring the policy changes for rare diseases.

Table 10.List of key stakeholders involved in the improvement of status of rare disease in China

Organization	Established/ Founded	Key Stakeholder contact	Purpose/Activity
Chinese Organization for Rare Disorders (CORD) *(www.hanjianbing.org)*	2013	Founder & Director - Kevin Huang	- **NGO** to establish an official platform of RDs, treatment and a database for patient information - Supports RD patient organizations - Raise awareness about RD via public education - Policy advocacy and research - Funded by several pharma companies
China Organization of Albinism (COA) *(http://www.albinism.org.cn/)*	2008 (Founded) 2011 (Govt. recognized)	Founder & Director - Lu Guan	- National, Non-profit organization to support Albino patients and families - Part of Albinism World Alliance (AWA) in 2012

Chinese Rare Disease Research Consortium (CRDRC)	September 14, 2013	Chairman - Qing K Wang Vice-Chairman - Pak Chung Sham	- Establishing national registry for RDs - Provide access to harmonized data and samples - Identifying 5-30 RD genes per year - Facilitate development of therapeutic strategies - - Joint efforts under alliance to support funding for RD research - Seek to launch a Rare disease research institute in China
China Rare Diseases Prevention and Treatment Alliance	February 28, 2013	Deputy Director - Han Jinxiang	- Launched in Jinan, China - Includes 17 medical institutions from 13 provinces in China - Committed to the establishment of RD treatment centers across the country - Assist in data collection of RDs, carry out epidemiological studies and improved treatment - Implementing Chinese Pilot Project (2013BAI07B02)
China-Doll Center for Rare Diseases *(http://www.chinadolls.org.cn/)*	May 2008	President - Yiou Wang	- **NGO** to provide care and help to patients with Osteogenesis Imperfecta and protect their rights - August 2009: established China-Dolls Rare Disorders Care Foundationv - March 2010, established Shandong Jinan China-Dolls Home of Care to provide service for Shandong patients
Beijing Rare Disease Care Center of the Hemophilia Home of China *(http://www.xueyou.org /)*	September 2009	Secretary General - Guan Tao	- **NGO** that provides treatment and financial aid for hemophilia patients
China Food and Drug Administration (CFDA) *(http://eng.sfda.gov.cn/WS03/CL0755/)*	March 2013	Director - Bi Jingquan	- Drafts laws, regulations and policies on the administration of food and different drugs

National Science Foundation of China (NSFC) *(http://www.nsfc.gov.cn/english/site_l/about/6.html)*	February 14, 1986	President - Prof Li Jinghai	- Institution directly under the jurisdiction of the State Council - Tasked with the administration of the National Natural Science Fund from the Central government - Support basic research and stimulate free exploration, identify and foster scientific talents, as well as promotes progress in science and technology and the harmonious socioeconomic development of the nation
China Social Assistance Foundation (CSAF) *(http://www.csaforg.cn)*	July 25, 2013	Chairman - Xu Jialu	- Established in Beijing; national public - fundraising foundation and governed by the Ministry of Civil Affairs of China - Support research, public education and social assistance to people in need - China Child Rare Disease Aid Fund (USD $804,531)
Shanghai Rare Disease Foundation	April 9, 2017	Chair - Dr Li Dingguo	- First foundation to look for new models on diagnosis, treatment and help to patients with LSDs - Establishment of Shanghai Rare Disease Prevention and Treatment Fund
China Social Welfare Foundation (CSWF)	September 2013	Vice-Chairman - Xiao	- Funding of 1 million yuan to set up a working commission on RDs
China Charity Federation (CCF) *(http://www.chinacharityfederation.org/English/NewsContent/121/1280.html)*	1994	Executive Vice-President - Wang Shufeng	- Nationwide non-governmental charity organization - Provides high cost orphan drugs to RD patients free of cost. Eg. Cerezyme
Illness Challenge Foundation *(http://www.chinaicf.org/)*			- Establishing platform and multilateral cooperation, solve urgent problems faced by people with RD together
Beijing Genomics Institute (BGI) *(www.genomics.cn)*	September 9, 1999	Chairman - Yang Huanming President - Wang Jian	- Non-governmental independent research institute - Gene sequencing to identify and support treatment of RDs
Sichuan Kelun Pharmaceutical Co Ltd *(http://en.kelun.com/)*	1996	Chairman - Liu Gexin	- Development of orphan drugs - Supports policy making in China

Baxter International Inc.			- Set up of "Hemophilia disease management system" - Donated 5 million IUs of hemophilia products - Introduction of ADVATE (recombinant FVIII therapies)
Huazhong University of Science and Technology (HUST) *(http://english.hust.edu.cn/)*	1907	Dean of School of Life Science and Technology - Qing KWang	- Involved in research and publication on RDs - Lead formation of CRDRC
Sichuan University's West China Hospital	1914	Team leader - Lu You	- Preparing to conduct the world's first human trial using CRISPR gene editing technology

(RD= Rare disease)

4.1.5. Future action

In order to improve China's efforts towards rare diseases, rare disease legislation requires coordination between the Ministry of Health, the Ministry of Human Resources and Social Security, the Ministry of Finance and the Ministry of Civil Affairs. Moreover, implementation of a rare disease law should be based on medical research and statistics on rare disease patients and prevalence rate. Concerted efforts towards rare disease diagnosis, treatment and scientific research centres; doctors; sufficient drugs; and financial support from the government is highly imperative.

Province like Qingdao has made significant efforts towards rare disease with government's progressive stance toward orphan diseases funding. It is clear that its local government considers funding for major diseases and orphan diseases to be a public health priority. The ability of Qingdao to fund high-cost orphan drugs is also helped by its strong financial resources. For manufacturers with high-cost orphan drugs, the city of Qingdao could represent a gateway to market access in China.

While Chinese drugs companies are reluctant to develop orphan drugs, Western pharmaceutical companies, including Pfizer and Roche, are seeing potential in a burgeoning global market. According to the 2014 market report by EvaluateGroup, sales of orphan drugs - not including generic drugs - is expected to reach US$176 billion in 2020.Orphan drugs will account for 19 percent of sales of prescribed drugs, and see annual growth of 11 percent, compared with just 4 percent for common drugs (72].

The Chinese government should take more responsibility for improving the availability and affordability of orphan drugs by incentivizing policies and public platforms for sharing of orphan drug information. Control of the high price of orphan drugs, combined with a joint funding model from both government and private enterprise can efficiently reduce the economic burden for affected patients in China (95].

4.2 INDIA

4.2.1. Introduction

Rare diseases in India are not yet clearly defined however, it is considered to be a disease that affects a small population or defined as affecting 1 in 5,000 individuals or less. Considering the large population of India which stands at around 1.3 billion, approximately 70 million people are estimated to have one or the other rare disease. This huge number indicates that the disease is now in no way rare and needs attention from various key stakeholders to help rare disease patients. Recently, in June 2017, India for the first time presented a national policy on rare disease which is seen as a significant step towards recognizing rare disease at a national level. However, there is still a long way to go in terms of early diagnosis of the disease, treatment options, and clinical expertise available.

It is known that 75% of all rare disease patients are children but it is also found in adults. In India, less than 1% of newborns are screened for genetic disorders which when compared in Chinese newborns is 59%. No orphan drug policy or any incentives for pharma companies are in place to motivate them to produce orphan drugs. Next section discusses the progress that has taken place in India over the last decade in the area of rare diseases.

Year 2011 and before

- In 2001, in a conference held by the Indian Drugs Manufactures Association (IDMA) a group of pharmacologists requested the Indian government to establish the Orphan Drug Act in India [97,98).
- Since 2008, Bayer Zydus Pharma runs a patient's assistance program in India for Nexavar™ (sorafenib). This drug is an orphan drug used for the treatment of hepatocellular, advanced renal cell and differentiated thyroid carcinoma. The program reduces the cost of monthly treatment for qualified persons to about a tenth of the regular pharmacy prices for the entire duration of treatment [99).
- In 2008, Sutent was launched to treat rare and difficult-to-treat forms of cancer. Pfizer developed a Sutent patient assistance programme which made the drug available to patients irrespective of their incomes. The programme offered eligible patients with a partial or fully subsidized treatment. V-Care Foundation is an NGO partner in India which manages this programme [100).
- Hemophilia incidence in India is estimated to be 1 in 5,000 and clotting factors needed for its treatment is expensive. In year 2010, the Uttar Pradesh government took an initiative to cover the cost of clotting factors for the patients in need [101).

Year 2012

- Dystrophy Annihilation Research Trust (DART) founded in 2012 is a parent founded and funded NGO based in Bengaluru. This NGO is a research lab which is developing a customized genetic treatment for 29 patients suffering from Duchenne muscular dystrophy (DMD).

Year 2013

- Aten Biopharmaceutical (Bengaluru) is one of the few local companies working to develop drugs for rare diseases in India. Established in 2013, the company has received some funding from the central Department of Biotechnology. These companiesare seeking government support to innovate drugs for a small market in a feasible and profitable way.

Year 2014

- On July 3, 2014, Ministry of health and family welfare constituted an expert committee under the chairmanship of Prof Ranjit Roy Chaudhary to formulate policy and guidelines for approval of new drugs, clinical trials and banning of drugs (Circular No. 12-01/14-DC Pt.47). It was decided to waiver clinical trial in Indian population for approval of new drugs, which have already been approved outside India in case of orphan drugs for rare disease and drugs indicated for conditions/diseases for which there is no therapy (102).

- First large-scale initiative to understand rare genetic disorder mechanisms and diagnosis was launched as "Genomics for Understanding Rare Diseases India Alliance Network (GUaRDIAN)" in the year 2014. This network performs next-generation sequencing (NGS), genotyping microarrays and extensive computational analysis. The collaboratory network, has developed an online portal where the disease information and clinical details along with the contact details can be submitted directly. Following this the investigation team contacts the patient along with sample collection procedure. Samples are then processed and analyzed. Cost of this testing can be between INR 10,000-80,000 (USD $ 150-1,100), however, this service is done at no cost to the public [103,104).

Year2015

- Strand Life Sciences, a Bengaluru based precision diagnostic company spearheaded a consortium of doctors, researchers and biotech companies that drafted a rare disease and orphan drug policy for the state of Karnataka. This document is under consideration of state health secretary. The framework is based on the USA Orphan Drug Act and aims to provide for federal grants for research, tax credits for clinical trials and 7 years of exclusive marketing of orphan drugs (105).

Year2016

- The first attempt to bring together all experts of rare disease under a common platform was initiated by Indian National Science Academy (INSA), conducted first of its kind rare disease workshop titled "To develop a scientific program or research on rare diseases" in 2016. The program deliberated on issues of rare disease definition, research avenues, policy framework to boost and incentivize R&D efforts and state government involvement. Drug Controller General of India (DCGI) head stated that genetic differences in Indian population necessitates Indian-centered studies, rather than using data from studies in other countries. Expert suggestions were also invited on the needs of changes in the drugs and cosmetic act to meet the requirements of researchin rare diseases (101).

- Karnataka submitted its rare disease policy in 2016. The policy was drafted by Vision group biotechnology team (VGBT) with the help of other stakeholders (106).

- In a meeting held between pharma stakeholders and Drug Controller General of India (DCGI) on May 4, 2016, to explore possibilities to provide cheaper medicines for patients with rare diseases, Indian Drug Manufacturers Association (IDMA) and the Organization of Pharmaceutical Producers of India (OPPI) were give the responsibility to formulate the definition for rare diseases, JDC (ER) was given the responsibility to revise timelines for orphan drug approvals, and a separate cell was suggested to address the issues of rare diseases, possibility of separate pricing mechanism for orphan drugs, and possibility of custom duty exemption (107).

- In November 2016, the Delhi high court ordered the government to finalize the policy on rare disease and directed the Centre to implement the policy without delay [108,109,110).

Year2017

- Bengaluru became the first city in India to have a center of excellence for rare diseases at the Indira Gandhi Institute of Child Health. India's first exclusive rare disease ward and free treatment facility are jointly staffed by the Organization for Rare Diseases India (ORDI). The center is supported by the Center of Human Genetics, Bengaluru. Since its inception the center has diagnosed

nearly 100 patients with rare diseases and provided treatments in case of treatable conditions or else given palliative care to patients in need. The center provides free clinical diagnosis, genetic counselling, prenatal care, treatment as well as daycare facilities to 15,000 families (111).

- Diagnosis of rare diseases on an average takes 7 years and a single test can cost between INR 25,000-30,000 (USO $350-400) which is a huge burden for most patient families. In an attempt to address this challenge, ORDI designed an innovative program called Rare Disease Care Coordination Center (RDCCC) at MS Ramaiah hospital, Bengaluru which serves as a nation-wide hub. The center gathers patient information, needs and their pain points and consequently arranges for consultation with rare disease expert to help the patients (111).

- According to an article study titled "Rare cancers: challenges and issue" published in the Indian journal of medical research states that "as per the Delhi Cancer Registry (DCR) data31, approximately 60.9% of males and 46.4% of women fall into the category of rare cancers (112).

- In April 2017, Indian Council of Medical Research (ICMR) launched "the Indian rare disease registry", aimed at addressing the unmet needs of patients with rare diseases and also help develop data and information to support R&D to enhance innovation. This effort will allow for more patient visibility suffering with rare diseases and would initially be hospital based or physician based. In the initial stages, the information will be gathered only for conditions which are treatable locally or globally and with time otherdiseases will be incorporated. The registry will benefit different stakeholders of rare diseases in different ways such as:

  1. **For patients:** Identification will increase access to treatment
  2. **For government:** Exact number of patients with rare diseases to help address their needs and provide required resources
  3. **For research bodies:** provide plethora of information available for R&D activities in India
  4. **For publications:** serve as a basis of several publications and hence will strengthen India's position as a global leader in healthcare and for clinical trials
  5. **Other benefits:** help monitor prevalence, incidence and mortality of diseases which in turn will help shape the policy decision and facilitate innovation and care for patients [113,114).

- In another initiative by ICMR, the National Initiative for Rare Diseases (NIRO) was organized jointly by ICMR, All India Institute of Medical Science (AIIMS), Jawaharlal Nehru University (JNU) and Pediatric Research and Education Society of India (PRESIDE) which invited projects for rare disease research (114).

- The "national policy for treatment of rare diseases" was rolled out in May 2017 and instituted an initial corpus of INR 100 crore (USD $15 million). The key points of the policy in short and long term are as below: **Due to implementation issue this policy was withdrawn at the time.**

  a. Immediate measures:

  1. Recommendation to the State governments to create a similar structure and share funding allocations with the Central government in 40:60 ratio. It has been noticed that even after the issue of policy by the Central government its implementation by State governments is still pending and ORDI is appealing for its implementation
  2. Creation of a web-based application for online application process to access the corpus funds
  3. Plans to create a patient registry housed by ICMR and to collect epidemiological data
  4. Define rare diseases suitable for India
  5. Develop material to create awareness in the general public, patients, their families and health care providers on rare diseases
  6. Develop and conduct training programmes for health care providers on rare diseases

  b. Long term measures:

  1. Establish system for reporting and data collection
  2. Measures to improve R&D for treatment, diagnostics, modalities, care and support which includes assisting devices, drug development for rare disease

3. Legislative measures to encourage local manufacturing of orphan drugs
4. Allow import of Enzyme Replacement Therapies (ERTs) and remove import duty on them as well as on assistive devices
5. Measures to control the prices of drugs for rare diseases and to ensure its affordability and health system sustainability
6. To encourage funding from public sector undertakings (PSUs) and corporate sector and to explore other options for sustainable funding for the corpus
7. To ensure insurance coverage for rare genetic diseases
8. The policy also endorses genetic counselling as well as pre-conception and ante-natal screening which will enable parents to decide whether to give birth to children with genetic disorders or not
9. Explore formulation of a plan for pilot and roll-out testing for rare genetic diseases in newborns
10. To establish Centers of Excellence (CoE) over a period of time for diagnosis and treatment of rare diseases [115,116].

- According to the sources in the Union ministry of health and family welfare, even after the policy introduction by the Central government, no state in India except Karnataka has availed the central scheme which subsidizes costly treatment of rare diseases. Only few states, like Delhi, Karnataka, and Tamil Nadu have included rare diseases on their health priority list [117].

- Different projects are running with regard to different rare diseases in different institutes such as AIIMS, PGIMER Chandigarh, CMC Vellore, and SGPGI Lucknow [118].

Year2018

- On 5th February 2018, an announcement by the Oraxion Therapeutics, a spin-off from Bengaluru based Aten Porus Lifesciences announced that the company has entered into an option agreement with a US-based biopharmaceutical company. The agreement provides the biopharma partner with the exclusive option to license its lead asset ORX-301 for the treatment of Niemann-Pick Type C disorder (NPC) and Focal Segmental Glomerulosclerosis (FSGS) [119].

- On February 28, 2018, at a conference organized by the NGO, Indian Organization for Rare Disease (I-ORD) in Delhi, Union minister for health and family welfare, Mr J.P. Nadda announced that after the formulation of national policy on rare diseases in 2017, the government is in the process of preparing a registry of such diseases [120,121].

- In early 2018, Open Platform for Rare Diseases (OPFORD), an idea conceived at the Center for Health Ecologies (CHET), Bengaluru and executed by Strand Life Foundation (SLF), Bengaluru was launched. This portal will allow access to information on specific diseases, diagnostics, therapeutics, clinical trial information, list of doctors, clinical geneticists, treatment centers and patient support groups [122].

- Another Centre of Excellence for Rare Diseases (CERD) was launched in Tamil Nadu at Voluntary Health Services (VHS) as a one-stop center to offer multidisciplinary facilities with doctors/clinical experts coming to treat children with rare diseases.The center will provide comprehensive care which will include medical and surgical management, rehabilitation, day care facilities and in-patient services [123].

- In March 2018, as per an article published in The Economics Times, the Insurance Regulatory and Development Authority of India (IRDAI) has directed all insurance companies not to exclude 'genetic disorders' in new health insurance policies issued and ordered not to reject claims on the basis of exclusion related to genetic disorders [124].

- In a shocking turn of events, the Union health & family welfare ministry on December 18, 2018 announced the roll-back of the national policy with a decision to review the policy for further revisions as there are severe gaps I the current policy structure. The issue came into light during a high court hearing on November 30, 2018 filed by some patients due to the delay in accessing the funds allotted under national policy [116]. Currently, the Health ministry has requested High court for nine months to update the policy which has been granted.

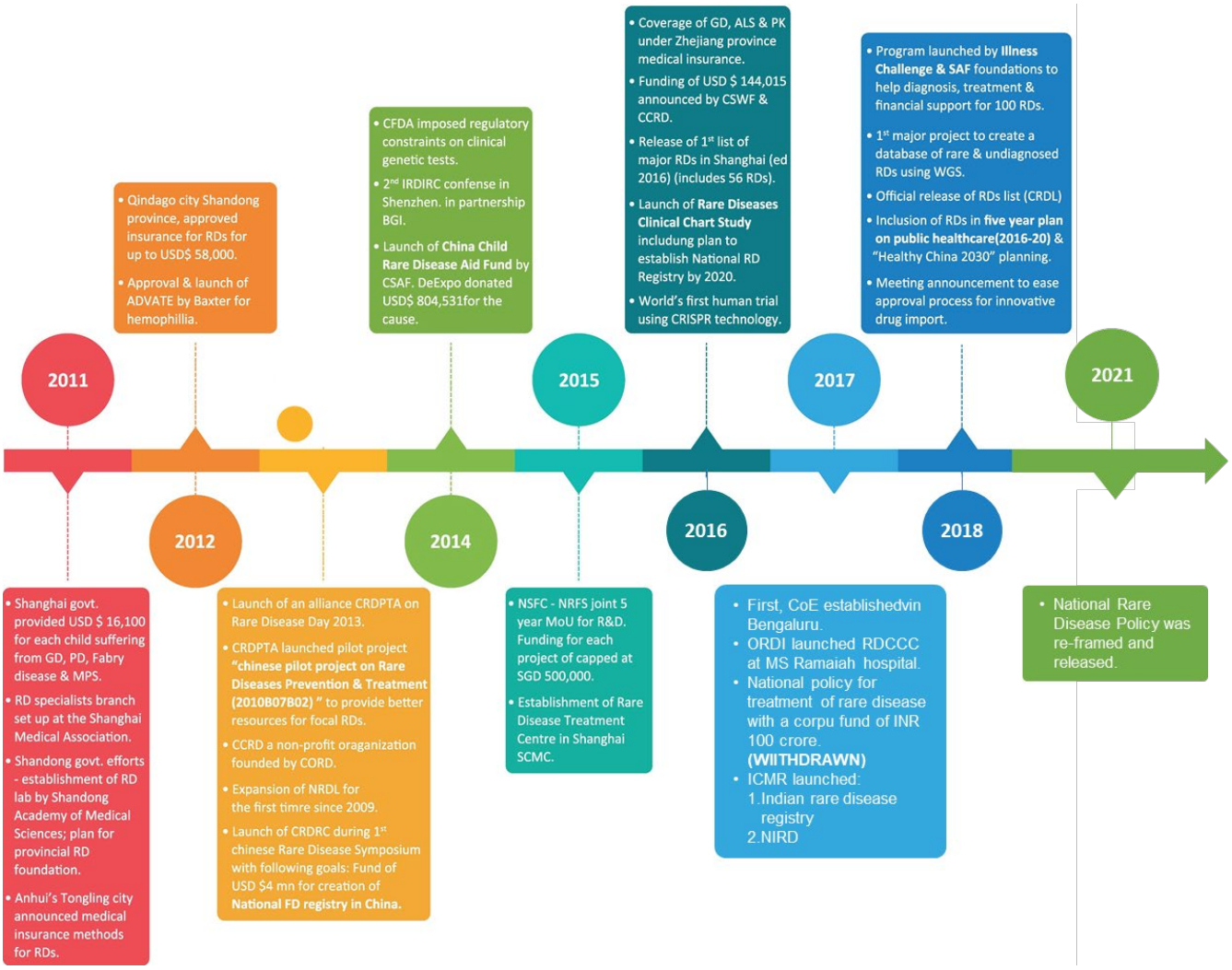
YEAR 2021

- Ministry of Health and family Welfare, Government of India formulated a National Policy for Treatment of Rare Diseases (NPTRD) in July 2017. Implementation of the policy, however, faced several challenges. A limiting factor in its implementation was bringing States on board and lack of clarity on how much Government could support in terms of tertiary care. When the policy was shared with State governments, issues such as cost effectiveness of interventions for rare disease vis-à-vis other health priorities, the sharing of expenditure between Central and State governments, flexibility to State governments to accept the policy or change it according to their situation, were raised by some of the State governments (1).
- Given the challenges in implementing the policy, the need for wider consultation and recommendations, a decision was taken to reframe the National Policy for Treatment for Rare Diseases. An Expert Committee was constituted by Ministry of Health and Family Welfare (MHFW) in November 2018 to review the NPTRD 2017. A comprehensive National Policy for Rare Disease was released on 30th March 2021 (1, 2).
- The Rare Diseases Policy aims to lower the high cost of treatment for rare diseases with increased focus on indigenous research with the help of a National Consortium to be set up with Department of Health Research, Ministry of Health & Family Welfare as convenor. Increased focus of research and development and local production of medicines will lower the cost of treatment for rare diseases. The policy also envisage creation of a national hospital-based registry of rare diseases so that adequate data is available for definition of rare diseases and for research and development related to rare diseases within the country (1,2).
- The Policy also focuses on early screening and prevention through primary and secondary health care infrastructure such as Health and Wellness Centres and District Early Intervention Centres (DEICs) and through counselling for the high-risk parents. Screening will also be supported by Nidan Kendras set up by Department of Biotechnology. Policy also aims to strengthen tertiary health care facilities for prevention and treatment of rare diseases through designating 8 health facilities as Centre of Excellence and these CoEs will also be provided one-time financial support of up to Rs 5 crores (~USD 680, 000) for upgradation of diagnostics facilities (3).
- A provision for financial support up to Rs. 20 lakhs (~USD 27,219) under the Umbrella Scheme of Rastriya Arogya Nidhi is proposed for treatment, of those rare diseases that require a one-time treatment (diseases listed under Group 1 in the rare disease policy). Beneficiaries for such financial assistance would not be limited to BPL families, but the benefit will be extended to about 40% of the population, who are eligible under Pradhan Mantri Jan Arogya Yojana (3).
- Besides, the Policy also envisages a crowd funding mechanism in which corporates and individuals will be encouraged to extend financial support through a robust IT platform for treatment of rare diseases. Funds so collected will be utilized by Centres of Excellence for treatment of all three categories of rare diseases as first charge and then the balance financial resources could also be used for research (3).

References

1. National Policy for Rare Diseases, 2021. Available at: Final NPRD, 2021.pdf (mohfw.gov.in)
2. Disquiet over govt's new policy for rare diseases. The Hindu. April 02, 2021. Available at: Disquiet over govt.'s new policy for rare diseases - The Hindu
3. Ministry of Health and Family Welfare, Union Health Minister approves National Policy for Rare Diseases, 2021. Posted On: 03 APR 2021 6:40PM by PIB Delhi. Available at: https://pib.gov.in/PressReleaseIframePage.aspx?PRID=1709369#:~:text=The Rare Diseases Policy aims,Health %26 Family Welfare as convenor.

Figure 3.Represent a timeline of the events that took place in last decade in the field of rare disease in India



4.2.2. Access to orphan drugs & their pricing

Treatment cost for rare disease are exceptionally high. For rare diseases such as Gaucher's disease, treatment may cost up to INR 1.5 crore (USO $215,000) per year which when compared with the average annual per capita income in India of just over INR 1 lakh (USO $1,433) is exorbitantly high and unaffordable for patients and their families to receive the treatment. Table 10 represents some of the orphan drugs available in India and their annual cost to patients. Orphan drugs in India are usually procured by the government and dispensed at public hospitals. Although several companies including Shire, Sanofi Genzyme and Pfizer have compassionate access programs. Under these programs, drugs under clinical trials or those which are not intended to be launched in the country are given to patients for free including the investigational drugs.

Currently, 12 Shire products (injectable) are available in Indian market, including treatment for haemophilia. Shire has in-process application with the Drug Controller General of India (DCGI) to introduce drugs to treat LSDs. The application is under review and it is to be decided if a clinical trial is needed in India or not. The company is also considering the launch of oncology drugs in India. In addition, Shire is supporting an initiative by Indian Council of Medical Research (ICMR) to compile a rare diseases registry and has also launched a new patient support programme (125].

Bengaluru is becoming a hub for companies that do commercial diagnostic testing. These include Strand Genomics, CentoGene, MedGenome and Eurofins India. According to Vijay Chandru, co-founder and chairman of Strand Life Sciences there is a rapid and cost-effective treatment option available with India and that is development of biosimilar of existing drugs such as ERTs. Innovator pharmaceutical companies should work licensing agreements with Indian manufacturers. Bengaluru-based Association of Biotech led Enterprises (ABLE) has suggested that the government should procure orphan drugs to encourage development of biosimilar (116].

Interest of pharma companies in expansion of orphan drugs is increasing, which is a result of proposed policy for rare diseases and increase in number of State government hospitals in procuring drugs for illness like haemophilia, which increased from 3 to 22 over the last decade. Introduction of Orphan Drug Act will give motivation to pharma companies in terms of market exclusivity, reduced/ waived regulatory fees, tax credit or subsidies on clinical trials to develop and manufacture orphan drugs.

In addition, healthcare and medical research budgets available are considerably small in India which needs reconsideration from the government given that most orphan drugs are often imported and are developed in western countries and hence costs a fortune. Similar drugs could be made in cost effective manner in India with proper policies and legislations.

Table 11.Shows the availability and efficacy of treatment and cost of rare diseases of immediate relevance in India as evaluated by a sub-committee of rare disease policy team

Disease	Enzyme	Wt. of the patient	Approx. annual cost (INR)*
Gaucher disease	Cerezyme (Genzyme)	10 kg	39,84,768
	Velaglucerase (Shire)	10 kg	71,86,340
	Taliglucerase		n/a
MPS I	Aldurazyme (Genzyme)	10 kg	46,78,464
Pompe disease	Myozyme (Genzyme)	10 kg	48,94,368
Fabry disease	Fabrazyme (Genzyme)	10 kg	18,29,712
MPS II	Elaprase (Shire)	10 kg	44,00,000
MPS II (0.5mg/kg/week) Vial 2mg	Hunterase (Green Cross-Korea) 3mg/6ml (0.5mg/ml) vial 1,43,520/-per vial	10 kg	1,72,22,400
MPS VI (lmg/kg/week) Vial 5mg	Naglazyme (USD 1755 per vial)	10 kg	1,09,51,200
MPS IV (2mg/kg/week) Vial 5mg	Vimizim (USD 1068/vial)	10 kg	1,33,28,640

*includes custom duty, CVD taxes, Octroi etc. (Source: I.C Verma sub-committee report) [109]

4.2.3. Key stakeholders involved in improving rare disease status in India

Table 12.List of key stakeholders who are involved in the progress of rare disease in India

Organization	Vear of establishment	Point of contact	Role/Activities
Indian Organization for Rare Diseases (I-ORD) *(http://www.i-ord.org/)*	2005	Chairman - Steven Gawron President- Dr Ramaiah Muthyala Vice President - Dr Gayathri K.	- NGO in India and USA - Umbrella organization and represents interests of all RDs, individual patients, patient support groups, health policy advocates and health care provider for RDs
Organization for Rare Diseases India (ORDI) *(https://ordindia.org/)*	2013	Founder & Director - Prasanna Shirai	- National umbrella organization representing the collective voice of all patients with RDs in India
Lysosomal Storage Disorders Support Society (LSDSS) *(http://www.lsdss.org/)*	December 2009	President - Manjit Singh	- NGO with aim to raise awareness about various rare genetic life-threatening LSDs - Advocate the needs for early diagnosis, screening and treatment of LSDs with various stakeholders
Ataxia Awareness Society (AAS) *(https://www.ataxiaindia.com/)*	March 2018	President - Swati Wagh Vice- President - Dr Apoorva Puranik	- NGO with aim to raise awareness about ataxia among patients as well as medical professionals - Help patients receive financial, medical, educational grants and other benefits from govt. or other sources - Registry of ataxia patients
Seek a Miracle Ataxia Group (SAMAG)	2006	Founder - Chandu George	- Non-profit support group working for ataxia and muscular dystrophies
Amrithavarashini (Society for Osteogenesis Imperfecta) *(http://www.amrithavarshini.org/)*	April 2011	Founder - Dhanya Ravi	- NGO to raise awareness and helps 01 suffering patients - Provides support of INR 500 per month to patients
Dystrophy Annihilation Research Trust (DART) *(https://dartindia.in/)*	2012	Founder & President - R.S. Anand	- DART is the first research lab in India focusing on DMD - Supports patients and families, raises awareness and medical advisory and rehabilitation
India Spina Bifda Association (ISBA) *(http://indiaspinabifidaassociation.org/*	1999	Founder - Vinita Jindel	- NGO aims to raise awareness about Spina Bifda

Metabolic Error and Rare Diseases Organization of India (MERD India) *(http://www.merdindia.com/index.html)*	2011	Founder - Vikas Bhatia Neelam Shroff	- The mission of MERD India is to promote awareness for Inborn Errors of Metabolism & Rare Genetic Disorders - Provide **moral and informative support** to the parents of such children and to campaign newborn screening in India
Pompe Foundation *(http://pompeindia.org/)*		President - Prasanna Shirol	- To support parents for treatment and create awareness among medical fraternity - Advocacy with Govt for a proper Health care model for Pompe Disease in India. - To promote early diagnosis and new born screening
Primary Immunodeficiency Patients Welfare Society (PID) *(http://www.pidindia.net/)*	2012	President- N. Chamraja	- To raise awareness of the disease in public and medical fraternity - Advocates creating database registry, local manufacturing of "human immunoglobulin", tax exemption of orphan drugs, set up of immunology research department at major hospitals
Hemophilia Federation India (HFI) *(http://hemophilia.in/)*	1983	Founder - Late Ashok Bahadur Verma President - Vikas C. Goyal	- National umbrella organization in India working for the welfare of PWH through a network of 76 chapters spread over 4 regions - To provide quality care, education, making treatment affordable and support economic rehabilitation of patients
Indian Rett Syndrome Foundation (IRSF) *(http://www.rettsyndrome.in/)*	2010	Founder - Dr Rajni Khajuria President - Samir Sethi Vice- President - Amil Kaul	- To raise public and professional awareness - To counsel and educate families and doctors
V Care Foundation (V CARE)	1994	Founder - Vandana Gupta	- NGO which works to help cancer patients and their families cope with the crisis in their live
Center of excellence for rare disorders (CERD), Tamil Nadu	2018	Voluntary Health Services (VHS) & Mediscan	- The center will provide the treatment for various RDs, give supportive treatment, monitor the patients, conditions regularly and also provide rehabilitation services
Sjogren's India (SI) *(http://www.sjogrensindia.org/)*	2006	Co-founder - Kirtida Oza	- Informal patient support group for providing education and counselling support to patients suffering from the Sjogren's syndrome

Shire		Country head - Vineet Singhal	
Strand Genomics *(https://strandls.com/StrandGenomics-issue-four)*			
Stand Life Foundation			
Genomics for understanding rare disease India alliance network (GUaRDIAN) *(http://guardian.meragenome.com/)*	2014	Co-Founder & Investigator - Dr Sridhar Sivasubbu & Dr Vinod Scaria	- Research collaboration involving basic scientists and clinicians to explore potential translational applications of genomic technologies
Aten Biotherapeutics			- Developing new therapeutics to treat Pompe with gene therapy and nanotechnology

RDs = Rare diseases; DMD= Duchenne muscular dystrophy; PWH = patients with hemophilia

4.3 MALAYSIA

4.3.1. Introduction

Rare disease is not officially defined in Malaysia however, as per Malaysian Rare Disorder Society (MRDS), it is defined as disease that affects less than 1 in 4000 individuals in a community. The GDP per capita of Malaysia is US $10,440 and health care expenditure per capita is USD 119 [126]. Malaysia is one of the few Asian regions with subsidized drugs. Patients can avail drugs with a co-pay of RM 5 if the drugs are included in national medicine formulary.

Over the past 10-15 years, the laboratory capacities in Ministry of Health (MoH) to diagnose rare diseases have amplified and in case of unavailability of the needed tests, the ministry offers outsourcing options. However, the funding available for such tests is RM 3000 (US$ 736) per year which is not sufficient to cover the costs. Moreover, the time taken for diagnosis increases in such cases, for example, a Pompe disease test can be done within 2 weeks locally whereas it takes 3 months to be sent and analyzed in Australia. Number of clinical geneticists have increased over the years still this number is just around a dozen [127,128].

Newborns are screened for inborn errors of metabolism (IEM) under Newborn Screening (NBS) Expanded. Although it is not mandatory and has not yet been incorporated into the public healthcare system of Malaysia. Expanded NBS is being conducted at two main centres: 1) Institute for Medical Research (IMR) and, 2) Centre for Advanced Analytical Toxicology Services (CAATS) on request by some of the private hospitals. Malaysia has a very high rate of NBS of rare disease with >95% of newborns being screened which is a step in a positive direction to curb rare and metabolic diseases (129].

Year 2011 and before

- In 2004, MRDS was formally established with the support and guidance from the Genetic unit, Department of pediatrics, University Malaya medical center.

Year 2012

- As a first move towards recognizing rare diseases in Malaysia was a statement "live saving and orphan drugs shall be appropriate procedures to enhance accessibility without compromising safety, quality and efficacy" in the Malaysia National Medicines Policy. This was a significant move for orphan drugs considering its absence in the first edition (130].

Year 2013

- In 2013, the Malaysian government highlighted its efforts to promote local pharmaceutical companies to venture into orphan drugs. And for this under federal government's Economic Transformation Programme, Early Point Project (EPP) status were awarded to pharmaceutical companies to develop an orphan drug ASEAN manufacturing and an export hub in Malaysia. Within the project margin, the government seeks to address multiple barriers to access quality orphan drugs in the country, such as low sales opportunity, complex regulatory environment and lack of knowledge for effective treatment of rare diseases. This project is spearheaded by a local pharmaceutical, Hovid Berhad in collaboration with AFT pharma (a New Zealand pharmaceutical company) (131].

Year 2016

- Asper a report from Universiti Sains Malaysia, Penang, Malaysian health ministry is working to develop a rare disease policy. A team at this university is formulating an access policy for orphan drugs. According to Assoc. Prof Asrul Akmal Safie, Azuwana Supian and Prof Mohamed Azmi Hassali it is important that different stakeholders such as policymakers, ministries, healthcare providers, families and NGO's need to support the formulation of these policies [132].

- During Annual Congress on Rare Diseases and Orphan Drugs (October 26-27, 2016) in Chicago, USA, Haq A.S.M of MoH Malaysia presented on "Access to orphan drugs: a Malaysian perspective" where he mentioned about the efforts of MoH in drafting guidelines for the management of orphan drugs. The framework will address issues relating to the designation, regulation, marketing and procurement procedures for orphan drugs. The major obstacle however, faced by MoH is affordability of rare disease treatment. With the increasing number of drugs being approved for rare diseases and expansion of genetic services in Malaysia, options such as managed entry agreements, increased public-private partnerships and international collaboration may be the way forward to ensure timely, safe and affordable availability of orphan drugs to those in need [133].

- Second Rare Disease Asia Conference 2016 was held in Kuala Lumpur (17-19 November) by World Through My Eyes and themed "Working in one voice". The conference aimed at bringing together stakeholders to advocate for rare disease patients in the region [134].

Year 2018

- Rising awareness about the cause has led to increased interest and serious consideration from the government towards the welfare of rare disease patients. Due to which a fund of RM 10 million (US$ 2.45 million) has been allocated under Budget 2018 to treat rare diseases with orphan drugs at the Hospital Kuala Lumpur's genetic clinic. This is a substantial increase from allocation of RM 8.5 million (US $2.09 million) annually since budget in 2009.

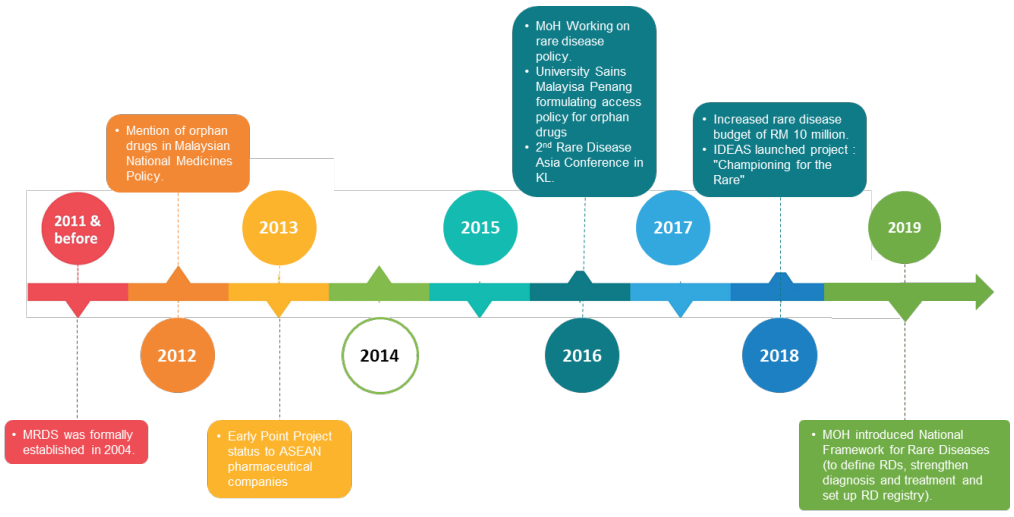
- On August 16, 2018, Institute for Democracy and Economic Affairs (IDEAS) launched a new project titled "Championing for the Rare" at Rare Disease Symposium. A Brief IDEAS paper titled "National policy on rare diseases: living with dignity, in search of solutions for rare diseases", co-authored by Prof Dr Thong Meow Keong and Dr Azlina Ahmad-Annuar from University of Malaya was presented to Dtao' Dr Haji Azman bin Bakar, Deputy Director General, MoH. The paper highlights challenges faced by rare disease patients and bringing stakeholders together to find solutions to those problems [135,136].

Year 2019

- In Nov 2019, MOH set up a national governance committee to manage rare diseases in Malaysia. In short term, the National Framework for RD has plans to clearly define RDs, strengthen labs for RDs, and craft policies and strategies to obtain drugs in Malaysia. In long-term, MOH plans to set up a registry of RDs collect and analyse data for developing and monitoring the health of the patients in evaluating the clinical management programmes conducted. [REF]

Keong T.M. et al., Whitepaper: Rare Diseases in Malaysia. Rare Disease Report 2019, IDEAS.

Figure 4.Shows the timeline of the progress in the field of rare disease in Malaysia



Abbreviation: MRDS = Malaysian rare disorder society, MoH = Ministry of health, KL= Kuala Lumpur, IDEAS= Institute for democracy and economic affairs

4.3.2. Key stakeholders involved in improving rare disease status in Malaysia

Table 13.Key stakeholders in the area of rare diseases in Malaysia

Organization	Established	Key stakeholder	Objective/Purpose
Malaysian Rare Disorders Society (MRDS) *(http://www.mrds.org.my/)*	2004	President - Nadiah Hanim Nadiah Hanim Vice-President - Allida Muhammad Said	- Voluntary organization which works for the welfare of RD patients and their families.
Malaysia Lysosomal Diseases Association (MLDA) *(http://www.mymlda.com/)*	2011	President - Ir. Lee Yee Seng Vice-President - Zabidi Ali	- Non-profit organization which advocates for RD patient's rights. - Raises awareness about LSD.
Spinal Muscular Atrophy Malaysia **(SMAM)** *(http://iknowsma.com/)*			- Spinal Muscular Atrophy Malaysia is an organization built to promote awareness and support for children and parents suffering from SMA.
We Care Journey *(https://wecarejourney.org/home)*	2015	Co-founder & President - Edmund Lim	- The group aims at the treatment of SMA and support the RD patients and their families affected by SMA.
Malaysia Metabolic Society **(MMS)** *(http://mms.org.my/about-us/)*	2005	Founder & advisor - Dr Choy Yew Sing	- Non-profit organization established by a group of parents and medical profession to help patients who suffered from rare diseases/ disorders, publicly known as inborn error of metabolism.
Hovid Berhad	1980	Managing director & Chairman - David Ho Sue San	- Pharmaceutical company that works on orphan drugs. - Part of EPP.
Institute for Democracy & Economic Affairs (IDEAS)	2010	CEO - Founding President - Siti Safura Jaapa Chairman - YAM Tunku Zain Al-'Abidin ibni Tuanku Muhriz	- Non-profit research institute dedicated to promoting solutions to public policy challenges. - Raise awareness about rare diseases and advocates national policy on RDs.

Abbreviation: RD= Rare disease, LSD= Lysosomal storage disorder, SMA = Spinal muscular atrophy, EPP= Early point project

4.3.3. Access and pricing of orphan drugs

As per a recent study by School of Pharmaceutical Sciences, Universiti Sains Malaysia and University Malaya Medical Centre, only 60% of the rare disease patients are receiving treatment in Malaysia. There are several reasons as to why rare disease patients have problems accessing affordable drugs, such as:

1. Lack of formal definition for rare diseases in Malaysia which complicates its effective monitoring and management. Consequently, no epidemiological study or registry exists which can be used as a baseline data for further action
2. Lack of experienced clinicians and diagnostic equipment in Malaysia. Most of the facilities are available in Kuala Lumpur (KL) and in very few visiting hospitals
3. Lack of orphan drugs due to high cost (may cost> RM 1 million per year (USO $240,855)

Malaysia is one of the few countries in the SEA region which provides public subsidies for rare diseases such as for ERT. The cost of treatment for ERT in Malaysia for a single patient can cost between RM 500,000 to RM 1 million per year. At present, funding for treatment is reliant on charities, public and industrial subsidy or out-of-pocket (OOP) payments. The government also provides dedicated funds to gain access to orphan drugs and special milk formula needed to treat rare inborn error of metabolism. However, even with the availability of innovative drugs being developed, they are often not registered with the Health Ministry's Medicine Formulary but can be provided via special approvals on a case-by-case basis [137,138].

The patient advocacy groups (PAGs), play an important role in the active fight for the welfare of rare disease patients. Their role involves holding awareness campaigns in the community and through the print, electronic and social media. In addition, they produce information booklets, organize charity fund-raising activities and attend the international conferences on rare diseases. PAGs are often supported in their rare disease programmes by pharmaceutical companies, other NGO's and philanthropists [139].

4.4 SINGAPORE

4.4.1. Introduction

Singapore law defines rare diseases as illness that are life-threatening and severely debilitating, and which affects less than 20,000 people. According to estimates Singapore has a GDP per capita of USD 54,007}, health care expenditure of USD 2426, and out-of-pocket expenditure of 58.6%, respectively. Around 2000-3000 individuals are estimated to be suffering from rare diseases.Singapore currently has no national policy on rare disease. Orphan drug are exempted under the act named "Medicines orphan drug act" of 1991. The next section details the activities that has taken place in Singapore in the last decade.

Year 2011 and before

- The National expanded newborn screening (NENS) programme launched in October 2006, offers more than 25-30 metabolic screening tests for inborn errors of metabolism (IEM) to all newborns in Singapore [140]. This test is available to all newborns but is not compulsory. The testing cost falls between SGD $35-45 for subsidized patients in public hospitals, whereas in private hospitals it is priced at SGD $140 [141].
- Medicines (orphan drugs) (Exemption) order under Medicines Act (chapter 176, sec 9) (G.N. No. S 470/1991) was introduced on November 4, 1991. However, the act was revoked with effect from November 1, 2016 [142,143].
- Rare disorders society (Singapore) (RDSS) established in 2011 is a charity which was started by parents of children with lysosomal storage disorder (LSD). In addition to raising awareness about rare disease, RDSS provides different programme and services to the affected children and their families to support them financially and in other ways. Few such programme are: medical intervention support scheme, power for life program, consumable support scheme etc. [144].

Year2015

- By the end 2015, MediShield Life (Singapore's basic health-care insurance) started to cover congenital illness for those diagnosed after March 1, 2013. The insurance premium costs about SGD $100 per year which is 30% higher than what it costs to normal population. This insurance gives support to the suffering families when they are turned away by private insurers [145].
- Singapore hosted 1st Rare Disease Asia Conference in February 2015. This conference brought together 25 patient groups from 13 different countries. During this conference, Rainbow Across Borders (RAB), a patient support organization was established as a regional umbrella alliance for rare diseases. In addition to regional collaboration it also focuses on developing the rare disease registry and directory across Asia [1].
- Asia Pacific Alliance for Rare Diseases Organizations (APARDO) meeting took place in Singapore. This alliance aims to bring together various rare disease organizations across countries to raise voice for rare diseases and influence national policies for rare diseases and orphan drugs [146].

Year2016

- RAB brought together hemophilia patient's groups from Thailand, Malaysia, Vietnam and Singapore at the "Principles of Hemophilia Care- a patient's perspective" for a round table meeting in January 2016 (29-31 January). The aim was to discuss the South East Asia principles of hemophilia care suggested by the Asia Pacific hemophilia working group (HWG) (147].

Year2017

- The ASEAN+ Rare Disease Network was established by RAB, with the aim to bring together patient support groups from across Southeast Asia (SEA) (Singapore, Malaysia, Indonesia, Philippines and Vietnam) and Hong Kong. As one of its initial initiatives, the network planned to launch the Rare Disease Impact study across the region to better understand the needs of rare disease patients and their caregivers that will ultimately catalyze strategic solutions for the management and care of rare disease suffering families. A pilot study for the same was conducted in Singapore during July-December 2016 and involves 152 patients and their caregivers across with different rare disorders specific to the country (148].

- Patient advocacy week (27 November- 1 December) held to train 46 patient group leaders from 11 Asian countries and more than2 dozen Shire employees on patient advocacy. The training was conducted by policy wisdom and was supported by RAB, APARDO and World Federation of Hemophilia (WFH) (149].

Year2018

- Asper RAB's estimates, the rare disease funds to be set up by the Singapore government will need at least SGD $200 million at the start to be sustainable (150].

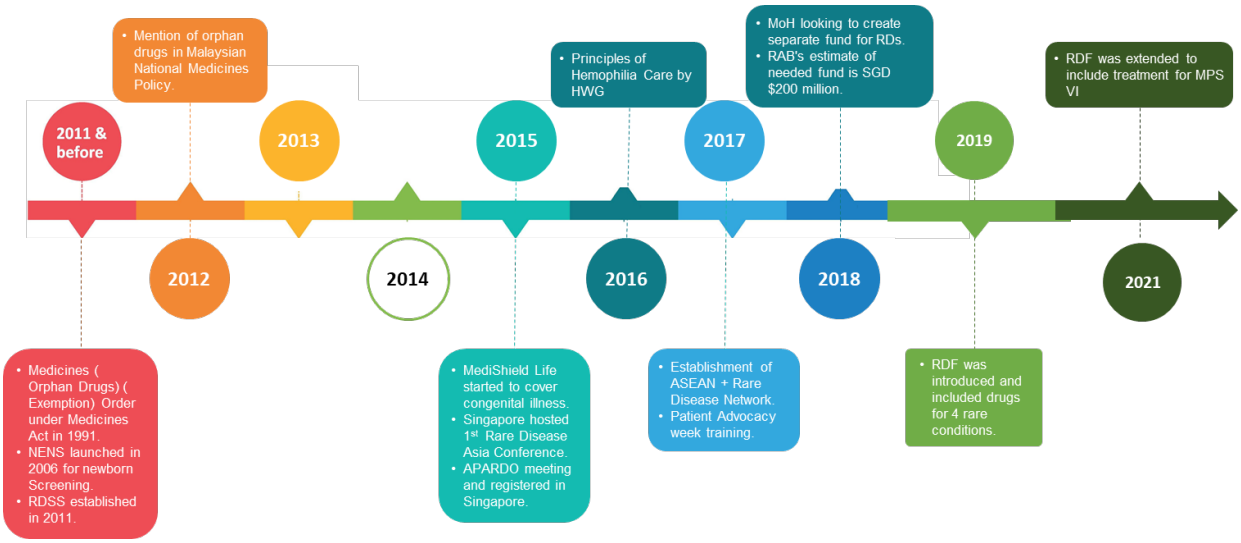
- As per Senior Minister of State Chee Hong Tat, the Ministry of Health (MoH) will release a proposal letter towards the end of 2018 with the aim to provide better support for children with rare diseases. In response to an adjournment motion by Junior member of Parliament, Dr Tan Wu Meng, Mr Chee mentioned that the government is looking into various options which includes insurance, discretionary funds such as Medifund, Medication Assistance Fund (MAF) and a separate fund composed of contributions from the government, companies, charities, community groups and individual donors to help rare disease patients [151].

- On Rare Disease on February 28, 2018, Illumina participated in a global company wide fundraising initiative (jeansforgenes) to support ROSS along with Unique- Understanding Chromosome Disorders in the UK, Global Genes and Rare Voices in Australia.

Year2021

- In August 2021, RDF was extended to include another rare disease drug called Mucopolysaccharidosis type VI (MPS VI) . Drug Galsulfase (Naglazyme) was included [152].

Figure 5.Shows the timeline of the progress in the field of rare disease in Singapore



Abbreviation: NENS = National expanded newborn screening, ROSS= Rare disease society Singapore; APARDO = Asia-Pacific alliance rare disease organization; HWG = Hemophila working group; MoH = Ministry of health; RAB= Rainbow across borders RDF - Rare disease fund MPS VI - Mucopolysaccharidosis VI

4.4.2.Key stakeholders involved in improving rare disease status in Singapore

Table 14.Key stakeholders in the area of rare diseases in Singapore

Rare Disorders Society Singapore (RDSS) *(http://www.rdss.org.sg/)*	2011	Founder -Kenneth Mah President -Patricia Ng Suat Gek Executive director - Kenneth Mah Yee Wah	- It aims to create awareness on various life threatening RDs. - Offers emotional, counselling and financial support to children, family or friends with RDs. - Directs patients to medical resources and raise funds.
Rainbows Across Borders (RAB) *(www.rabasia.org)*	2015	Chairman - Gregory Vijayendran Chairman - Adj Assoc Prof Ng Kee Chong Executive director - R. Rajakanth	- Promotes regional collaboration and networking among patient support organizations within Asia-Pacific region.
ASEAN+ Rare Disease Network	2017	Project director - Alison Chang	- The network aims to better understand the needs and pain points of the RD patients and caregivers to help manage and utilize the resources better.
Carcinoid-Neuroendocrine Tumor Society (Singapore) (CNETS) *(http://www.cnets.org)*	2009	Founders - Dr Paul Ho, Lam Wei Choong and William Claxton	- The CNETS is a support group for carcinoid and neuroendocrine tumor patients, family caregivers, researchers and physicians
Asia-Pacific Alliance of Rare Disease Organizations (APARDO)	2015		
National University Hospital		Assoc Prof Denise Goh	- Heads the pediatric genetics and metabolism division
KK Women's and Children's Hospital		Dr Tan Ee Shien	- Senior consultant with the genetic service

(RD= Rare disease)

4.4.3. Access & pricing of orphan drugs

A drug can be designated as orphan drug in Singapore, but the designation is based on doctor's or dentist's reference. Drugs can then be imported for a specific rare disease and is given top registration priority. To be considered as an orphan drug in Singapore the drug should not hold a previous product license under the Medicine Act and needs to be approved by a competent health authority either from the country of origin or from the country of use. However, no incentives for pharmaceutical companies are offered to market their drugs in Singapore. Market exclusivity for orphan drugs is 10 years which is same as other drugs. Based on some secondary research it was found that enzyme replacement therapy (ERT) with Myozyme for Pompe disease can cost SGD $10,000 per week. For Gaucher's disease the ERT may cost up to SGD $ 24,000 per month. These costs often increase with age and adds to the burden of the families [153,154].

Year2019

- Launched in July 2019, Rare Disease Fund (RDF) is a charity fund - managed by KK Women's and Children's Hospital (KKH), which is a part of SingHealth Fund and is supported by the Ministry of Health. The RDF charity funds combines community donations and 3-to-1government matching to provide long-term financial support for patients with rare diseases who require high-cost treatments. With the latest expansion in disease coverage, the RDF covers six life-saving medicines which treat four rare disease conditions [152].

Include this year 2019 in the timeline also (this was requested in last modifications).

They are as follows:

1. Primary bile acid synthesis disorder - Cholic acid
2. Gaucher disease (Type 1 or 3) - Imiglucerase (cerezyme), Velaglucerase alfa (VPRIV), Taliglucerase alfa (Elelyso)
3. Hyperphenylalaninemia due to tetrahydrobiopterin (BH4) deficiency - Sapropterin dihydrochloride (Kuvan)
4. Pompe disease - Alglucosidase alfa (Myozyme)

4.5 PHILIPPINES

4.5.1. Introduction

Rare disease is defined as a genetic disorder which affects less than lin 20,000 individuals in the country. GDP per capita of Philippines is USD 2588 and healthcare expenditure per capita is USD 410. Currently, rare disease affected Filipinos receive limited support in terms of finance and medical expertise. There is a lack of information and experienced doctors to provide accurate diagnosis and treatment for the patients. As rare disease is known to affect a small population within the country, there is a little interest among research institutions in the country to study these disorders in detail. However, with the introduction of rare diseaselegislation the situation is rapidly changing for local population suffering with rare disease.

Year 2011 and before

- Newborn Screening (NBS) is a method for early detection of genetic and metabolic disorders in infants and is active since 1996. NBS was integrated into the public health delivery system with the passing of the Newborn Screening Act of 2004 or RA 9288 (155]. In the initial act newborns were screened only for 6 conditions (NBS 6-test). The facility for NBS is available at> 7000 islands in the country. However, there are only 10 geneticists in the entire Philippines [3,156].

- In February 2010, the Department of Social Welfare and Development (DSWD) participated in the observance of the 8th National Rare Disease Week (NRDW) as per the declaration by Presidential Proclamation No. 1989. The declaration aims to raise awareness about rare diseases and their impact on patients and their families. Support from policy makers, researchers, health professionals, civil service organizations, and other health workers is needed in order to emphasize the focus on this disease area (157].

Year 2012

- Asper a report presented by Anthony P. Calibo, Officer-in-charge, Child Health Development Division, Department of Health (DoH) granted funds worth Philippine peso 11 million (US$ 212,547) for a period of 2 years (2012-2014) to Rare Disease Medicine Access Program. The funds were allocated in parts:

  1. Philippine peso 10 million for ERT therapy of type 2 Gaucher disease patients per year
  2. Philippine peso 1 million for patient navigation (158].

Year 2014

- Newborn screening was expanded from NBS 6-test to Expanded Newborn Screening (eNBS) since December 2014. Under eNBS 25-26 conditions are tested. Acknowledging the benefits of eNBS for newborns, the DoH is aiming to transition fully from the NBS 6-test to eNBS. At present, only 28% of all newborns in the Philippines are screened for rare diseases. Currently, the cost of NBS is Philippine peso 550 (USD 14) which is covered by PhilHealth and an expanded screening which costs Philippine peso 1500 (remaining Philippine peso 950 is covered by patient). Currently, there are 14 Continuity Clinics nationwide to handle the long term follow up of a confirmed patient (159].

Year 2016

- On March 3, 2016, the Rare Diseases Act of the Philippines (Republic Act 10747) was introduced as a law. This act will help rare disease patients have better access to comprehensive healthcare.

1. As per this act the Philippine Health Insurance Corporation (PhilHealth) has been mandated to include the benefit package for rare disease patients, medical assistance under Sin Tax Reform of 2012.

2. Under this act, the DoH is responsible for creating a Rare Disease Registry and to include all patient affected by rare diseases.

3. In addition, rare disease patients will be covered under Patients with Disabilities (PWDs), and can avail the privileges such as priority programs and discounts. Under this classification, patients with rare diseases will qualify for discounts on healthcare services and medicines as specified in the Republic Act 9442. Amendment to this act was presented in 2006, Republic Act 7277 also known as "Magna carta for disabled persons, and for other purposes".

4. Provisions to support the R&D for rare diseases by providing regulatory and fiscal incentives and facilitating the manufacture and importation of affordable orphan drugs and products [160].

Year 2017

- In 2017, The DoH in collaboration with the University of the Philippines National Institute of Health (UP NIH) held the 1st Philippine Rare Disease Symposium. The collaboration aims to set up a rare disease registry along with an effective referral system to improve support, treatment and information for rare disease patients. A technical group will be set up to identify the needed treatment and services to be later included in the medical assistance program and PhilHealth benefits package [161).

Year 2018

- Rare Disease Medicines Access Programs (RDMAP)- DoH aims to provide health care access to patients with rare diseases. The current beneficiaries of this programme are Type 1 and 3 Gaucher's disease with ERT infusion [162).

Year 2020

- In 2020, the Department of Health (DOH) had proposed to create the Integrated Rare Diseases Management Program and institutionalized allocations in the annual health budget specifically to improve treatment and access. Amongst other DOH plans was expansion of rare disease list which were all delayed due to the emergency brought by COVID-19. [REF]
- REF - Virtual Round Table Discussion: Theme: No one should be left behind amid the continuing pandemic - facilitating the implementation of the Rare Disease Law for 2022. The Stratbase ADR Institute. 27th Jan 2022.

Year 2022

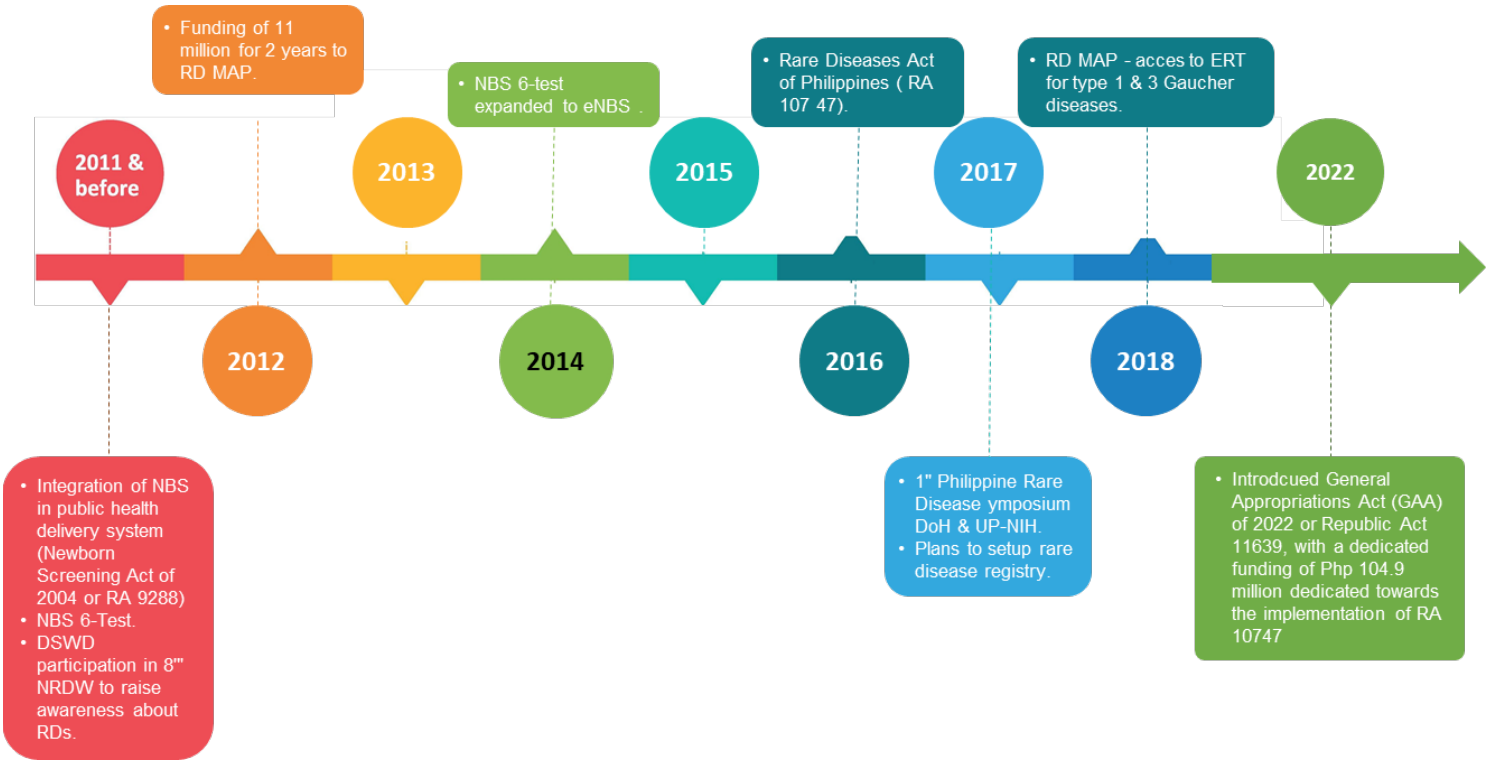
- Philippines successfully included General Appropriations Act (GAA) of 2022 or Republic Act 11639, which includes a funding of Php 104.9 million dedicated towards the implementation of RA 10747 (Rare Diseases Act) introduced in 2016. [REF]
- On January 27, the Stratbase ADR Institute, in partnership with UHCWatch and the Philippine Society of Orphan Disorders, held a virtual roundtable discussion (RTD) titled "No one should be left behind amid the Continuing Pandemic - Facilitating the implementation of the Rare Disease Law for 2022." RTD gathered stakeholders from academia, government agencies, patient organizations and private sector to discuss programs and support required for effective utilization of the allocated funds and opportunities for collaboration better implementation of the Rare Diseases Act. [REF]
- REF - Virtual Round Table Discussion: Theme: No one should be left behind amid the continuing pandemic - facilitating the implementation of the Rare Disease Law for 2022. The Stratbase ADR Institute. 27th Jan 2022.

4.5.2. Access & pricing of orphan drugs

Like Singapore's Named Patient Basis scheme, the Philippines has a Compassionate Use scheme. The scheme allows importing of orphan drugs on a named-patient basis prior to product registration. The process takes between 3-6 months. The applicant is required to obtain a Compassionate Special Permit (CSP) from the Director of FDA, which provides restricted use of an unregistered drug.

Orphan drug designation is given to drugs which is used for patients with rare diseases but there should be no existing drug available in the Philippines with similar effect. Currently, Orphan drug act is under consideration by the government.

Figure 6.Shows the timeline of the progress in the field of rare disease in Philippines



Abbreviation: NBS= Newborn Screening, RA= Republic act, RDMAP = Rare disease medicine access program, DoH = Department of health, UP **NIH=** University of the Philippines national institute of health.

4.5.3. Key stakeholders involved in improving rare disease status in Philippines

Table 15.Key stakeholders in the area of rare diseases in Philippines

Organization	Established	Key stakeholder	Objective/Purpose
Department of Health (DoH)		Secretary -. Dr.Francisco Duque III	- Government body responsible for legislations to support RD patients.
Philippines Society for Orphan Disorders Inc. (PSOD) *{https://www.psod.org.ph/}*	2006	Founding chair - Dr Carmencita David Padilla President - Cynthia Magdaraog	- NGO which works for the welfare of rare disease patients in Philippines.
Pharmaceutical & Healthcare Association of the Philippines (PHAP) *(http://www.phap.org.ph/index.php)*	1946	Executive director - Teodoro B. Padilla	- PHAP and its member companies represent the research-based pharmaceutical and health care industry.

Abbreviation: RD= Rare disease, NGO = Non-governmental organization

4.6 THAILAND

4.6.1. Introduction

In Thailand, no official definition of rare diseases is outlined by health authorities, but a definition by the Office of Royal Society is accepted and according to which, rare disease is defined to affect 1 in 2500 people or less. Approximately, 6% (3.5 million) of the entire Thailand population is affected with rare disease. The total prevalence rate of rare diseases is equivalent to that of diabetes. Rare disease patients face many challenges which includes lack of specialists, delayed diagnosis as well as the lack of medication and newborn screening. 97% of the newborns are screened in Thailand. Social welfare benefits do not cover rare diseases. Only 22 rare diseases medical experts are present nationwide and 17 of which are in Bangkok (163].

It is well established that in SEA region no national registries exist so far. At best some of these countries have either separate lists or databases in individual institutions or hospitals. Thailand is one of the very few nations which has proposed plans to create a nationwide database of lysosomal storage diseases (LSDs). In terms of research, limited funding is available. However, there is a Thailand Center of Excellence for Life Sciences (TCELS) which is actively working to strengthen the infrastructural and research efforts in the country in life science and biopharmaceuticals (164].

Year2012

- Even without a legislative framework for rare diseases or orphan drugs, the recognized definition of the disease has led to the inclusion of the Orphan Drug List into Thailand's National Drug List in 2012 (165]. National Drug List consists of 50 orphan drugs. Procurement process of medicines in the country is decentralized and is undertaken by individual health facility or hospital. Only few high-cost and orphan medicines are centrally supplied and funded by the Government Pharmaceutical Organization (GPO) on behalf of National Health Security Office (NHSO) (166].
- Sanofi Genzyme (PAL fund) granted a fund of USD $10,000 to the Genetic LSD Foundation of Thailand to support LSD community especially in the underserved areas of the country. The grant was used to facilitate communication amongst patients, physicians and the advocacy group. Further, these funds allowed LSD foundation to create a database for continuous dissemination of vital information to LSD patients for optimal care (167].

Year2015

- The Care-for-Rare Foundation, along with the Chulalongkorn University of Bangkok, has initiated a "German-Thai alliance for better care of children with rare diseases" in order to raise more awareness for rare diseases in South East Asia. The foundation hosted its first international "European-South-East-Asian (PID) Meeting: From Bench to Bedside" in January 2015 in the Thai capital (168].

Year2016

- Thailand Rare Disease Network (ThaiRDN) established as a pilot project with aim to develop service platform and share resources to assist the rare disease community.

- In November 2016, special seminar on rare disease policy was held and was attended by various stakeholders including Thai Ministry of Public Health (MOPH), NHSO, clinical geneticists and patient groups [169].

Year2017

- The Newton Fund by UK, a research fund of£ 1 million (USD $ 1.3 million) was awarded for the best research and innovation to promote economic development and social welfare in developing countries. Four countries are eligible for the funds which includes India, Thailand, Malaysia and Vietnam, respectively. Individual project may receive funds up to£ 200,000 (USD $ 261,400) to advance their research.

  The UK-Thailand Research and Innovation Partnership Fund, established in 2017, was the first official research and innovation partnership programme between the UK and Thai government. One of the awarded projects has successfully identified around 100 undiagnosed cases of rare genetic diseases in children. The collaboration aims to speed up the diagnosis of the rare genetic diseases from an average of 7 years to only 2 weeks.

  Under this partnership both the countries agreed upon five priority area of mutual interest including- health and life sciences, agritechnology, future cities, environment and energy and digital innovation and creativity. Both countries agreed to invest at least Bt 1,200 million (USD $ 37 million) from 2014 to 2021 [170].

4.6.2. Birth defect prevention and treatment efforts in Thailand

A pilot project for birth defect prevention and treatment led by Prof. Pornswan Wasant was established in 2008, whereby Thailand Task Force on Birth Defects and Disabilities was organized. Birth Defects Association (Thailand) received funding from ThaiHealth Promotion Foundation with following major outcomes:

During 2011-14:

1. Pilot program on Birth Defects Registry (BDR), initially developed as case record form (CRF) and later into online BDR in 22 out of 77 provinces
2. Development of health district models to integrate a holistic approach on prevention and care for 5 selected diseases (down syndrome (DS), neural tube defects (NTD), cleft lip palate (CLP), limb anomalies (LA) and Duchenne muscular dystrophy (DMD)) in 11 health districts
3. Completed manual and care map for selected diseases for provincial and community hospitals
4. MoU was signed in 2012 between 4 ministries (health, education, social welfare and human security) and 2 internal organizations (NHSO and ThaiHealth Promotion Foundation) including Birth Defects Association (Thailand)
5. Development of national network with involvement of pediatrician and obstetricians from 8 medical institutions
6. Development of country action plan jointly by Department of Medical Services and Ministry of Public Health
7. Working with stakeholders and policymakers at national, provincial and local level.

Plans during 2015-17:

1. Working towards national policy
2. Reinforcing the holistic approach in 26 health districts including Bangkok
3. Increasing awareness for the birth defect prevention using folate supplementation in females of child bearing age especially in secondary school girls [171].

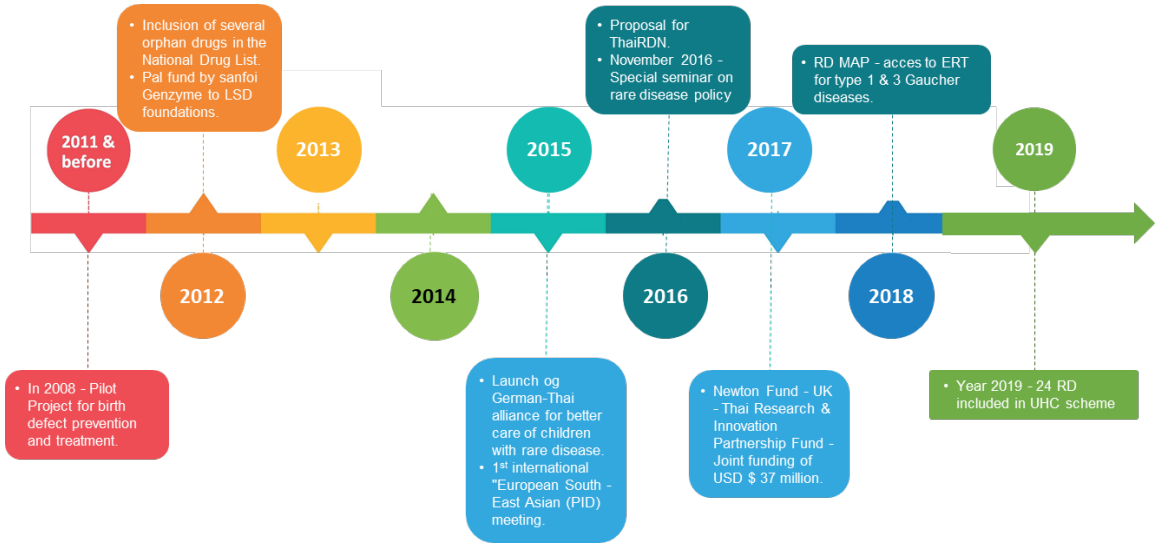
During 2019-22:

1. In 2019, Thailand took it first step towards improving access to RD drugs by adding at least 24 diseases into the UHC scheme, to enable patients to access to early treatment. [REF 1]
2. The Notification of the Ministry of Finance RE: Reduction of Tax and Exemption of Import Duties No.3, published in the Government Gazette on March 23, 2020, listed orphan drugs to be exempted from duty tax. [REF 2]
3. In Jan 2022, Thailand hosted its first "Southeast Asia Rare Disease Summit" under the theme of 'Bringing Rarity to Reality, to raise awareness, discuss and find solutions to issues related to rare diseases in the region. [REF 1]
4. REF 1- https://www.thaipbsworld.com/about-3-5-million-thais-who-suffer-from-rare-diseases-have-no-access-to-treatment/
5. REF 2- https://pharmaboardroom.com/legal-articles/orphan-drugs-and-rare-diseases-thailand/

4.6.3. Access and pricing of orphan drugs

Most orphan drugs are not available in Thailand and are imported which makes them highly unaffordable. These drugs are not covered by the country's universal healthcare scheme [172,173]. Given the fact that orphan drugs are often not reimbursed or covered in Thailand, it is both surprising and appreciative effort on the government's part to provide Hemophilia and Gaucher disease treatment to patients. One of the major issues that affect the orphan drug funding is inconsistent method of cost-assessment [173]. In Thailand, in 2016, the cut-off incremental cost-effectiveness ratio was fixed to be below THB 160,000 per quality-adjusted life year (QALY). Surprisingly, for type 1 Gaucher disease, there budget impacts and equity issues which made funding for this disease a positive economic choice, regardless of the high ICER which was THB 6,300,000 per QALY or 40 times higher than the ICER cut-off. This has established to be a positive move for orphan drug funding and points to the fact that while making decisions for such drug funding's, cost-effectiveness is not the only parameter to be considered. Several other factors such as participation of different stakeholders, strong government commitment for the cause, establishment of guiding methods and procedure and solid enforcement should be deliberated. The progress in Thailand's orphan drug market access will increase awareness in funding bodies across the SEA region [1].

Figure 7.Shows the timeline of the progress in the field of rare disease in Thailand



Abbreviation:ThaiRDN = Thailand rare disease network.

4.6.4. Key stakeholders involved in improving rare disease status in Thailand

Table 16.Key stakeholders in the area of rare diseases in Thailand

Thalassemia Foundation of Thailand *(http://www.thalassemia.or.th/)*	1989	President - Prof Em Khunying Soodsarkorn Tuchinda	- Foundation to support thalassemia patients and support funding for research.
Thai Rare Disease Foundation (Thai RDF) *(http://www.thairdf.com/)*	2016	President - Preeya Singhnarula	- An umbrella organization to help and support patients with different rare diseases.
Genetic LSD Foundation *(http://www.lsdthailand.com/lsd_news/25550819.htm)*	2009	President - Boon Putthipongthanachot	- Advocacy and support group for LSD patients and their families
Thailand Center of Excellence for Life Sciences (TCELS) *(http://www.teels.or.th/)*	2004	Chairman - Dr SakarindrBhumiratana	- To support and promote life sciences, research and innovation etc.

Abbreviation: LSD= Lysosomal storage disorder.

4.7 VIETNAM

4.7.1. Introduction

Vietnam is one of the South East Asian regions with low GDP per capita of USO 1775 and low health expenditure per capita of USO 142 compared to its counterparts such as Singapore, Taiwan etc. The country is also known for its high mortality rates (19.5 per 1000 live births). This region has very limited healthcare benefits for the population with no rare disease and orphan drug policy.
Rare diseases awareness is inadequate and there is no official definition of the disease. As per National Hospitals of Pediatrics (NHP) or now known as Vietnam National Children's Hospital (VNCH), Vietnam is known to have about 100 out of more than 7,000 rare diseases [174]. However, the number of patients suffering with rare diseases is unknown due to lack of a national registry.

Year 2011 and before

- In 2000, Vietnam joined the World Federation of Hemophilia (WFH) as a national member organization (NMO) and in 2001, the bilateral cooperation began to expand the limited bleeding conditions treatment and care services in the country.
- In 2011, the Hemophilia Treatment Centre (HIC) Twinning Program of the WFH was established between the National Institute of Hematology and Blood Transfusion (NIHBT) and Alfred hospital, Australia. Australian HTC helped establish a NIHBT comprehensive care team to attend patients from Hanoi and northern provinces along with raising awareness about the disease across the country.
- Another Twinning Program by WFH was undertaken to support the Vietnam Hemophilia Association (VHA) in partnership with the Irish Haemophila Society [174].

Year 2013

- In 2013, the National Center for Newborn Screening and Management of Rare Diseases was opened at the National Hospital of Pediatrics. Currently, 31% of the newborns are screened in Vietnam. The screening is done for free and is funded by government.

Year2014

- In November 2014, a major milestone was achieved by the community of rare disease patients in Vietnam, with the launch of the country's first Rare Disease Patient Club by the NHP. NHP is the only hospital in the country which provides LSD treatments in the northern provinces [174].

Year2016

- In Thanh H6a, Vietnam, on September 21, 2016, Global Alliance for Progress (GAP) Program (2016-19) a MoU was signed between the MoH of the Socialist Republic of Vietnam - NIHBT and the WFH. Before 2001, very few hospitals in Vietnam (Hanoi, Ho Chi Minh city and Hue) provided basic care for hemophila patients. The estimated prevalence of Hemophilia in the country is around 6000 patients and until 2016, only 2400 patients were identified.

The main objective of GAP program is to identify 1000 new patients with hemophilia and related bleeding disorders. In addition, the program aims to establish a national registry supported by MoH. The program will also help to expand the care services of the network of seven HTCs in Hanoi, Ho Chi Minh City, Hue, and Can Tho through staff training. In addition, ten satellite HTCs and ten VHA chapters will help provide basic care, help procure factor concentrates through a national tender, and reduce state insurance co-payments for factor concentrates. The GAP program is funded by companies such as Bayer, Biogen, Biotest, CSL Behring, Grifols, Kedrion, Novo Nordisk, Pfizer, Shire and Swedish Orphan Biovitrum [175,176].

Year2017

- Effective from 2017, Vietnam's New Pharmacy Law, which was approved by the National Assembly is an effort to bring real change in Vietnam's local healthcare market. Key initiatives under this law includes: 1) removal of the country's local clinical trial requirement, 2) introduction of patient assistance programs and 3) prioritization of orphan drugs. Amongst Association of Southeast Asian Nations (ASEAN) countries, it takes the longest time for a new molecule to enter into Vietnam market which is around~ 5.4 years after their global introduction. This when compared with Malaysia (3.2 years) and the Philippines (3.3 years) is still longer. New Pharmacy Law will enable high quality treatment and improved access to healthcare for Vietnamese rare disease patients [177].

Vear2018

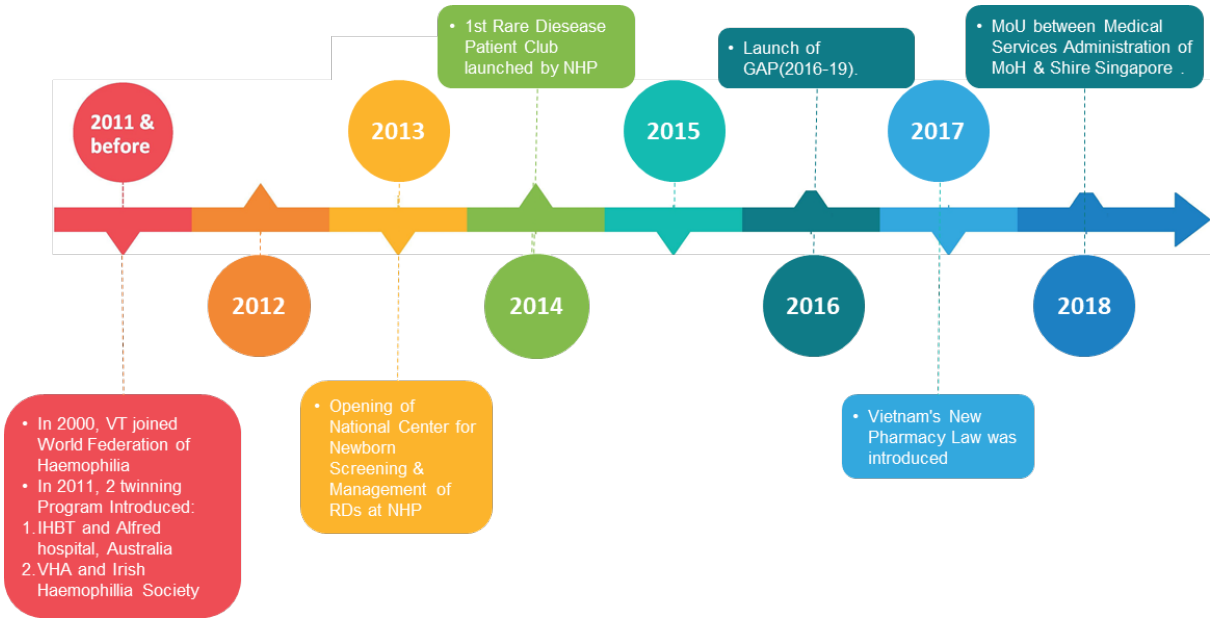
- On April 20, 2018, Medical Services Administration of MoH and Takeda Singapore signed a joint MoU to collaborate on improving the diagnosis, treatment, therapy access and management of rare diseases in Vietnam until 2023. In addition, MoU will help support education programme for medical professionals and develop a management programme for rare diseases. Hemophilia and primary immune deficiency (PID) are complex rare disorders with need for continuous research efforts and innovative treatment for positive impact on rare disease patients [178].

4.7.2. Access and pricing of orphan drugs

In the recent years, foreign investments in healthcare is encouraged by the government. However, there are too many restrictions on the type of activities that can be undertaken. For example, Vietnam is a full member of the World Trade Organization since 2007, constraints exist on the right to import and trade medicinal products and establish 100% owned subsidiaries. The establishment of innovative pharmaceuticals is also very restricted. In the past local clinical trials have been mandated for new molecules which have been launched in foreign market for less than 5 years. As a result of these restrictions, Vietnamese patients have very limited access to innovative medicine and support compared to other ASEAN countries. According to an available data, only 15% of the 143

new drug entities available globally between 2007-11 were made available in Vietnam. Lack of patient advocacy groups, government policies and universal coverage of rare diseases is a big drawback for the rare disease patients. R&D in the area is inadequate which needs support from government, research institutes and charities. However, with the introduction of several private-public partnerships (for example, Shire & Vietnam MoH) the situation is expected to change in the future [174].

Figure 8.Shows the timeline of the progress in the field of rare disease in Vietnam



Abbreviation: VT= Vietnam, NHBT = National institute of hematology and blood transfusion, VHA = Vietnam hemophila association, RD= Rare disease, NHP = National hospitals of pediatrics, GAP= Global alliance program, MoU = Memorandum of understanding.

4.7.3. Key stakeholders involved in improving rare disease status in Vietnam

Table 17.Key stakeholders in the area of rare diseases in Vietnam

Vietnam Hemophilia Association (VHA) *(http://hemoviet.org.vn/)*		
National Hospitals of Pediatrics (NHP)/Vietnam National Children's Hospital	1969	HOD, Endocrinology, medical genetics and metabolism at NHP - Dr Vu Chi Dung

Abbreviation:HOD = Head of the department, NHP = National Hospital of Pediatrics, RD= Rare disease.

4.8 HONG KONG

4.8.1. Introduction

Hong Kong has one of the world-renowned public health policies and a healthcare system of high standard. Yet Hong Kong lacks a clear definition of rare diseases or a national policy for the same. In the absence of a definition, the needs of these patients are often neglected. And as such patients cannot benefit from the current safety namely Samaritan Fund or public-funded medication. As per a report, only patients with 6 diseases receive support from the Expert Panel on Rare Metabolic Diseases, often through stringent criteria yearly on a case by case review scheme. It is encouraging to note that some pharmaceutical companies in Hong Kong are willing to invest in rare disease R&D and expensive orphan drugs. Unfortunately, such orphan drugs are not included in the Health Authority (HA) Drugs Formulary (179]. The country is also lacking in comprehensive evidence on the epidemiology and economics of rare diseases, as well as a complete and integrated rare disease patient registry. As per Hong Kong Alliance for Rare Diseases (HKARD), a patients' support group for rare disease patients and their families, estimates 7,500 rare disease patients in the city.

Year 2013

- The Chinese University of Hong Kong (CUHK) launched the territory's first screening program for inborn errors of metabolism (IEM) with a funding received from Joshua Hellman Foundation for Orphan diseases worth HK $1 million. The departments of Chemical Pathology, Obstetrics and Gynecology, as well as Pediatrics jointly launched the first newborn metabolic screening program in Hong Kong. The program can test 30 kinds of IEM. CUHK established the Centre of Inborn Errors of Metabolism in July 2013 to offerthe screening program (180].

Year 2015

- In 2015 the launch of pilot screening programme for newborn babies for inborn errors of metabolism (IEM) was announced. The scheme was launched in October 2015, and was available only at Queen Elizabeth Hospital and Queen Mary Hospital. During the first 6 months (the first phase of the scheme), 21 kinds of IEM were tested, and 3 more were included in the second phase.

Year 2016

- Rare disease gained more public awareness in Hong Kong, as evident by legislative council debates on rare disease in 2016-17.
- HKARD submitted several proposals in relation to the 2017 Policy Address and 2017-2018 Budget to the government to demand better facilities for research and treatment especially for rare diseases. Several demands have been made by HKARD in the proposal under several categories such as:

1. Diagnostic tests: At present, treatment options are available for a limited number of conditions (roughly 500 rare disorders or ~7%) and are available at limited local medical institutions at astronomical costs. Hence, there is a pressing need for better-coordinated, multi-specialist diagnostics for suspected cases of rare disease which will be supported by clinical genetics-related medical staff and their proper training for diagnosis and treatment of rare diseases.

2. Drug treatment: At present, only 6 enzyme replacement drugs and 2 rare cancer drugs are subsidized for rare disease treatment in the country and is based on the assessment of expert panel for rare genetic diseases. Funding of HK $45 million is earmarked every year to cover the costs of orphan drugs which is only 0.8% of the total medical expenditure of Hong Kong of HK $57 billion. There is a need for better use of the funding to cover other rare diseases. In addition, expansion coverage of the Health and Medical Research Fund (HMRF) should be increased to encourage rare disease medication and clinical trials. Further demands to set up an "orphan drug" mechanism has been made.

3. Patient's registry: Currently, there is a lack of national level rare disease registry, however, all the universities, medical departments and patients' group have their own sets of data, making it difficult to estimate the overall medical and social burdens of rare diseases on patients. This underscores the soaring need on governments part to make allocation of resources in the next fiscal year to enable the Children's Hospital (managed by the HA) to take the lead in coordinating a joint effort by the two medical schools in Hong Kong, in collaboration with the other hospitals, to pilot a rare-disease patients registry for selected rare diseases. Further, effective use of an electronic health-record sharing platform to gradually build a comprehensive rare-disease patients registry is a necessity of the hour.

4. Prevention and screening: In 2015, pilot screening programme for newborn babies for IEM was launched. The programme expansion to other hospitals and private medical institutions should be done. Furthermore, newborn screening should be mandated as a standard procedure in hospitals.

5. Social support: Rare disease patients should be entitled for rights to live with dignity and enjoy quality of life. This will include provisions such as case managers to support rare disease patients, optimizing the Comprehensive Social Security Assistance (CSSA) scheme mechanism (provision for patients to apply for CSSA support living with their families) and other incentives [181].

- The Comprehensive Social Security Assistance (CSSA) Scheme is designed to provide financial assistance to individuals and families in need so as to bring their income up to a prescribed level to meet their basic needs. From 1 February 2017 onwards, the amount of assistance payable per month of Normal Disability Allowance and Higher Disability Allowance is HK $1695 and HK $3390 respectively [182].

Year2018

- In March 2018, a scheme was initiated by the HKARD and other non-profit groups, respiratory specialists and a pharmaceutical company to provide free drugs for idiopathic pulmonary fibrosis, Nintedanib. The drug was registered in Hong Kong since 2016 but was not listed in the HA Drug formulary. Until now, the drug costed HK $20,000 (USD $ 2,550) a month. However, the patients still need to pay for the first two years for the treatment and afterwards free medication will be offered until patient's physician changes the prescription.

  While private patients can get the drugs from their own specialists, public patients have to bring the prescription and visit any one of the designated community pharmacies under the three charities involved, namely the Hong Kong Pharmaceutical Care Foundation, HKSKH Lady Maclehose Centre and St James' Settlement [183].

- Hong Kong to open its first children's hospital in 2018.

Year 2021-2022

- To strengthen support for RD, the Government has increased funding for the HA by $25 million from 2021-22 onwards to support Hong Kong Children's Hospital (HKCH).
- On drug subsidy, the mean test mechanism of the Samaritan Fund (SF) and the Community Care Fund (CCF) Medical Assistance Programmes in late April 2021, including modifying the calculation of annual disposable income and the validity period of financial assessment for recurrent applications. [REF]
- REF - https://www.info.gov.hk/gia/general/202105/05/P2021050500461.htm

4.8.2. Access & pricing of orphan drugs

No orphan drug legislation prevails in Hong Kong and thus many rare disease patients have limited access to prevention, diagnosis and treatment compared to other countries. From 2016 to 2017, medical and health expenditures in the city amounted to HKD $57 billion. Investment in Hong Kong healthcare has been strongly governed by criteria such as patient numbers, clinical evidence and cost-effectiveness, resulting in sizable proportion of patients being neglected by the health system, and especially has been detrimental to rare disease affected patients. At present, Under special programmes several Ultra-expensive drugs are available in Hospital Formulary for use on individual rare disease patient table 18 [184]. Only HK $45 million (0.8%) of total health care budget is spent on rare disease treatment.

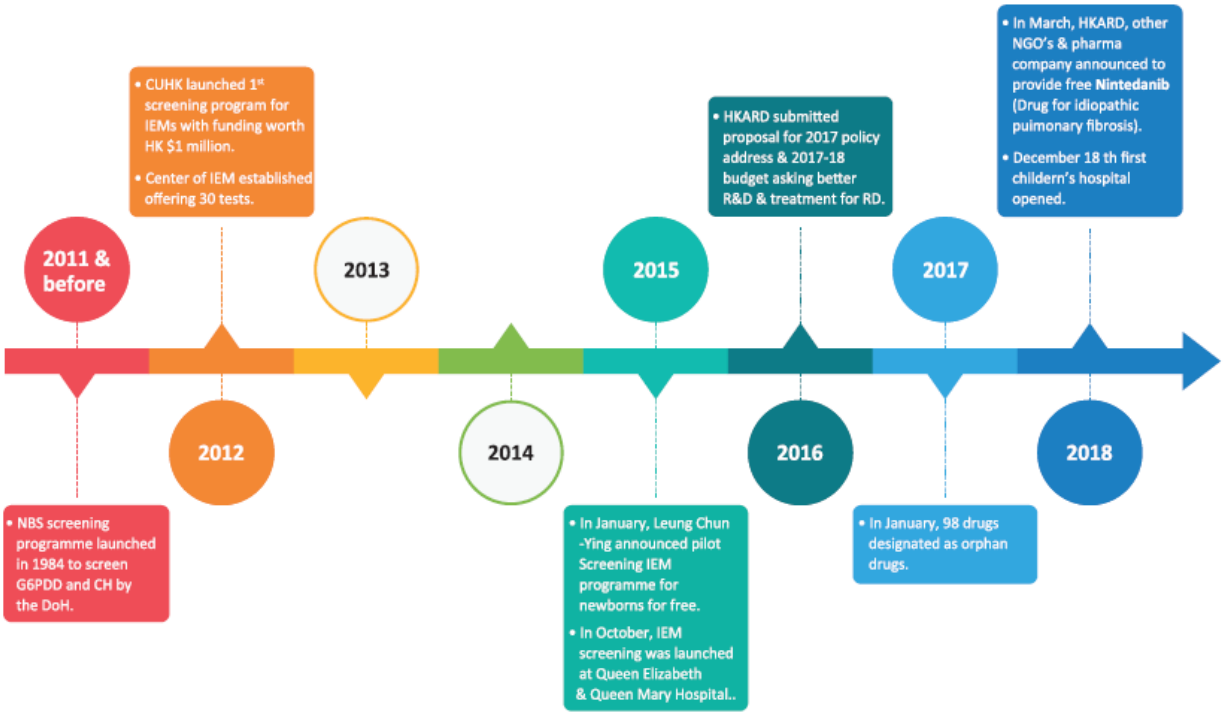
Table 18.Drugs currently subsidized in Hong Kong

Disease/Condition	Enzyme Replacement Therapy
Galsulfase	Agalsidase Alfa
Idursulfase	Agalsidase Beta
Imiglucerase	Alglucosidase Alfa
Laronidase	Dinutuximab Beta
Nusinersen	Eculizumab
Tafamidis	Elosulfase Alfa
Tafamidis Meglumine	Tisagenlecleucel

Source: [185]

As of January 2017, 98 drugs are designated as orphan drugs. Drugs which are on the list covered by the National Health Insurance Administration can be reimbursed. However, the unlisted drugs can be reimbursed if approval is sought prior to drug usage [186].

Figure 9.Shows the timeline of the progress in the field of rare disease in Hong Kong



Abbreviation:NBS = Newborn Screening, RA= Republic act, RDMAP = Rare disease medicine access program, DoH = Department of health, UP NIH= University of the Philippines national institute of health.

4.8.3. Key stakeholders involved in improving rare disease status in Hong Kong

Table 19.Key stakeholders in the area of rare diseases in Hong Kong

Organization	Established	Key stakeholder	Objective/Purpose
Hong Kong Alliance for Rare Diseases (HKARD) *(http://www.hkard.org/)*	2014	President - Tsang Kin-ping	- To promote public education on RDs, policy advocacy and support and assistance of patients, families and carers.
Samaritan Fund *(https://www.swd.gov.hk/en/index/site_pubsvc/page_medical/sub_samaritanf/)*	1950	Legislative Council	- Provides financial assistance for needy patients for special needs which are not covered by the standard fees and charges in public hospitals and clinics.
Hong Kong Rett Syndrome Association *(http://www.hkrett.org/)*	2013	Chairman - Samuel Yeung Yip	- Provides support to parents of young patients of Rett syndrome.
Hong Kong Angelman Syndrome Foundation (HKASF) *(http://www.hkasf.org/en/aboutus.php)*	2016	Chairman - Rose Chang & Joe Ng	- NGO to support patients with Angelman syndrome, their families.
Tuberous Sclerosis Complex Association of Hong Kong (TSC) *(https://tscahk.word press.com/)*	2015	Founder - Rebecca Yuen	- To promote mutual and community support by fostering public understanding of the little-known disorder of TSC.
Hong Kong Neurofibromatosis Association *(https://hknfa.org.hk/)*	2016		- To support neurofibromatosis patients and families.
Hong Kong Spinocerebellar Ataxia Association (HKCAA) *(https://www.hkscaa.org/main.php)*			
Hong Kong Red Cross John F. Kennedy Centre Alumni Association *(https://www.jfkcaa.org.hk/)*			
Hong Kong Mucopolysaccharidoses & Rare Genetic Diseases Mutual Aid Group (HKMPS) *(http://www.mps.org.hk/en/)*	2005	President - Ellie Ching	- To support and educate families and patients about MPS and other RDs. To advocate for RDs and assist in R&D and other therapies.

The Hong Kong Society for Rehabilitation *(https://www.rehabsociety.org.hk/)*	1959	President - Dr David Fang	- They promote rehabilitation and empowerment of people with disabilities or health conditions through innovations.
Joshua Hellman Foundation for Orphan Disease *(http://www.jhforphandisease.org/)*		Founder - Christina Hellmann	- To advance the awareness, diagnosis, treatment and research of RDs, and improve the welfare of children with RDs.
Hong Kong Credible Care Volunteers Association Limited			
Sudden Arrhythmia Death Syndromes Foundation			
Lawmaker		Fernando Cheung Chiu-hung	- Advocates implementing policy for rare diseases.
Rare Disease Expert		Lam Ching-wan's	- Proposed rare disease definition - A patient who has undergone most medical tests but not diagnosed after three months should be recognized as a rare disease patient, enabling them to receive treatment more quickly.
Path of Democracy & Executive Director of the Hong Kong Academy of Politics & Public Policy		Raymond Mak	- Supports and advocates the rare disease related issues.

Abbreviation:RDs = Rare diseases, MPS= Mucopolysaccharidosis

4.9 INDONESIA

4.9.1. Introduction

Indonesia is one of the countries in the APAC region which is lagging far behind in healthcare system. Rare disease is not officially defined and no legislation for rare disease or orphan drug is established. Patients with rare diseases lack access to proper medication and treatment in the region, which occasionally leads to premature death. Indonesia does not have any newborn screening policy which means higher undiagnosed cases of rare diseases and further complications. Only screening done for newborns is for congenital hypothyroidism. Total percentage of newborn screened every year is< 1%, which is very low when compared to other APAC countries [187]. Low health coverage of 48% population further adds to the trouble of limited treatment options for rare disease patients.

Year 2014

- In January 2014, the Indonesian government launched a new healthcare system policy, Badan Penyelenggara Jaminan Sosial (BPJS Kesehatan) under which all Indonesians intend to be covered by 2019. The program recognizes the need that a quarter billion of the population will need advanced medical technologies for diagnosis and treatment [188].

Year 2016

- First time in 2016, Indonesia celebrated 1'l Rare Disease Day to create awareness about the cause.

Year 2017

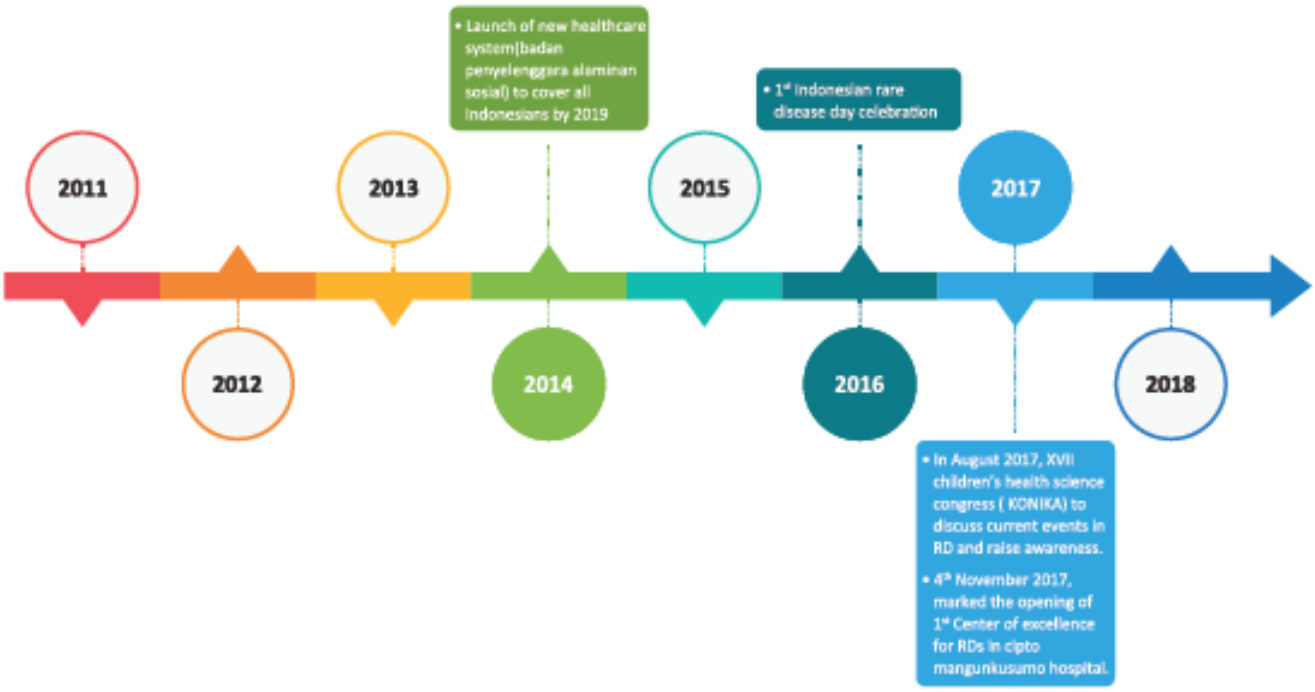
- From 8-11 August, 2017 at Yogyakarta, XVII Children's Health Science Congress (KONIKA) seminar was held. The seminar which is conducted every three years invited pediatricians from all over Indonesia to discuss about the current activities in the field of rare disease and to raise awareness about the cause. As a donation special medical formula were given for children with Maple Syrup Urine Disease (MSUD).

- On November 4, 2017, Indonesia opened its 1st Center of Excellence for Rare Diseases in Cipto Mangunkusumo Hospital. The center aims to provide its services in the form of multidisciplinary team, diagnostic laboratory in conjunction with Human Genetic Research Center and Indonesia Medical Education and Research Institute Universitas Indonesia (IMERI UI), and patient organization to support rare disease affected families [189].

4.9.2. Access & pricing of orphan drugs

Orphan drugs can be prescribed as off-label drugs. Registration of drugs or orphan drugs is a complicated and often unclear process. However, on a positive side Indonesia allows for expedited review of orphan drugs without a formal program.

Figure 10.Shows the timeline of the progress in the field of rare disease in Indonesia



Abbreviation: VT= Vietnam, NHBT = National institute of hematology and blood transfusion, VHA = Vietnam hemophila association, RD= Rare disease, NHP = National hospitals of pediatrics, GAP= Global alliance program, MoU = Memorandum of understanding.

4.9.3. Key stakeholders involved in improving rare disease status in Indonesia

Table 20.Key stakeholders in the area of rare diseases in Indonesia

Organization	Established	Key stakeholder	Objective/Purpose
Indonesia Rare Disorders (IRD) *(http://inarare.org/)*	2015		- Community with aim to support patients and families with RDs. - Increases awareness about RD via information, cooperation, advocacy and procurement of activities.
Yayasan MPS & Penyakit Langka Indonesia *(https://www.penyakitlangkaindonesia.org/)*	2016		

Abbreviation: RD= Rare disease.

4.10 NEW ZEALAND

4.10.1. Introduction

At present New Zealand does not have an official definition of rare diseases. It is due to the fact that there is no government/national policy or programme specifically designed to this category. New Zealand organization for rare disorders (NZORD) follows the EU definition of rare disease which defines it as an occurrence of 1 in every 2000 individuals (190]. Approximately, 377,000 people are known to be affected by rare diseases in the country. Currently, no national policy on rare disease or orphan drugs exist due to which no exclusive tax incentives or research grants are offered to promote the cause of rare disorders. However, New Zealand is one of the few countries with a universal coverage and subsidized medicines for its residents. Patient co-payment is only $5 and is free for children.

Newborn metabolic screening programme is in place in New Zealand for last 40 years. This programme screens newborns for free to identify metabolic disorders. When diagnosed early, treatment can be started at an early stage and helps prevent the permanent damage or debilitating effects on children. Current programme screens newborns for 20 conditions. The National Screening Unit (NSU) of the Health ministry holds the responsibility for the funding, monitoring and strategic direction of the screening programme.

Year 2012

- NZORD submitted a proposal to the National Health Committee for the development of a rare disease action plan for New Zealand.

Year 2014

- The Pharmaceutical Management Agency (PHARMA() made provisions to spend NZ$25 million over 5 years under a pilot commercial project which improved access to 9 medicines (1 more drug is under consideration) (191].

Year 2015-2016

- In an effort to identify the challenges faced by the people suffering or related to rare disorders several programmes were initiated by NZORD. In September 2015, the Patient Support group survey was launched, and the General Practitioner Survey commenced in February 2016. Outcome of both surveys was that improvements are highly sought, especially there is a need to improve educational resources which could benefit both patients and medical clinicians (190].

- During Rare Disease Day 2016 event, NZORD launched a support group named "Syndrome without a name" (SWAN) which aims to support the patients and families affected by unknown genetic conditions (192].

- Since 2003, NZORD has been recommending the government to enforce folic acid fortification of food items. This has proven to be a safe method in improving maternal health and significantly reducing neural tube defects (NTDs). Several other countries such as Australia, USA and South Africa already have schemes for mandatory fortification in place. In June 2016, New Zealand bakery industry made a significant progress with voluntary folic acid fortification of bread [193,194].

Year 2018

- In June 2018, the New Zealand government published a report titled "The health benefits and risks of folic acid fortification of food". This report aims to provide government decisions makers and the general public of the health benefits and risks on human health of folic acid fortification of food [195).

    - PHARMAC is an agency on behalf of district health boards which decides on which drugs are to be subsidized for community use. In July 2018, PHARMAC published an updated policy for assessing medicines for rare conditions, and established a commercial process seeking funding applications from pharmaceutical suppliers specifically for medicines for rare disorders [196).

- In addition, PHARMAC has been focusing on policy making and funding for orphan drugs for rare diseases. Current work is emphasizing on three areas:

  Policy- Corroborating adjusted policy settings and setting up a clinical subcommittee.

  Commercial- Call of funding proposals from medicine suppliers for better access to orphan drugs for rare disease patients.

  Stakeholder engagement- To keep stakeholders informed about PHARMAC work [197).

- On June 20, 2018, Minister of Health, David Clark sent a letter to the Chair of PHARMAC which states that one priority for the year 2018/19 is to "work on ensuring fair consideration of medicines for people with rare disorders, and in particular, progressing the initiatives identified following the rare disorders pilot" [198).

- According to NZORD recent reports, the government has decided to reduce the organization funding's which is threatening to the existence of this organization. During the election, then contesting party and now the government had promised to establish a separate fund of N$ 20 million (USD $14.6 million) for 4 years to allow rare disease patients access to vital and life-saving medicines [190).

- PHARMAC also decided to widen access to previously funded ERT for the treatment of Gaucher's disease. Tagliglucerase is to be introduced in the system from August 1, 2018 and will replace the current funded treatment of imiglucerase.

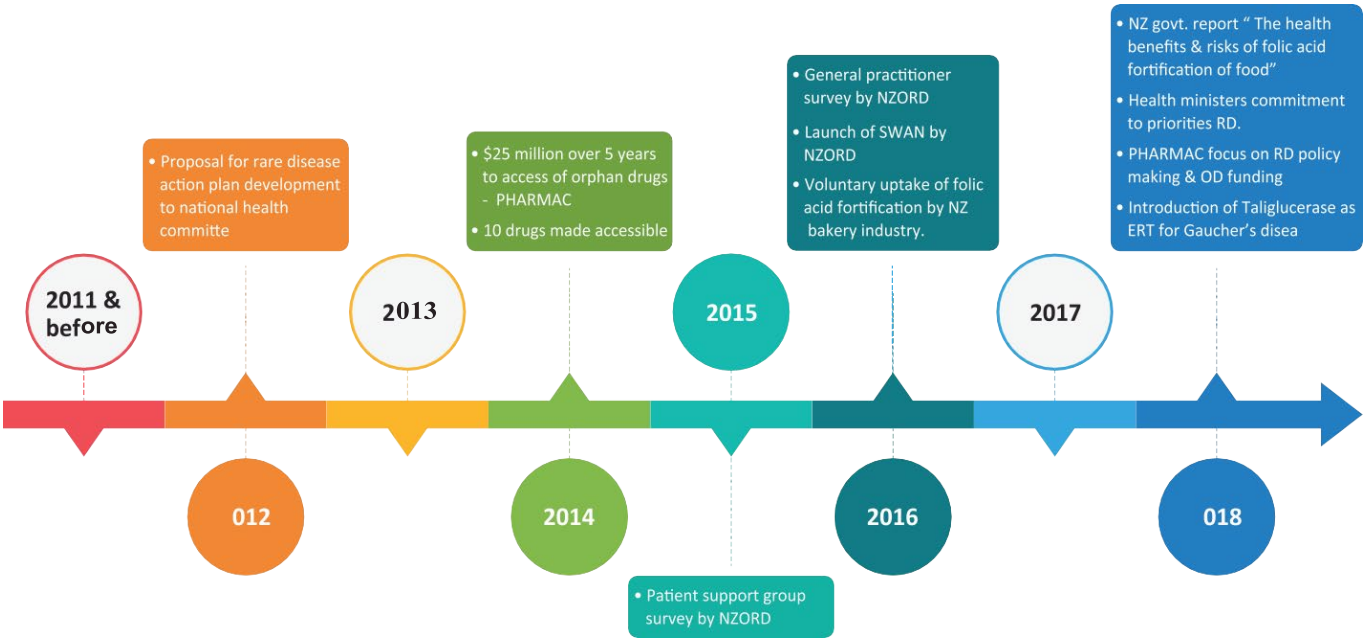
4.10.2. Access & pricing of orphan drugs

Currently, the only way for reimbursement of orphan drugs in New Zealand is through getting the drugs listed on Pharmaceutical Schedule which is decided by PHARMAC. Decision as to which drugs will be included in the schedule is dependent on two factors: cost-effectiveness and affordability. Given the high costs of orphan drugs they are often denied a place in the list, making it difficult for the rare disease patients to access them.

Another way for rare disease patients to access certain drugs is via applying for Named Patient Pharmaceutical Assessment (NPPA). Patients can apply for NPPA when the required drug is not listed in the pharmaceutical schedule. This application is made by a clinician. Criteria's exist to be considered under this application and assessment is then done. Once approved the clinician is informed of the decision [199).

AFT pharmaceuticals is one of the limited number of local pharmaceuticals which are committed to the development of orphan drugs. AFT has been integral part of establishing the Asia Pacific Orphan Drug Alliance (APODA) which is comprised of pharmaceutical companies operating within this region who have expertise in orphan drugs [200). Research funds for rare diseases are limited in the country.

Figure 11.Shows the timeline of the progress in the field of rare disease in New Zeal and



Abbreviation: PHARMAC = Pharmaceutical management agency, NZORD = New Zealand organization for rare disorders, SWAN= Syndrome without a name, NZ= New Zealand, RD= Rare disease, ERT = Enzyme replacement therapy.

4.10.3. Key stakeholders involved in improving rare disease status in New Zeal and

Table 21.Key stakeholders in the area of rare diseases in New Zealand

Organization	Established	Key stakeholder	Objective/Purpose
New Zealand Organization for Rare Disorders (NZORD) *(https://www.nzord.org.nz/)*	2000	Chief Executive - Lisa Foster	- National organization which supports New Zealanders living with rare diseases and their families.
Lysosomal Disease New Zealand (LDNZ) *(https://www.ldnz.org.nz/)*	2000	Chairman - John Forman	- A charitable trust dedicated to improve contact between families affected by LSDs within NZ, and supporting research into the causes and treatment of LSDs and improvements in the clinical care of affected people.
Syndromes Without a Name (SWAN) *(http://www.swannz.org.nz/)*	2016		- Support group for NZ patients and families affected by an undiagnosed genetic condition. - Launched by NZORD.
Pharmaceutical Management Agency (PHARMAC) *(https://www.pharmac.govt.nz/J*	1993	Chief-executive - Sarah Fitt Stuart Mclauchlan David Clark a	- Entity which decides on behalf of District Health Boards, which medicines and pharmaceutical products are subsidized for use in the community and public hospitals.
AFT Pharmaceuticals		-	

Abbreviation: NZ= New Zealand, LSDs = Lysosomal diseases

4.11 AUSTRALIA

4.11.1. Introduction

Australia is one of the countries in the world with some of the best practices for rare diseases. However, no official definition has been presented by the government but Australian Therapeutic Goods Administration (TGA) defines rare diseases as a condition which affects not more than 2000 individuals or the equivalent of 1 in 10,000 people in Australia at any time [201]. As per Department of Health (DoH), about 1.2 million residents in Australia are affected by rare diseases and approximately 400,000 of those are children.

Year 2011 and before

- Since 1995, Life Saving Drugs Program (LSDP) is providing subsidized drug access to rare disease patients.
- Orphan drug policy was established back in 1997 in Australia to support manufacturers to overcome the hurdle of high cost orphan drugs so patients can have better access to available treatments.

Year 2012

- Australia's National Alliance for rare disease, Rare Voices Australia (RVA) was established in 2012, which brings together 200 patient organizations to raise a unified voice for health policy and a healthcare care system for people living with rare diseases.

Year 2015

- In Western Australia, Office of Population Health Genomics (OPHG) was established by DoH to incorporate newly gained genomic knowledge into the public health system. A significant landmark was achieved by OPHG with the presentation of 1st rare diseases strategy "Western Australia Rare Diseases Strategic Framework 2015-2018". The strategy has 4 main focus points: [202]

  1. To advance rare diseases planning in WA and rest of the Australian territories
  2. To promote patient-specific approach for rare disease patients
  3. To provide high-quality health and support system for patients and their families
  4. To promote world-class research for rare diseases

- During 2015-2016 Budget in Victoria, the government assigned AUD $25 million to advance a state-wide genomic sequencing programme. The funding was allocated to Melbourne Genomics health alliance which included seven different facilities to ensure early diagnosis of rare disease conditions for up to 2500 children and adults.

Year 2016

- In 2016, Australian patients got access to world-class technology called gene sequencing in order to receive more accurate diagnosis of their rare condition. The technology is available at Sydney's Garvan Institute but it can be outsourced however, the facility is available to limited population. More importantly, diagnosis which takes years now can be done in 8-12 weeks. As per Garvan institute this service could potentially triple the diagnosis rate of rare disease from 20% to 60% [203].

Year 2017

- Rare Voices Australia (RVA) established a National Alliance of Rare Disease Registries following the impetus from the publication of an article in the Internal Medicine Journal in 2017 [204]. This umbrella organization aims to:
  1. Unify existing rare disease registries in Australia
  2. Create National rare disease registry standards for better cooperation amongst different registries
  3. Workout strategies to get sustainable funding from sources such as government bodies and others to support current and new registries.
- In June 2017, RVA put forward a National Rare Disease Framework: 6 Strategic Priorities [205,206].
- Newborn bloodspot screening has been existent in Australia since 1960's. The screening has evolved over time and currently newborns are screened for more than 25 conditions and the facility is offered free of cost to the newborns under government-funded public health service. However, in 2017 Newborn Bloodspot Screening National Policy Framework was put forward to help deliver and support the screening [207,208].

Year 2018

- On January 24, 2018, the Australian government announced an investment of AUD $69 million in funding for research in rare cancers and rare diseases. The funds allocated includes: AUD $26 million for 19 projects under Medical Research Future Fund's "Rare Cancers, Rare Diseases and Unmet Needs Clinical Trials Program", AUD $10 million call for research into rare diseases and cancers is expected soon and an additional AUD $33 million will be provided next year to further the research [209].
- On January 28, 2018, the Turnbull Government announced its commitment to retain and improve the LSDP. The decision includes to provide ongoing access to eligible patients and to consider new medicines that include a fit-for-purpose clinical effectiveness and cost effectiveness assessment. The reform was supported by Health Minister Greg Hunt MP [210].
- RVA hosted its biennial National Rare Disease Summit on 16-17 November 2018. The summit aims to establish the role of rare disease policy in transforming lives of rare disease patients and how collaboration will support in effective implementation and improvement of the policy. In addition, role and participation of general physicians (GPs) in care coordination, preventive care and enhancing life of rare disease patients was on the agenda. This will emphasize on their part in any initiatives which is undertaken nationally to improve the diagnosis and management of rare diseases [211].

Year 2020

- On February 2020, Australia launched the National Strategic Action Plan for Rare Diseases (Action Plan) as a first concerted effort to address rare diseases in Australia. The Action Plan has three pillars - Awareness and Education, Care and Support, and Research and Data. Australian government has committed to provide AUD 3.3 million for activities to implement the Action Plan. [REF 1]
- REF 1: Department of Health, National Strategic Action Plan for Rare Diseases, Canberra, www.health.gov.au/resources/publications/national-strategic-action-plan-for-rare-diseases, viewed 05 February 2022.
- In May 2020, the National Health Reform Agreement (NHRA) was signed between the Australian government and all state and territory governments as a commitment to provide better and coordinated care to rare disease community. The 2020-25 NHRA addendum provides ensures Australians get access to new, life-saving highly specialised therapies in public hospitals. The funding will be split 50 per cent Australian government and 50 per cent local government. [REF 2]
- REF 2: Department of Health, National Health Reform Agreement, Canberra, www.health.gov.au/initiatives-and-programs/2020-25-national-health-reform-agreement-nhra viewed 5 February 2022.

4.11.2. Access and pricing of orphan drugs

Orphan drug policy was established back in 1997, which aimed to provide better access and range of treatments for rare diseases. The programme supports manufacturers to overcome the high cost of marketing drugs which has proved to be commercially unviable because of small patient population. The characteristic features of the orphan drug policy are [212]:

1. Provides a legal outline for orphan drug designation,
2. Waiver of application fee and no annual registration fees for orphan drugs,
3. 5-year exclusivity time-period

Orphan drug designation exists in Australia and there is a list of drugs which have received orphan drug designation prior to July 2017 (213]. However, no market exclusivity (other than what is given for other drugs) and financial incentive is offered such as fee reduction for marketing authorization approval. Some non-financial incentives are accessible including pre-licensing access and regulatory assistance. Pricing for drugs is fixed.

In Australia, drugs and treatments are usually funded by Pharmaceutical Benefits Scheme (PBS). Drugs are included in PBS based on their cost-effectiveness. However, treatments for rare diseases do not meet the criteria for inclusion in PBS and hence they are funded under other scheme, the Life Saving Drugs Program (LSDP). In 2016-17, the program.....nine rare disease conditions. WITH "In 2018-19, LSDP has supported 430 patients with a total cost of AUD $133.6 million. At present LSDP funds sixteen medicines to eligible patients at zero cost for the treatment of ten rare disease conditions. **(see Table 21)** (214].

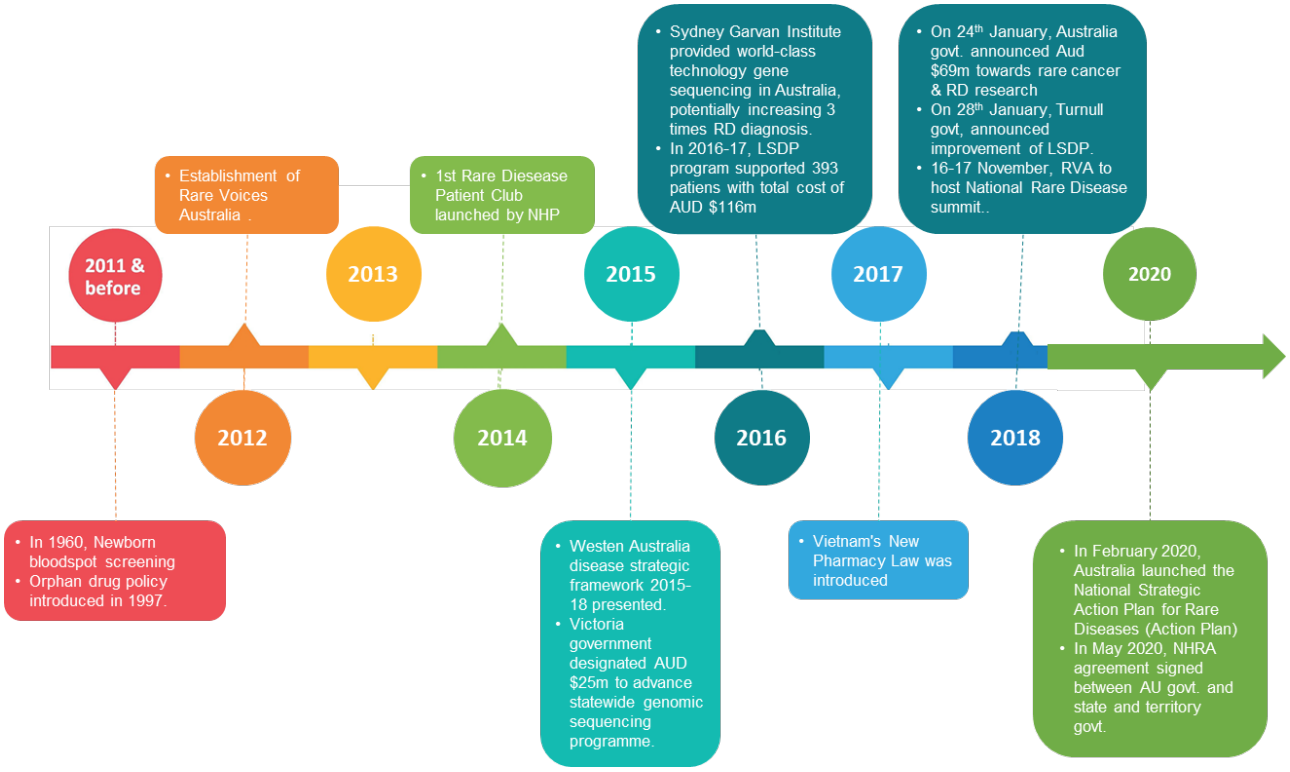
Even though Australia has a world leading health system, waiting time for patients to access orphan drugs in Australia is 2-4 years longer than for countries such as the UK, Canada, Germany and the Netherlands. In certain cases, it can be as long as 8 years after their launch overseas [216]. There is a multi-criteria decision analysis is necessary to decide on the orphan drugs being reimbursed.

Table 22.List of drugs funded by Life-saving drugs program {LSDP)

	Disease condition	Drug	Brand name
1	Gaucher disease (Type 1)	Imiglucerase Velaglucerase Taliglucerase Miglustat	Cerezyme® VPRIV® Elelyso® Zavesca®
2	Fabry disease	Agalsidase alfa Agalsidase beta Migalastat Galafold ®	Replagal® Fabrazyme®
3	Mucopolysaccharidosis type I (MPS I)	Laronidase	Aldurazyme®
4	Mucopolysaccharidosis type II (MPS II)	Idursulfase	Elaprase®
5	Mucopolysaccharidosis type IVA (MPSIVA)	Elosulfase alfa	Vimizim®
6	Mucopolysaccharidosis type VI (MPS VI)	Galsulfase	Naglazyme®
7	Infantile-onset, juvenile late-onset or adult late-onset Pompe disease	Alglucosidase alfa	Myozyme®
8	Paroxysmal nocturnal haemoglobinuria (PNH)	Eculizumab	Soliris®
9	Hereditary tyrosinaemia type I	Nitisinone	Orfadin®
10	Later-infantile onset Batten disease	Cerliponase alfa	Brineura®

Source: [215]

Figure 12.Shows the timeline of the progress in the field of rare disease in Australia



Abbreviation: RD= Rare disease, LSDP= Life-saving drugs program, RVA= Rare voice Australia

4.11.3. Key stakeholders involved in improving rare disease status in Australia

Table 23.Key stakeholders in the area of rare diseases in Australia

Organization	Established	Key stakeholder	Objective/Purpose
Rare Voices Australia (RVA) *(www.rarevoices.org.au)*	2012	Chair - Joanna Betteridge	- RVA is an advocacy, education, public awareness group.
Australian Pompe's Association	1997	President - Raymond Saich	- Supports the needs of Australian Pompe patients, families and carers.
Genetic Alliance Australia *(www.geneticalliance.org.au)*	1988	Executive Director - Jan Mumford	- Charity for peer support group and connects other families. - Educational resources and counselling services.
Centre for Genetics Education *(www.genetics.edu.au)*		Director - Kate Dunlop	- Provides education information and resources. - Information about newborn screening and genetic testing. - List of genetic services and counselling.
Steve Waugh Foundation *(www.stevewaughfoundation .com.au)*	2005	Chairman - Bob Mansfield	- Grant support for children and families suffering with RDs. - Fundraising and networking events.
Australian Paediatric Surveillance Unit (APSU) *(http://www.apsu.org.au/)*	1993	Director - Prof Elizabeth Elliott	- Responsible for active surveillance of uncommon rare childhood diseases, complications and adverse effects of treatment.

4.12 KOREA

4.12.1. Introduction

South Korea presently does not have specific rare disease legislation in place in, nor a national plan or strategy for rare diseases or orphan drugs, yet several actions have been initiated by the Ministry of Health and Welfare. In 2003, Korea Food and Drug Administration (KFDA) defined rare diseases as any disease which affect population 20,000 and is without appropriate treatment and substitutional treatment options [217). Orphan drug guideline was established in 2003 which specifies exclusive marketing rights for 6 years to promote R&D of orphan drugs. There is an insufficient number of rare disease specialists in Korea. As per Korean National Health Insurance (NHI) consensus, there are 500,000 rare disease patients in the country. These diseases are covered under NHI and patients only need to pay 10% of their medical expenses while the rest is covered by the insurance. Low-income families are fully covered by NHI.

Year 2011 and before

- In 1991, the Ministry of Health and Social Affairs adopted a newborn screening program which covered low-income families. The screening service was extended to cover all newborns in 1997, which tested for 6 conditions (Phenylketonuria, congenital hypothyroidism, Maple syrup urine disease, galactosemia, congenital adrenal hyperplasia and homocystinuria). The test is offered in two formats: (1) the basic version which covered the above 6 metabolic conditions and (2) a more comprehensive version which screens for a higher number of metabolic conditions(:::: 60 types). The basic version is provided free of cost under the Korean National Insurance program (for newborns not covered under NHI the test costs SKW 37,000 (USD $33)), whereas the extended version costs an additional SKW 150,000 (USD $ 132) [218,219).

- In 1998, Korea established Orphan Drug Act and legislation on orphan drug designation (Notification No. 1998-23) [220). Orphan drug designation provided exemption from re-examination after drug approval. At present, the incentives of orphan drug designation includes a fast track review for marketing approval and reduction in application fee by 50% if domestic clinical trial data is submitted [221).

- In 1999, Orphan Drug Center was established which is a non-profit organization and supplies rare disease medication. The center is supported by KFDA [222).

- Since 2001, the government introduced medical subsidy program on rare diseases. From this point on the government has expanded support for rare disease patients and endorsed a research program under which low-income patients suffering with rare diseases receive subsidized orphan drugs [223).

- The Ministry of Health established a Genetic and Rare Disease Centre in 2004. The center deals with the subsidies for medical expenses related to rare diseases, organizes national reference centres (established in 2006) and research in the field of genetic and rare diseases. The Rare Disease Centre also acts as an information centre and a helpline service for patients.

- Since 2009, NHI provided rare disease patients with financial support to strengthen the safety net and to prevent disease-driven poverty of common population. Once an individual is identified as a rare disease patient, they are entitled for reduced coinsurance rate which is 5% for registered cancer patient and 10% for the registered rare disease patients.

- A research grant for rare diseases was granted in 2008 with a funding total of KRW 8 billion (USD $ 5.5 million). The funding was meant to advance basic and clinical research in the field of rare diseases [222].

- Rare Genomics Institute Korea was established in 2011. It's based on the model similar to that of Rare Genomics USA. The objective of this organization is to develop Next Generation Sequencing-based diagnostic services for undiagnosed rare disease patients.

Year 2012

- In 2012, the Korean Rare Disease Knowledge Base (KRDK) was established, a web-based research-oriented data repository which aims to provide following services: rare disease review and research information; clinics and a laboratory directory; a mutation database; a patient registry and biobank. The database uses Orphanet as the main source of information.

Year 2014

- In early 2014, post-genome project was announced with a funding of USD 540 million to develop and commercialize new genomic technologies [224].

- Korea became one of the few countries within the APAC region with an implemented legislation for promoting orphan drugs R&D. Joint efforts by the Korea Organization for Rare Disease (KORD), lobbying amongst hospitals, and advanced clinical and genetic data exchange management technologies has led to favorable environment for the development of orphan drug developers. Still there are lot of constraints for the access of orphan drugs for rare disease patients. However, the Ministry of Health and Welfare introduced a new legislation exempting certain drugs from the 'economic evaluation'. With this, the Ministry will not hold a drug approval due to lack of clinical evidence instead it will refer to a drug's lowest price amongst the G7 countries as its base price to determine its economic value. As per the Chief of Division of Pharmaceutical Benefits, Bureau of Health Insurance Policy, Dr Sun Young Lee, the Ministry is also considering a comprehensive policy to maintain reasonable price, provide support for local companies to enter the global pharma market [225,226].

Year 2015

- On December 2015, South Korea government passed "Rare Disease Management Act" with the aim to reduce individual and social burden caused by RDs and to contribute to improving people's health and welfare by setting and implementing comprehensive policies on the prevention, treatment and research of RDs. [227]

Year 2016

- A Seoul-based startup, 3billion Inc. established in 2016, a spin-off from Korea's biggest genetic sequencing firm Macrogen, screens for over 4,000 rare diseases at once by analyzing entire genome. Currently, this is offered as the most comprehensive and cost -effective rare disease screening service as claimed by the 3billion CEO, Keum Chang-won [228, 229].

Year 2017

- On August 11, 2017, the KFDA (or now known as the Ministry of Food and Drug Safety) designated Nusinersen, for Spinal muscular atrophy and Tacrolimus, for keratoconjunctivitis as orphan drugs with the amendment of regulation on the designation of orphan drugs. The rare drug designations will place the drugs on a fast-track system giving it priority review during the drug approval process [230].

- On December 29, 2017, the Ministry of Health and Welfare announced a four-year roadmap to build a national system for the management of rare diseases by 2021. According to the plans, medical centers will be established specializing in the R&D of early diagnosis and treatment of rare diseases and medicines in the coming future. Other plans include national registration of patients of rare diseases, training of doctors and other medical staff for providing expert services in the diagnosis and treatment of rare disorders, as well as counselling for sufferers and financial assistance for patients [231].

- As per a new policy change, the Ministry of Food and Drug Safety allows for individual import and use of medical equipment for which no replaceable option is available in Korea given relevant approval has been obtained. The change was initiated by the parent of a juvenile diabetes patient who was looking for a medical equipment for the diagnosis and treatment of rare disease available in other country.

Year 2018

- As per a report by the Korea Herald, the Ministry of Health and Welfare has decided to include 100 newly designated rare diseases to the illness list which previously included 827 conditions. Beginning in January 2019, the patients will only have to pay 10% of their total medical bills. With the updated subsidy program, around 1,800 patients are expected to benefit [231).

4.12.2. Access and pricing of orphan drugs

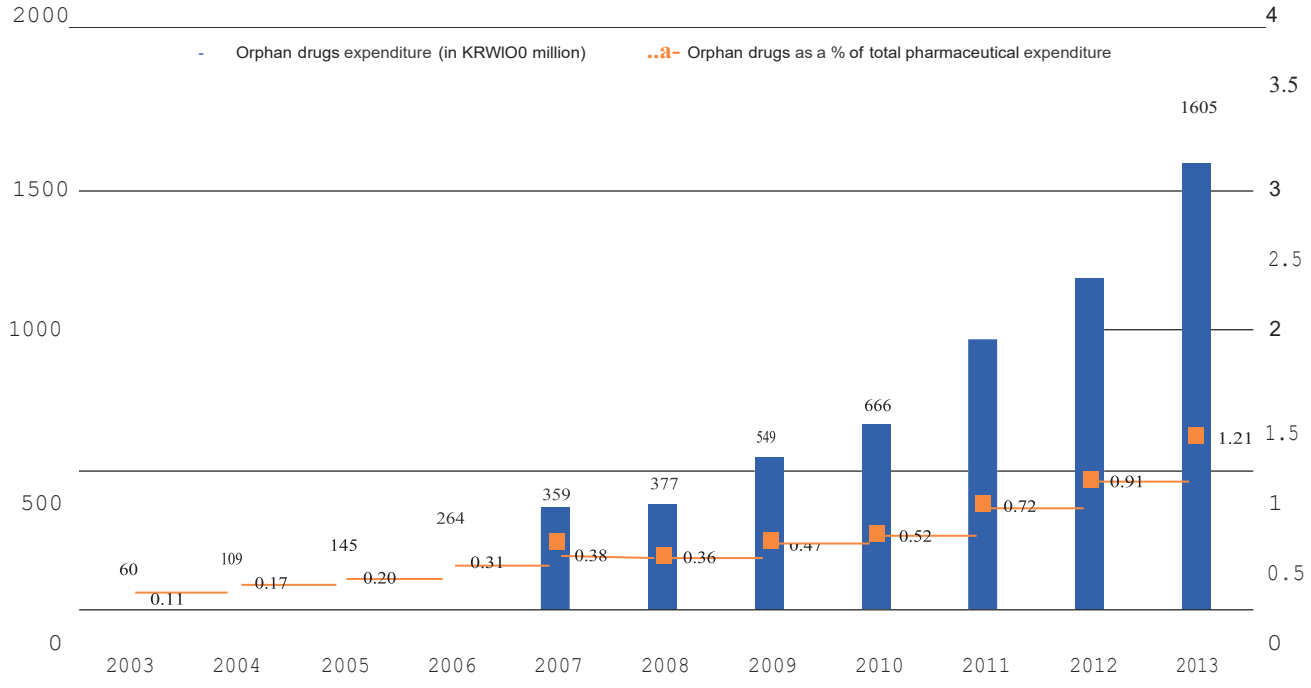
Korea has been one of the very few countries which has several pharmaceutical companies investing in orphan drugs. Green Cross Pharma, established in 1967, is only the second pharmaceutical company in the world to develop Hunterase for the treatment of Hunter syndrome. The drug was released in South Korea in 2012 and was designated as an orphan drug by the FDA in 2013. South Korea has about 70 patients identified with Hunter's syndrome still the drug showed a steady sale of SKW 23 billion (US$ 21.32 million) in 2017 with the drug priced at SKW 2 million (US$ 1,854) a bottle [232).

Another company SK Chemicals Co., established in 1969, has significantly improved existing haemophilia treatment with the adoption of a single-chain molecular structure for Afstyla for the first time in the world. The drug has entered the USA and EU markets and was allowed to be sold in Australia in 2017. IsuAbxis Co. is another Korean pharmaceutical making its way into the orphan drugs market. In 2013, the company commercialized Abcertin, a treatment for Gaucher disease and launched Fabagal, for Fabry disease in 2014. There are other drugs in the company pipeline: a novel drug for haemophilia (ISU304) and a biosimilar for heamtoglobinuria (ISU305) [232).

In addition, the Ministry of Food and Drug Safety granted orphan drug status to several drugs such as: a hemangiosarcoma treatment of Hanmi Pharmaceutical Co., a tuberculosis treatment of LegoChem Biosciences Inc., a growth hormone deficiency treatment of Genexine Inc. and a Duchenne dystrophy treatment of Bioleaders Corp. Such drugs which are granted orphan drug designation receives tax benefits on their development costs an obtain exclusivity of 6 years [233).

As per a report, currently 184 orphan drugs have been approved by the Ministry of Food and Drug Safety in South Korea [220). As per an article by Kim et al. (2013), orphan drugs expenditure in Korea has witnessed a rapid surge from KRW 6 billion in 2003 to KRW 160.5 billion in 2013 with an average annual growth of 41%. This share in terms of NHI's pharmaceutical expenses showed a growth from 0.11% to 1.21% [233).

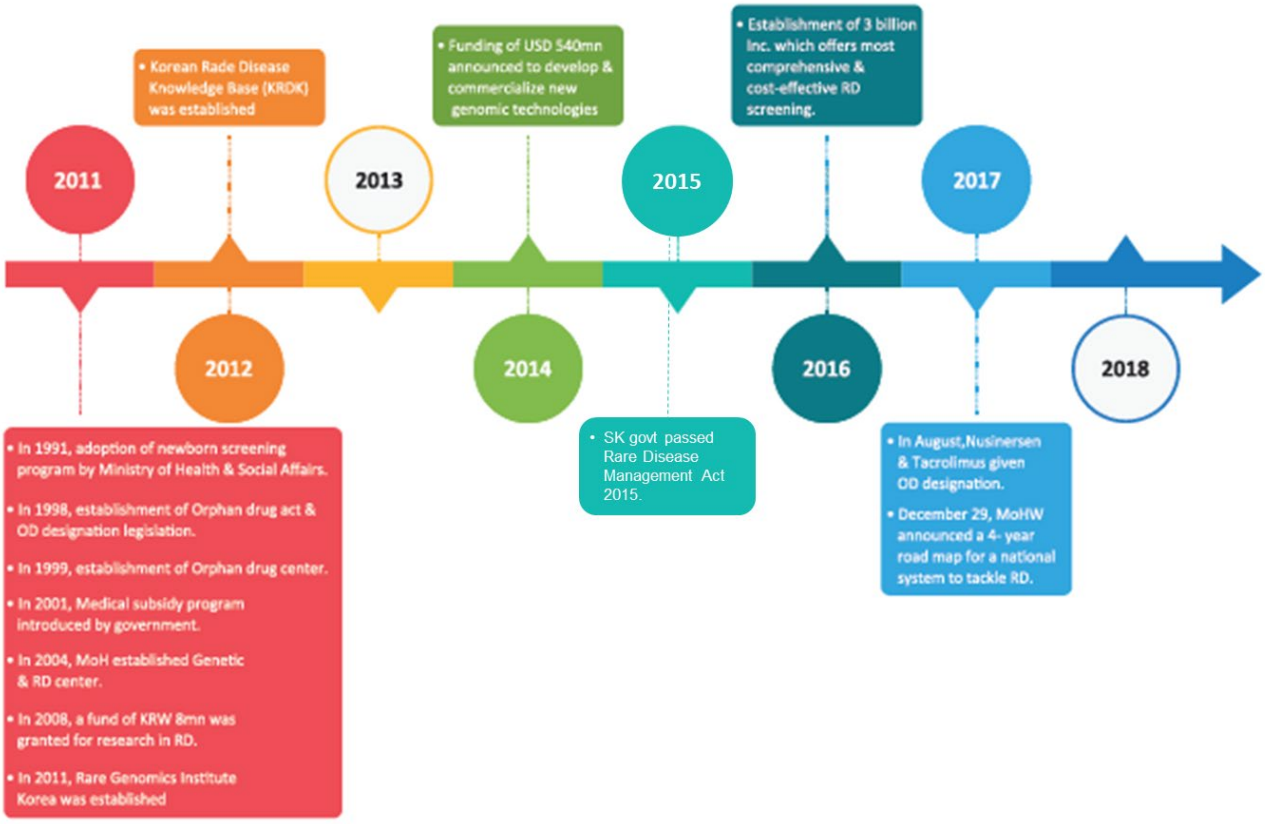
Figure 13.Orphan drugs expenditure profile in Korea, in KRW100 million between the period of 2003-13



Source: [233)

In general, Korea has reimbursed orphan drugs about one-half to two-third of the actual cost of the drug and doctor visits. Lobbying by patients and patient groups have led to some success in gaining better reimbursements for the suffering population. However, the reimbursement levels have been extremely low for some drugmakers. Shire Human Genetic Therapies attempted to negotiate with Kore National Health Insurance Company for higher reimbursement before the sale of Elaprase, a treatment for Hunter syndrome in Korea. The drug was approved for sale in Korea in 2008. The insurance company determines the extent of reimbursement on case-by-case basis and is strongly gravitated towards keeping overall medical spending on a lower side [3).

Figure 14.Shows the timeline of the progress in the field of rare disease in Korea



Abbreviation: NBS= Newborn Screening, RA= Republic act, RDMAP = Rare disease medicine access program, DoH = Department of health, UP NIH= University of the Philippines national institute of health.

4.12.3. Key stakeholders involved in improving rare disease status in Korea

Table 24.Key stakeholders in the area of rare diseases in Korea

Organization	Established	Key stakeholder	Objective/Purpose
Korean Organization for Rare Disorders (KORD) *(https://www.kord.or.kr:55308/index.php)*	2001	Manager - Jin-ah Kim	- Social welfare organization which promotes rights and welfare of RD patients - Shares information with RD community about national policy development and overseas programs
Korea Hemophilia Foundation *(http://www.kohem.org/eng/load.asp?subPage=l 10)*	1991	President -Tai-ju Hwang	- Supports and educates patients to get correct treatment - Develop their quality of life
ALS (amyotrophic lateral sclerosis- Association *(http://www.kalsa.org/)*	2001	President - Kwang-woo Lee Vice president - Jung-joo Sug	- Educates and supports patients financially - Provides inputs and assists on policies formulation by communicating with government - Encourages communication with doctors for better research and for access to novel treatments

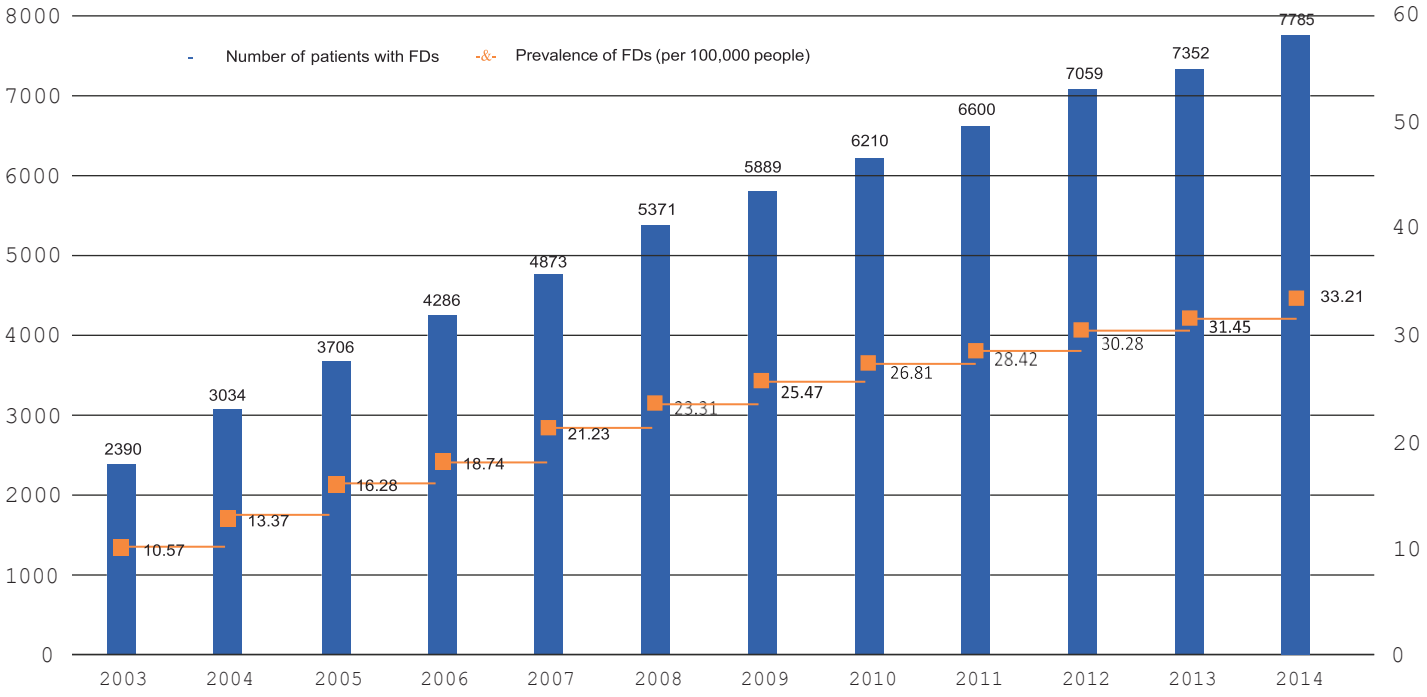
4.13 TAIWAN

4.13.1. Introduction

Rare diseases are defined in Taiwan as disorders with a prevalence of less than 1 in 10,000 individuals, which are difficult to treat and are genetic in nature. Taiwan adopted the Rare Disease and Orphan Drug Act in 2000 and became the fifth country to adopt such legislation worldwide. The act was modeled after the "Orphan Drugs Act" in the US and Japan. Taiwan Foundation of Rare Diseases (TFRD) proposed "Rare Diseases Law" from a more comprehensive perspective, covering genetics consultation, prevention of rare diseases, medical welfare, international cooperation and public awareness in addition to the topic of orphan drugs.

As per a recent publication in PLoSone, the prevalence of rare diseases and the related economic burden have increased substantially nationwide over the last decade, and these trends are likely to continue. Given the high cost of orphan drugs, drug expenditures accounted for almost 90% of health expenditures for rare diseases [234].

Figure 15.Graph representing increasing prevalence of rare diseases in Taiwan between the period of 2003-14



Source: [234]

Currently, no comprehensive specialist centres exist however, till date 11 rare disease genetic counselling centres have been approved nationwide. No national registry for rare disease is established but a national disability registry is in place and hemophilia registry is under development.

Year 2011 and before

- Enactment of Rare Disease and Orphan Drug Act in Taiwan took place in January 2000.The legislation includes topics such as R&D, orphan drugs manufacturing and their acquisition, diagnosis and treatment of rare diseases. It provides financial subsides and exclusive marketing rights (10 years) for orphan drugs. Since the implementation of act Taiwan has observed greater international cooperation and public awareness regarding the availability and accessibility of orphan drug treatments [3]. Rare disease advocacy groups played a vital part in shaping of the national policy and they also provide strong support to rare disease patients.

  Taiwanese rare disease patients are eligible to receive 80% reimbursement for orphan drugs, while low-income citizens can receive 100% reimbursement. This has made Taiwan as one of the best practice models for comprehensive rare disease management. In case of services which are unavailable in Taiwan, patients can avail subsidized access to overseas diagnostic services [235]. For international diagnostic services, subsidy is offered by Department of Health (DOH) of 40%, TFRD of 40% and remaining 20% is born by patients. In addition, Ministry of Health and Welfare (MOHW) has set up an orphan drug and nutritional supplement supply centre to provide medical institutions with specific orphan drugs and life-sustaining nutritional supplements for emergency use [236].

- Since 2001, rare disease patients were further assisted under Physically and Mentally Disabled Citizens Protection Act.

- Newborn screening (NBS) is existent in Taiwan since 1982 where children were tested for five disorders. Since 2002, TFRD has been encouraging population to take advantage of expanded NBS with nearly 30 disorders at their own expense. In 2005, ~81% newborns received expanded NBS. However, in July 2006, DOH subsidized the expanded NBS but only reveals results of 11 treatable diseases. Taiwan is one of the very few countries to offer screening for LDS disorders [237].

Year 2014

- In late 2014, Rare Disease and Orphan Drugs Act and the Nursing Personnel Act were amended. The Nursing Personnel Act is to provide additional assistance for rare disease patients, especially those in a care facility. The amendments were intended to ensure government's financial backing of supportive and palliative care for rare disease patients which is not covered by the National Health Insurance (NHI). In addition, it included provisions to accelerate the review process for necessary medications to be covered by the NHI, and to establish an emergency drug supply mechanism to combat drug shortages [212].

Year 2016

- Asper NHI, in the year 2016, 218 rare disease classifications were approved by Rare Diseases and Drugs Committee. Total of 7820 patients suffering with rare diseases were supported and a total medical expenditure of USD $ 150.13 million and total drug expenditure of USD $138.77 million respectively.

4.13.2. Access & pricing of orphan drugs

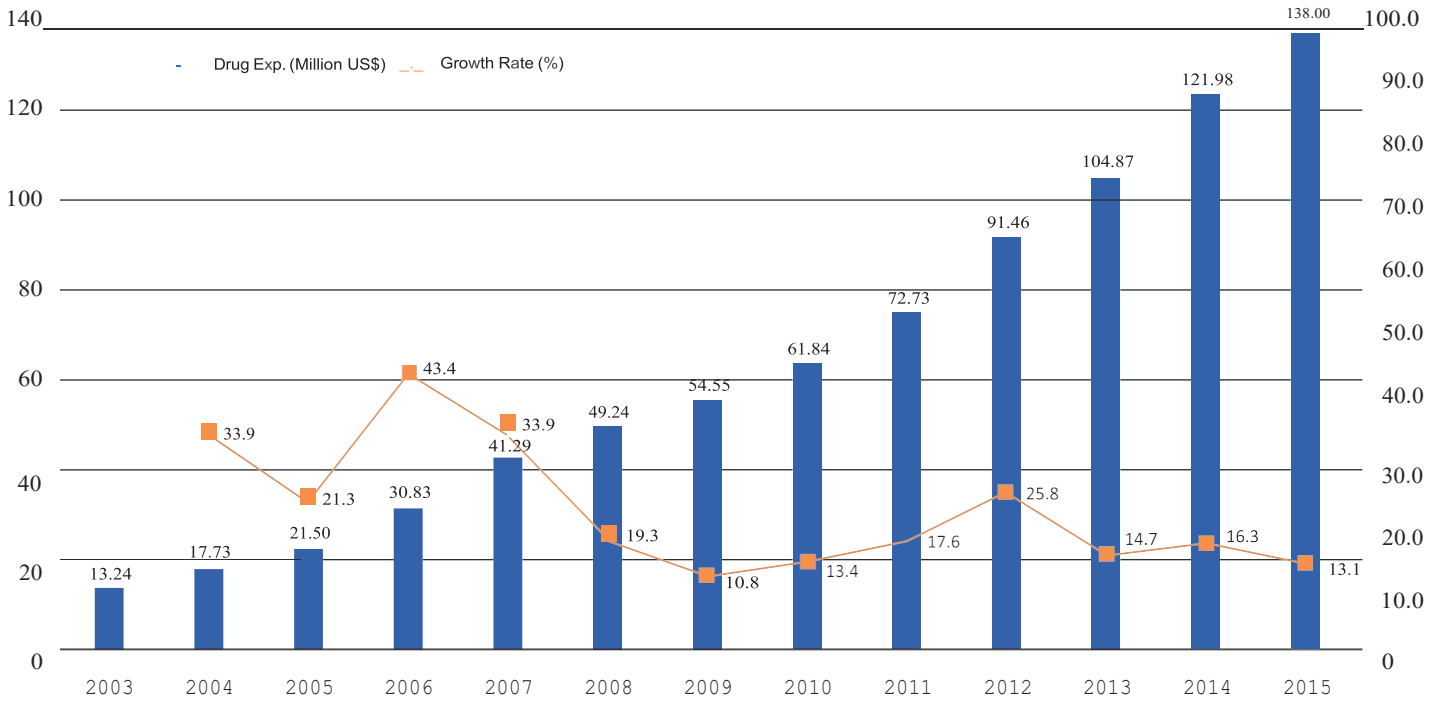
Orphan drug act offered several financial and non-financial incentives for the development of orphan drugs for treating rare diseases [236]. The Ministry of Health and Welfare (MOHW) offers incentives to importers and manufacturers of designated orphan drugs which includes simplified market approval procedure, reduced registration fee, grants and a 10-year grant of marketing exclusivity.

Taiwan has an orphan drug designation system and as of January 2017, 98 drugs received orphan drug designation. No clinical trial is required for drugs if they are approved by US FDA. Accelerated review for orphan drugs is available. No formal policy is in place for early access to orphan drugs but unregistered medicines can be imported upon request. Price negotiation happens to gain the best prices to support rare disease patients.

Importers or manufacturers of designated orphan drugs have to apply for listing of the drugs by the National Health Insurance Administration (NHIA) before reimbursement of the drug costs are borne by rare disease patients. However, patients or medical institutions can apply for a permit to import a designated orphan drug without market approval or a non-designated orphan drug on an ad hoc basis. For reimbursement of orphan drugs that are not on the NHIA reimbursement list, approval by the Review Committee has to be sought prior to usage of the drugs [238].

Taiwan NHI has almost reached Universal Health Coverage with 99.9% of the citizens and legal residents covered under NHI single-payer system. Estimated orphan drug expenditure in 2003 was USD $13.24 million. With the increase in number of rare disease patients and high price of orphan drugs, the expenditures increased to USD $138 million in 2015. The growth rate of drug expenditure between 2003-15 was 10.8% to 43.4% [234,238]. It is pivotal to noted that since 2002, over two-third of drugs with orphan drug designation have been included in NHI's reimbursement list. Table 24 shows the most common of rare diseases in Taiwanese population and the share of expenses borne by NHI which indicates the generous reimbursement and high-quality treatment that these patients are able to receive. Annual expenditure on orphan drugs have increased upto USD $216 million in 2018. [238-1]

Figure 16.Represents the increase in drug expenditure for rare disease in Taiwan over the period of 2003-2015



Source: [234]

Table 25.Shows NH/ datafor top 10 rare diseases affecting Taiwanese population and the expenditure on the patients in year 2015

Rank	Disease (Abbreviation)	No. of patients	Drug Exp. (USD $ million)	Drug Exp. Per patients (USD $)	Medical Exp. (USD $ million)	Medical Exp. Per person (USD $)
1	Fabry disease	155	39.8	256,819	70.0	258,092
2	Glycogen storage disease	101	22.3	221,027	22.6	223,092
3	M ucopolysaccha ridoses	75	19.0	253,719	19.2	256,539
4	Primary pulmonary hypertension	294	16.0	54,526	16.7	56,753
5	Gaucher's disease	26	8.6	331,643	8.7	333,057
6	Multiple sclerosis	1,089	7.9	7,249	9.3	8,511
7	Paroxymal nocturnal hemoglobinuria	43	7.3	170,757	7.4	172,131
8	Thalassemia major	289	3.9	13,550	4.8	16,615
9	Wilson's disease	403	3.5	8,768	3.8	9,341
10	Tuberous sclerosis	465	1.8	3,876	2.2	4,705
11	Total of Top 10 rare diseases	2,940	130.3	44,320	134.6	45,792
12	Total of rare diseases	7,820	138.8	17,746	150.1	19,198

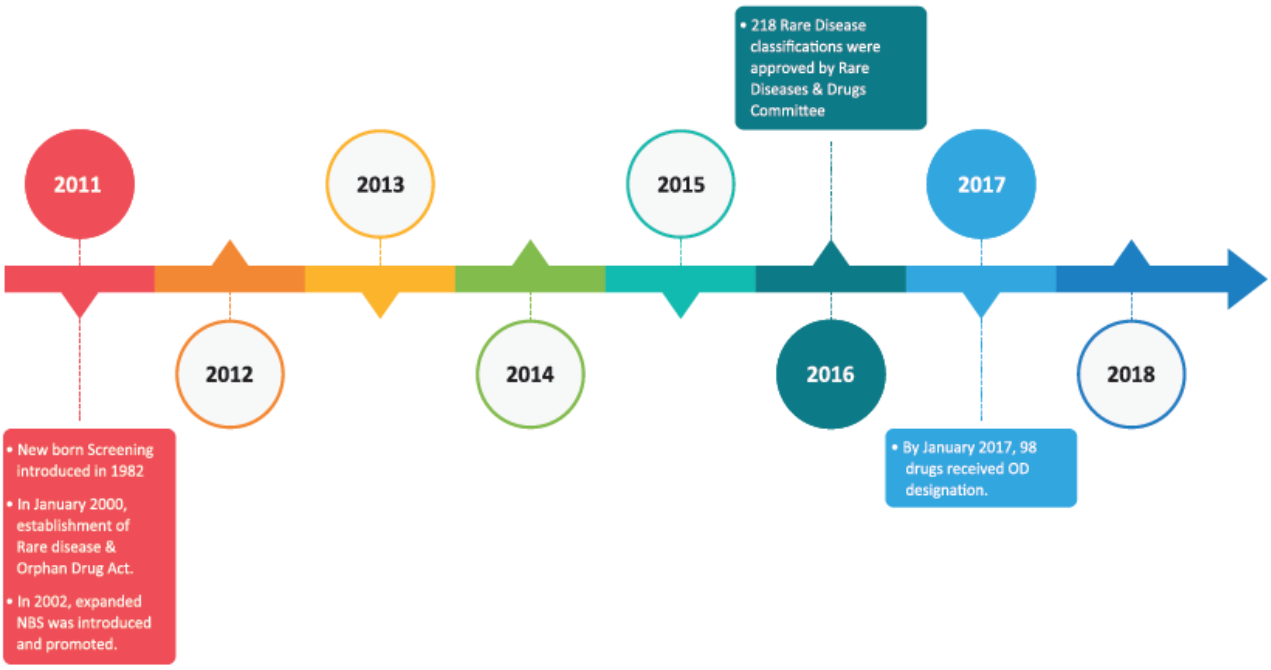
Source: {238}

Note:

The above data is collected from the patient with the catastrophic illness card seeks for medical attention

(Drug Exp. = Drug Expenditure)

Figure 17.Shows the timeline of the progress in the field of rare disease in Taiwan



Abbreviation: NBS= Newborn Screening, RA= Republic act, RDMAP = Rare disease medicine access program, DoH = Department of health, UP NIH= University of the Philippines national institute of health.

4.13.3. Key stakeholders involved in improving rare disease status in Taiwan

Table 26.Key stakeholders in the area of rare diseases in Taiwan

Organization	Established	Key stakeholder	Objective/Purpose
Taiwan Foundation for Rare Disorders (TFRD) *(http://www.tfrd.org.tw/tfrd/)*	1999	Founder – Sere WU Chairman - Dr Shuan-Pei Lin	- Support rare disease patients to receive medical treatment and rehabilitation, securing orphan drugs and special nutrients. - Provides education, employment and long-term care to patients.
Debra International *(http://www.eb.org.tw/ap/index.aspx)*	2009		
Taiwan Organization for Disadvantaged Patients *(http://www.rare.org.tw/_sam0/intro.php?kind_id=15&web_name=TODP)*			

5. THE HEALTHY ASIA PACIFIC 2020 INITIATIVE

Asia Pacific Economic Cooperation (APEC) economies have joined hands to achieve a positive health reform in the region. This gave birth to an initiative called "APEC's Healthy Asia Pacific 2020", a program aimed to develop sustainable and high performing health systems with inclusive "health in all policies" and a holistic "whole-of-government', "whole-of-society" and "whole-of-region" approach. This program was supported by the Ministers at the 26th Ministerial Meeting in 2014. This initiative will focus on 4 key areas:

1. Continuing to advance unfinished health-related Millennium Development Goals (MDGs) in a manner that complements activities of the post-2015 development agenda, including de-stigmatization and equality.

2. Strengthening the prevention and control of non-communicable diseases, including mental illnesses, disabilities, violence and injuries. This includes adopting a holistic and multi-sectoral approach that provides continuous health management and early diagnosis/treatment.

3. Strengthening health systems to support Universal Health Coverage, providing the whole population with access to safe, effective, quality, affordable and sustainable primary health care.

4. Improving health emergency preparedness, surveillance, response and recovery systems for public health emergencies, including pandemic events and natural disasters (326).

In a continued effort at the 7th APEC High-Level Meeting on Health and the Economy (HLM7) held at Ho Chi Minh City, Vietnam in 2017, the APEC leaders launched a new initiative to address the challenges in diagnosing and treating rare diseases in the region. This program will be aimed at improving the economic and social inclusion of rare disease patients and their caregivers, to ensure a more inclusive Healthy Asia Pacific 2020. A number of stakeholder consultation were conducted by APEC Life Sciences Innovation Forum (LSIF) Rare Disease Network (RDN) in Australia, China, Republic of Korea, Chinese Taipei, Thailand and Vietnam to understand firsthand the experience with rare disease. In order to gain in-depth perspective and patient experience, RDN connected with not only government officials, academics, industry partners but also with patients.

Followed by which at inaugural APEC Policy Dialogue on Rare Diseases in Beijing China (June 2018), a 2-day long, candid dialogue and discussion led to the collaboration on the development of "APEC Action Plan on Rare Disease". In brief this action aims to facilitate alignment on rare disease policies and regulations, forge implementation on best practices and promote multisectoral collaborations and patient partnership. The action plan consists of 30 targets across 10 pillars:

1. Define rare diseases and orphan products with policies and processes

2. Raise public and political awareness of rare disease issues

3. Promote innovative research and development

4. Build human resource capacity in medical, nursing, nutrition, and other allied health and non-health sectors

5. Facilitate early, accurate, and systematic diagnosis

6. Coordinate patient-centered care across medical and other health disciplines, life course, and location

7. Deliver new and accessible treatments to patients

8. Support financial and social needs of patients and their families

9. Manage pooling and usage of patient data securely and effectively

10. Prioritize comprehensive domestic rare disease policy integrating Pillars 1-9

Every pillar has recommendation to achieve the targets. A detailed view of which could be found from **http://www.apec.org** (APEC_ActionPlan.pdf)

6. STATUS OF RARE DISEASES IN BENCHMARK COUNTRIES

6.1 UNITED STATES (US)

In the US, as per the Rare Diseases Act of 2002, a disease is considered rare if it affects fewer than 200,000 individuals in the country (239]. In other countries, rare disease is defined based on prevalence rates. In the late 1970's, patients and their families affected with rare diseases felt disregarded and deserted. Efforts led by a mother (Abby Myers), a congressman (Henry Waxman) and the actor (Jack Klugman) to garner public and government attention towards the needs and problems of rare disease patients gave birth to National Organization for Rare Disorders (NORD). This coalition played instrumental role and led the Congress to pass world's first orphan drug legislation in 1983. This was a major milestone in the development of national rare disease policy and transformed the landscape for orphan drug development. Before the act took effect, only 10 new drugs were developed in the preceding decade however, this number surged to more than 500 new drugs in the succeeding three decades. The success of Orphan drug act in the US encouraged other countries to consider and introduce orphan act in their respective countries (240].

ODA provides special status to drugs that treat a rare disease and drugs are given orphan designation/status. Under this status the sponsor of the drug is entitled for various orphan drug development incentives including tax credits (50%) for qualified clinical testing and marketing fee exemption (241]. Orphan drugs get priority review and accelerated approval with 7 years market exclusivity. In addition to financial incentives, USA provides scientific advice, protocol assistance and pre-licensing access to orphan drugs. However, there is no control on the pricing of these drugs by the government. On June 29, 2017 as per US FDA Orphan Drug Modernization Plan, Commissioner Scott Gottlieb committed to eliminating the existing backlog on orphan drug status to ensure continued and timely response to all new requests for designation within 90 days of their receipt. Rare diseases are covered under Medicare for 95% reimbursement subject to prior authorization for reimbursement after a copayment of USO $4350 (241].

Children's National Health System developed the Children's National Rare Disease Institute (CNRDI), a center focused on advancing the care and treatment of individuals with rare genetic disorders. The center's goals are to improve the lifespan and quality of life of rare disease patients, track patient outcomes and treatment regimens, create database to advance rare disease research, knowledge gathering and training (clinicians, genetic counsellors, nurses, researchers and allied health professionals). The NORD has designated CNRDI as its first Center of Excellence for clinical care for rare diseases (242].

The Office of Rare Diseases Research (ORDR), launched a pilot project in 2012 to establish the Global Rare Diseases Patient Registry and Data Repository (GRDR) [now known as Rare Diseases Registry (RaDaR) Program]. The goal was to establish a data repository ofde-identified patient data, aggregated in a standardized manner, to enable analyses across many rare diseases and to facilitate various research projects, clinical studies and clinical trials. This should facilitate drug and therapeutic development and improve thequality of life for the millions of people suffering from rare diseases (243].

In July 2012, the US Food and Drug Administration (FDA) Safety and Innovation Act was signed in to a law. The law was welcomed by the NORD's stakeholders as *"the most groundbreaking measures for rare disease patients and their families since the Orphan Drug Act of 1983". The Act ushers in several significant changes including "accelerated patient access to new medical treatments; the development of Humanitarian Use Devices, or medical devices for small patient populations; accelerated development of "breakthrough therapies"- those that show early promise; enhanced consultation with rare disease medical experts; a rare pediatric disease priority review voucher incentive program; and resolution of conflict-of-interest issues related to FDA advisory committee participation"* (244).

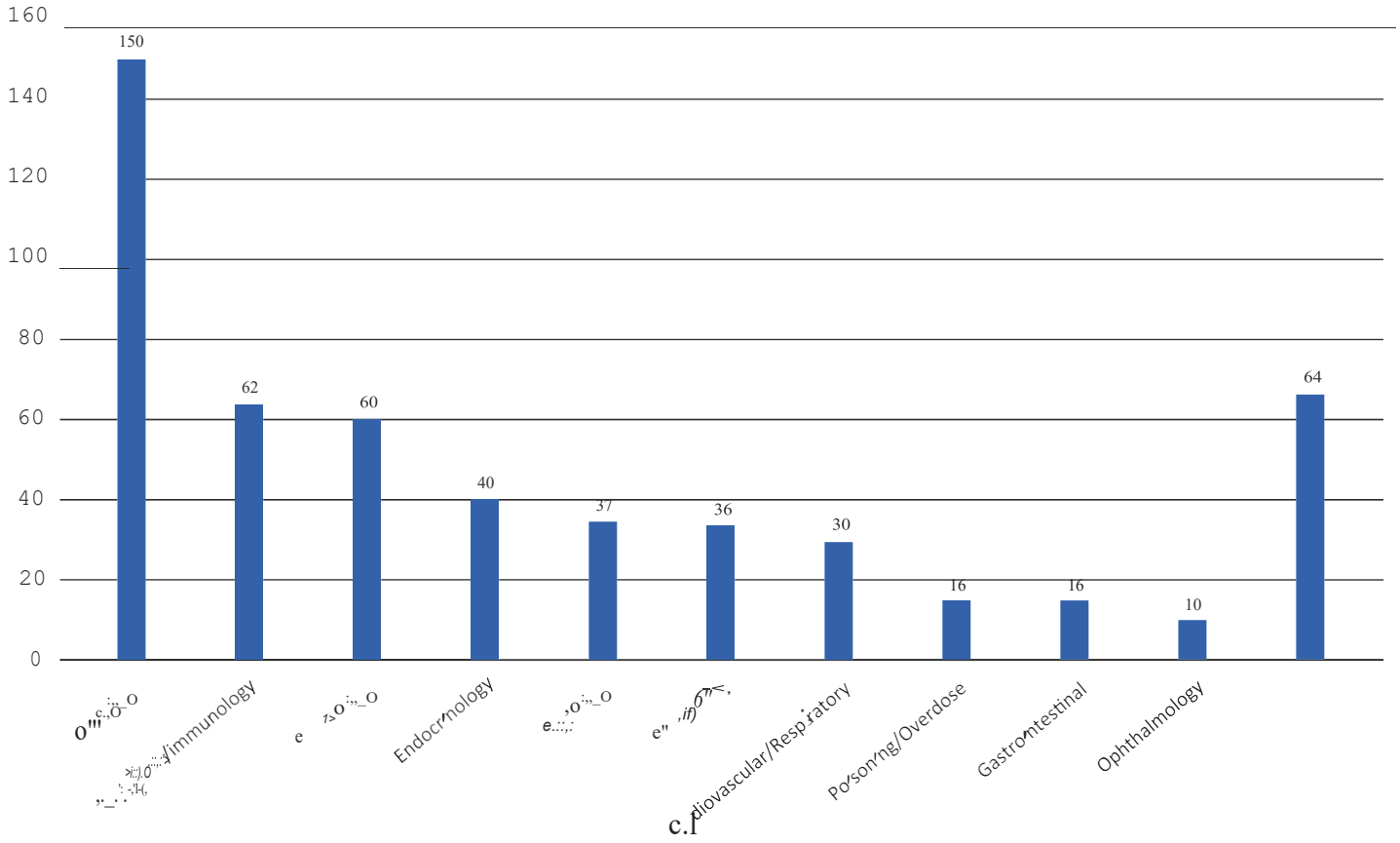
In the same year, Congress introduced the Ultra-orphan Life-saving Treatments Act of 2012 - or ULTRA Act- designed to promote the discovery and development of safe and effective drugs and biologics to treat ultra-rare diseases (defined as diseases affecting 6000 or fewer individuals). The act is meant to open-up the Accelerated Approval pathway to drugs for extremely rare conditions. This legislation will empower the FDA to consider the full scope of existing scientific data when reviewing surrogate endpoints for use under the Accelerated Approval Pathway, instead of requiring prior clinical data that is nearly impossible to collect for ultra-rare diseases (245).

In October 2015, the FDA announced awarding of 21 new clinical trial research grants totaling more than US$ 23 million over the next 4 years, to boost the development of products (drugs, biologics, medical devices or medical foods) for patients with rare diseases (246). The grants were awarded to investigators from both academia and industry working at national and international trials. The grants were awarded through the Orphan Products Clinical Trials Grants Program.

In the year 2016, the National Institute of Health (NIH) and National Human Genome Research Institute (NHGRI) announced plans to create new Centres for Common Disease Genomics (CCDG) and to support the next phase of the Centres for Mendelian Genomics (CMGs created in 2011) pending the availability of funds, the plan was to fund the CMG programmes (specifically for rare diseases) via approximately US$ 40 million over a 4-year period. NHGRI also announced the intention to fund a new Coordinating Centre for approximately US$ 4 million over 4 years to facilitate research collaborations among the programme grantees, and to contribute to data analysis and program outreach. In February 2016, NIH released its strategic fiscal plan for 2016-20 which placed a heavy focus on funding R&D in the field of rare diseases. The plan sought to help and support those patients within the NIH Clinical Centre's Undiagnosed Diseases Program (247).

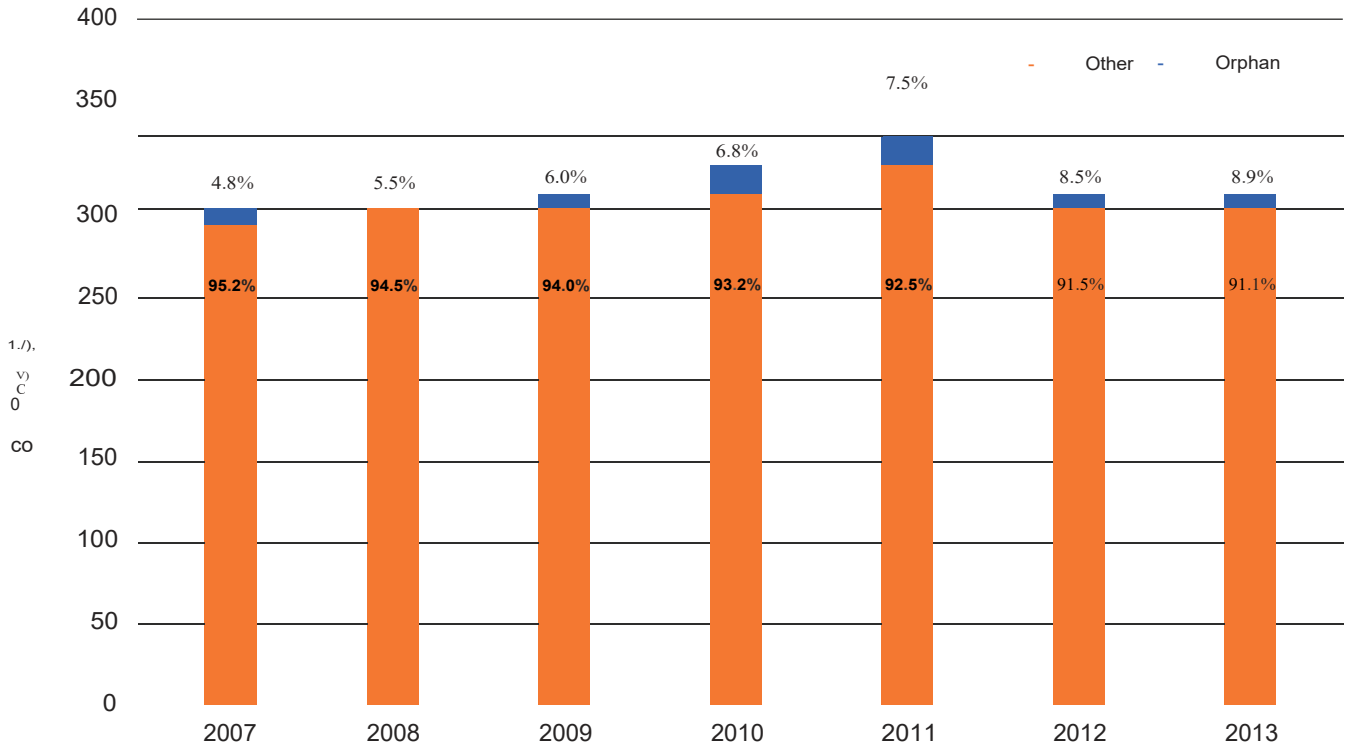
According to Giannuzzi et al., total of 521 drugs were approved as orphan drugs between the period of 1983-2015 for various indications as shown in Figure 18 below (248). Early in 2017, the Centre for Drug Evaluation and Research (CDER) at the FDA, which oversees the approval of small molecules and antibodies, reported approval of 22 novel drugs in 2016. Nine out of these 22 novel drugs (~41%) were approved for rare diseases. The 9 approved drugs were: Anthim, Defitelio, Exondys 51, Lartruvo, Netspot, Ocaliva, Rubraca, Spinraza and Venclexta. Exondys 51 is indicated for Duchenne muscular dystrophy and Spinraza is indicated for spinal muscular dystrophy (SMA), respectively (249).

Figure 18.Approved US orphan indications in USA between 1983-2015



Source: [248]

Figure 19. Example of US pharmaceutical spending on orphan and other drugs



Source: [250,251]

As per the above study, an increase in orphan drug expenditure was observed between the period of 2007-13. However, this increase was related to an increase in the number of orphan drugs that had been approved by the FDA. On a higher level, orphan drug expenditures when compared with the total health care expenditure is minimal. For example, in 2013, US spent USD 37 billion on oncology medicines which represented 1.3% of the USD 2.9 trillion spent on health care [252,253]. As per the author's analysis, total expenditures in 2013, was approximately 11 % of total USA healthcare spending, while total orphan drug spending represented approximately 1% of total USA healthcare spending (254]. In addition, the study predicted that the spending on orphan drugs between the periods of 2014-18 will increase from 8.8% in 2014 to 9.5% in 2018, an increase of 0.7%.

Over the years, payers have raised concerns about managing their drug budgets amid perceived high costs of orphan drugs and increasing numbers of such drugs FDA approvals. Patients' spending on orphan drugs may also seem disproportionate compared to spending on other drugs. The findings from the above analysis suggest that these concerns might not be justified. Many blockbuster orphan drugs also have nonorphan indications and thus treat a larger population of patients than those with only orphan diseases. From an equity perspective, overall spending on orphan drugs (including spending on orphan indications only) as a share of total drug spending is proportional to the estimated 8-10 % of Americans with an orphan disease. Moreover, estimated spending on orphan drugs as a share of total drug spending will remain below 10 % through 2018. Addressing barriers to access and coverage of orphan drugs in the USA may be warranted [251,255].

Figure 20.Rare disease policies and orphan drug acts as active in America

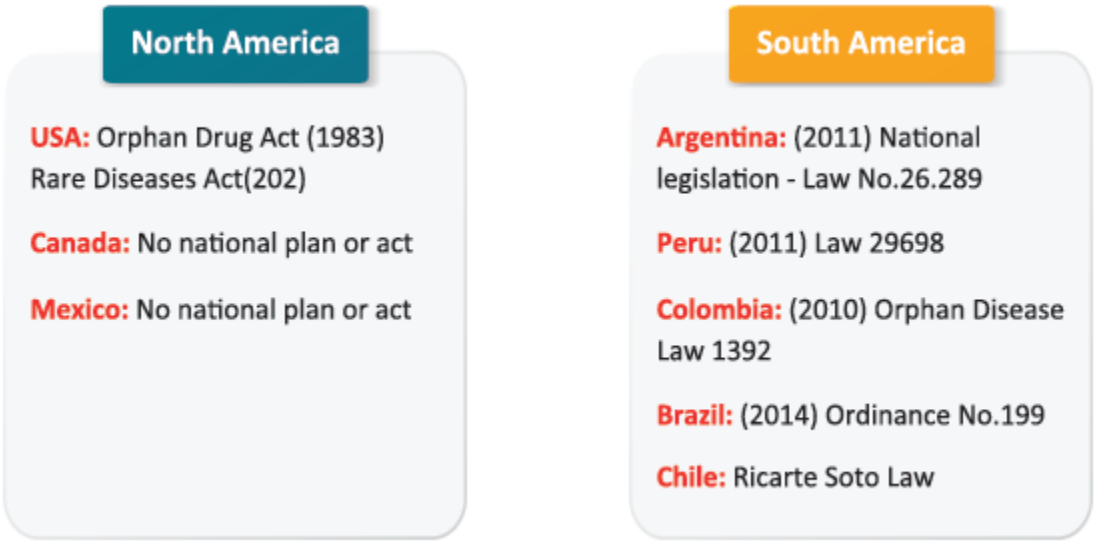


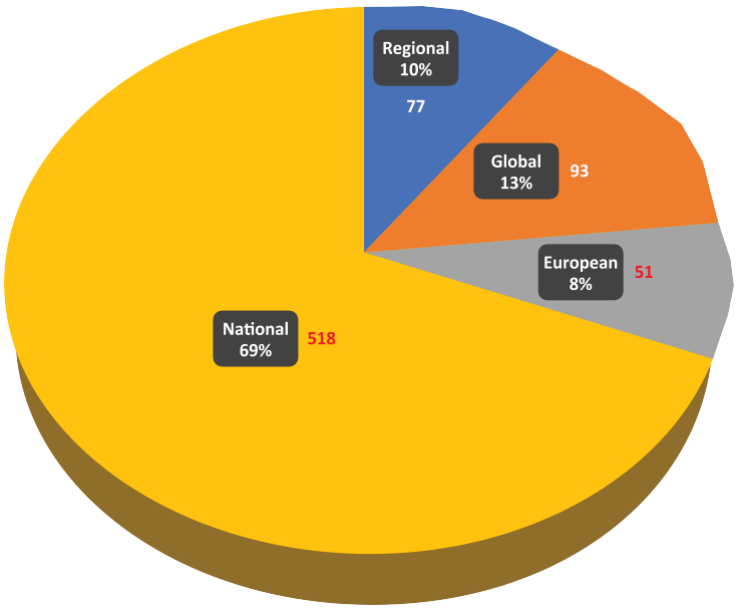
Table 28.Incentives for the development of orphan drugs

Financial/Non-financial incentives	USA	EU	Japan
Market exclusivity	7 years	Usually 10 years (6 years for highly profitable product)	10 years
Tax rebate on development costs	50%	Available in some member states	15%
Financial subsidy/ Research grants	Funded by Office of Orphan Products Development	Available in some member states and also funded by European Commission (EC)	Funded by government
Waiver of fees	100%	Yes (variable)	Yes (variable)
Protocol assistance	Yes	Yes	Yes
Access to centralized procedure		Yes	
Access to continuous regulatory assistance	Yes		
Fast-track review	Allowed	Allowed	Allowed

6.2 EUROPE

In Europe, diseases are considered rare when they affect fewer than 5 individuals in 10,000 or in other words 1: 2,000 individuals. Over 27 million people are affected by rare diseases in Europe alone. In 2000, orphan drug legislation was approved by the European Parliament. This legislation grants, among other things, a ten-year market exclusivity for any new orphan drug. Europe is one of the most progressive continents in terms of policies and efforts towards helping rare disease patients. According to the Orphanet Report series "Rare Disease Registries in Europe" published in May 2018, there are 747 disease registries in Europe and out of which: 51 operate at the European level, 93 at global, 518 at national and 77 at regional level (212].

Figure 21.Distribution of European rare disease registries by geographical scope as per the Orphanet database



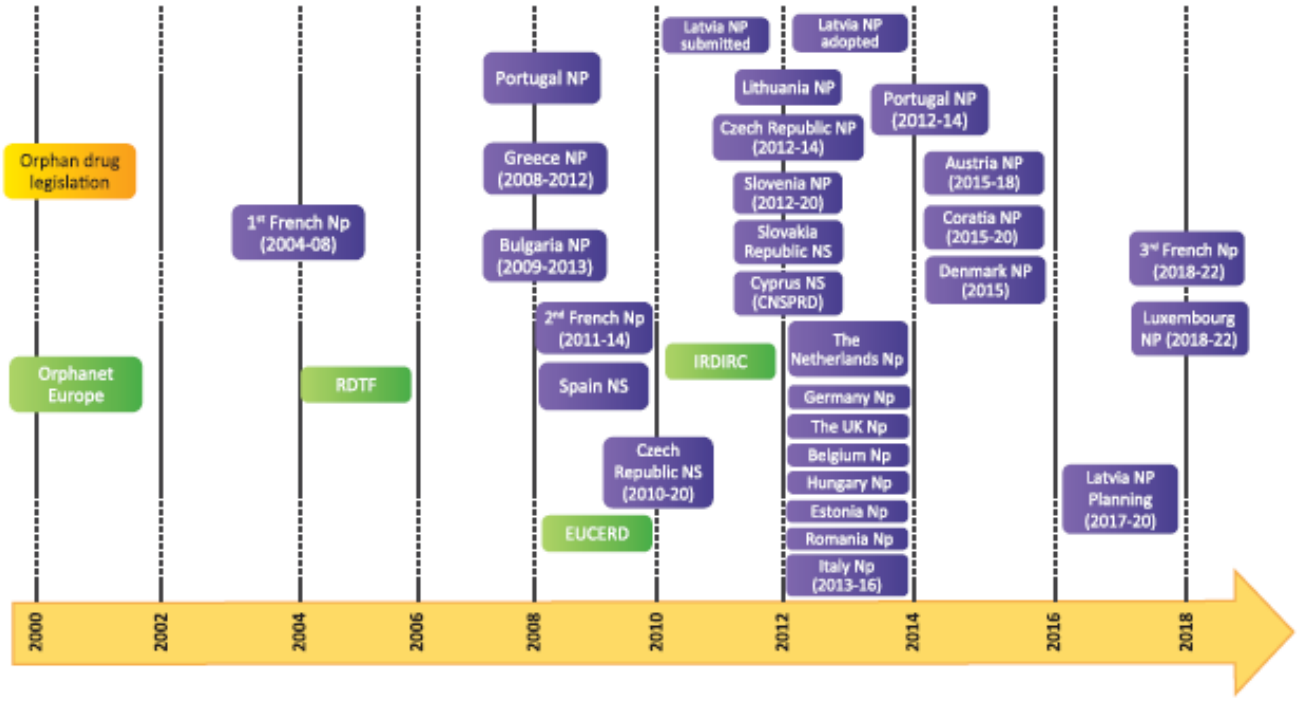
Total no.of registries =747

Several rare disease related activities have taken place in Europe over the last decade. Apart from few major pioneering European countries such as France and Germany, several other countries have made attempts to progress the cause of rare disease patients with new initiatives or national plans. **Figure 22** is a screenshot of some of the major activities from European Union in the field of rare diseases.

- Orphanet Europe was established in 1997 in France with the aim to collect scarce information available on rare diseases at the time in order to improve disease diagnosis, treatment and care. In year 2000, Orphanet was undertaken as an endeavor by 37 European countries and was supported by several grants.

• Rare Disease Task Force (RDTF) was established in 2005, a forum for discussion and exchange of information and knowledge of rare diseases at national and European level.

Figure 22.Evolution of initiatives for rare diseases in European countries between the period of 2000-2018



Abbreviation:NP= National Policy, NS= National Strategy, RDTF = Rare Disease Task Force, EUCERD = European Union Committee of Experts on Rare Diseases, IRDiRC = International Rare Diseases Research Consortium

Source: Reproduced from reference Rodwell C, 2014 [256]

Sweden, Poland and Malta have not adopted any rare disease plan or strategy till date. However, Poland prepared a National Plan for Rare Diseases (NPRD)- the roadmap by the end of 2012 but no execution is in place. As it can be seen from Figure 22, many of these European countries national plans or strategies have either ended (e.g. Italy, Austria, Bulgaria etc.) or about to end soon. Worryingly enough, there are no updates whether these countries are going to renew the plans or not. And so these European countries should be recommended to update or renew their plans. France has been a good example and a flag bearer with its 3rd national plan in place. Another major concern that has been noticed is that many of these countries do not have a dedicated funding for rare diseases but funds come from their annual health budget. In addition, the extent of implementation of these national plans widely varies.

Since the implementation of Orphan Medicinal Products Regulation in 2000 (Regulation (EC) No 141/2000), 143 orphan drugs received market authorization in the EU. Marketing authorization of orphan drugs is just the first stage and patients can access these medications only when the reimbursement or health technology assessment (HTA) decisions are in place by national health systems [256]. Among European countries, France and Germany have centralized national funding, better access to rare disease treatments, robust research initiatives, coordinated networks, and cross-border collaborations in place for rare diseases [257].
In a new development on December 16th 2021, the United Nations adopted its first ever UN resolution on "Addressing the challenges of persons living with a rare disease and their families." This is a ground-breaking Resolution which is adopted by all 193 UN member states [257-1] France has included RD in its agenda of the 2022 French Presidency of the European Union Council as an important step to improve the lives of those livign with RD. EURORDIS Rare Disease Europe (a unique, non-profit alliance of 988 RD patient organizations from 74 countries working together to improve the lives of 30 million Europeans living with RDs) has welcomed this move and believes that France has a proven track record of taking actions in this field. France and EURORDIS also pledged their support for a European Action Plan for Rare Diseases [257-2].

6.3 FRANCE

France has a gross national income per capita (2015) as 40,580$ USO with a healthcare spending of 15% (% GDP) (257]. A disease is considered rare in Europe if it affects less than 1 person in 2,000 people. In France, this translates to less than 30,000 people affected by any given disease. According to French National Plan drafted in 2004, 3 million people were affected in France alone with 27 million in Europe. Few thousands are affected by 50 rare diseases each, while hundreds each by 500 diseases and several dozen people are affected by thousands of rare diseases. Several rare diseases are more common than others. For example,

- Sickle cell anemia - 15,000 individuals
- Amylotrophic lateral sclerosis - 8,000 individuals
- Cystic fibrosis - 5,000-6,000 individuals
- Duchenne muscular dystrophy - 5,000 individuals
- Leukodystrophy- 400-500 individuals
- A few cases of progeria (premature ageing) - < 100 cases in the world

Efforts of France in the area of rare disease led to the adoption of European legislation on orphan drugs in 2000. Over the years, France has taken several initiatives in the area of rare diseases in collaboration with patient's associations, especially, Association franc;:aise contre les myopathies (AFM). Some of the initiatives were:

- Creation of an orphan drugs mission in 1995
- Establishment of a telephone help line service for patients in 1995
- Online information server, Orphanet in 1997
- Since 2001, promoting and provide financial support of clinical research on rare diseases in hospitals
- Since 2002, Access to the list of clinical trials by the Agence franc;:aise de securite sanitaire des produits de sante (AFSSPS)
- Creation of a Groupement d'Interet Scientifique - Institut des Maladies Rares in 2002 (258] - France was the first country in EU to set up a national rare disease plan in 2004 for the period of 2005-2008 with fund allocation. The priorities of this national plan, entitled "To ensure equity in the access to diagnosis, to treatment and to provision of care" included 10 strategic priorities:
  1. Increase knowledge of the epidemiology of rare diseases;
  2. Recognize the specificity of rare diseases;
  3. Develop information on rare diseases for patients, health professionals and the general public;
  4. Train health professionals to better identify rare diseases;
  5. Organize screening and access to diagnostic tests;
  6. Improve access to treatment and quality of healthcare provision for patients;

7. Continue efforts in favor of orphan medicinal products;
8. Respond to the specific needs of accompaniment of patients suffering from a rare disease and develop support for patients' organizations;
9. Promote research and innovation on rare diseases, in particular on treatments;
10. Develop national and European partnerships in the domain of rare diseases.

The first national plan provided for the funding of 131 centers of expertise "centre de reference maladies rares" (Reference Centers for Rare Diseases) in France. In 2008, second level of network of 501 centers were recognized to work in close connection with the Reference Centers. They are known as "centre de competences maladies rares" (Competence Centers for Rare Diseases) and are equivalent to regional centers of expertise. French Ministry of Health developed emergency cards to be used by the patients when necessary. Funding for the first national plan was provided under the general health system budget with ad hoc funding on the basis of rare disease projects(> €100 million for the first plan) [255].

On 30 September 2010, the French Alliance for Rare Diseases ("Alliance Maladies Rares"), in collaboration with EURORDIS, organized a national conference on rare diseases in the context of the Europlan project. The theme of the conference was "The French plan in the European landscape". The conference gathered a wide range of stakeholders and focused on lessons drawn for the first plan for the benefit of other European countries [255].

Based on the success of the first national plan second national plan for rare diseases was elaborated during 2009-2010 by the MoH in with collaboration of the Ministry of Higher Education and Research. The second plan was launched on 28 February 2011 on Rare disease day, with the budget allocation of €180 million for the period between 2011-2014. The ten priorities of the first plan were consolidated into three main objectives:

1. Improve the quality of care for rare disease patients;
2. Develop research on rare diseases;
3. Expand European and international cooperation in the field of rare diseases.

The above three objectives embody activities such as:

- Quality assessment and networking cooperation of the existing French Reference Centers;
- Improvement of access to genetic diagnosis;
- Development of neonatal screening of rare diseases;
- Proper use and facilitated access to drugs, orphan medicinal products and any other medical product necessary for the patients;
- Information and training of health professionals;
- Information for patients;
- Strengthening of research.

The second national plan included 15 measures and 47 specific actions. The key measures of the plan included:

- Creation of a Foundation for Scientific Cooperation on Rare Diseases (Foundation maladies rares - French Foundation for Rare Diseases - FFRD) to coordinate and facilitate research on rare diseases;
- Creation of a National Rare Diseases Data bank (called "Banque nationale de donnees maladies rares" - BNDMR) to allow mapping of patients' needs and delivered healthcare, and to facilitate their recruitment for clinical and epidemiological studies and clinical trials. The national registry BNDMR will be based on the collection of a minimum data set, common to all patients and rare diseases and all the Reference and Competence Centers;
- Improvement of the monitoring of various activities relating to rare disease patients, which includes the adoption of the Orphanet nomenclature for the patients' follow-up;

- Access to next-generation sequencing (NGS) technology for genetic diagnosis. Most of the French academic laboratories will be equipped at the end of the second year of the plan with NGS facilities to optimize genetic diagnosis of a large set of rare diseases. Various levels of NGS will be implemented during the plan for speeding up and maximal diagnosis coverage;
- Coordination of rare diseases Reference Centers and their regional centers into a limited number (around 20) of coherent "national networks for rare diseases" (called "filieres de sante maladies rares"), gathering all rare disease relevant stakeholders and centered on a homogenous group of rare diseases. These networks aim to allow a better and easier orientation of patients towards appropriate diagnosis, treatment, social care and follow-up anywhere in France. They aim also to allow better coordinated initiatives of the Reference Centers in their research, information and education activities. These French networks would be connected to the future European Reference Networks (ERN) developed for rare diseases.
- Creation of a "permanent working group" for the monitoring of Reference Centers and the future national clinical networks;
- Measure to ensure access and reimbursement of new drugs or drugs necessary to patients but prescribed outside of their marketing authorization;
- Enhancement of rare disease clinical practice guidelines ("PNDS") development;
- Training of medical doctors and paramedical professionals;
- Better coordination of health care and social care;
- Improvement of information for rare disease patients supporting Orpha net and Maladies Rares Info Service and the creation of a European unique number for rare disease help lines [255,259].

The Third French National Plan (2018-2022) is underway. In France, currently national neonatal screening (NBS) programme exists for 5 disease conditions: phenylketonuria, congenital adrenal hyperplasia, congenital hypothyroidism, sickle cell disease, and cystic fibrosis. Haute Autorite de sante (HAS) recommended expansion of neonatal screening to include Medium-chain acyl-CoA-dehydrogenase (MCAD) deficiency because this screening will prevent each year 5 deaths and the occurrence of neurological sequelae in 2 children under 5 years of age, with an incremental cost-effectiveness ratio below 10,000 € per life year and per quality adjusted life-year (QALY) gained [260].

Various initiatives are in place by the French HAS to promote development of orphan medicinal products which includes research support via national funding programmes: The Hospital Clinical Research Programmes (PHRC). During orphan medicinal product development, Agence nationale de securite du medicament et des produits de sante (ANSM), organization founded in 2012, responsible for the assessment of the safety, efficacy and quality of health products and novel therapies, provides free scientific advice. Other financial incentive is provided in the form of tax exemption and non-financial incentives such as free early advice and fast track process of the assessment for reimbursement by the Transparency Committee (TC) are performed by the HAS. Market exclusivity for orphan drugs is 10 years in EU [255].

The authorization of orphan drugs in France follows centralized system in EU where authorization time for reimbursement decision takes average of 19 months and decisions are made by Committee for orphan medicinal products (COMP). Market authorization is required for orphan drugs to be accessible yet there are provisions to help patients get early access for with and without market authorized orphan drugs via pre-licensing access which in many countries is known as "named patient procedures". Orphan drugs are often reimbursed between 65-100%. The reimbursement strategies differs in countries throughout EU. In France however, the focus is on standard of evidence that requires clinical value evidence and measures of innovation with no formal cost-effectiveness analysis for orphan drugs. The primary consideration is literature reviews and cohort studies when clinical evidence and cost-effective evidence are limited based on data from manufacturers. Even with the high prices of orphan drugs, they are often reimbursed in the country due to the fact that these drugs have relatively low impact on the budget due to small patient sizes [255].

6.4 GERMANY

Approximately 4 million of the total population (~s2 million) live with rare disease in Germany. In 2009, the German Federal Ministry of Health (BMG) released a report titled "Measures to improve health in people with rare diseases". The aim of the report was to analyze the current level of care provided to rare disease patients at the time and to advance ways to provide better care. The report clearly indicated the need for improved health care system for rare diseases patients which included the prevention, diagnosis and therapy respectively. Moving forward in this direction, on 8 March 2010, the German Federal Ministry of Health founded the National Action League for People with Rare Diseases (Nationales Aktionsbundnis fur Menschen mit Seltenen Erkankungen (NAMSE)). Along with the German Federal Ministry for Education and Research (BMBF) and the Alliance of Chronic Rare Diseases (ACHSE) - NAMSE was entrusted to establish a National Plan of Action for People with Rare Diseases by 2013 and support the establishment of national centers of expertise. The National plan was adopted in August 2013 which included 52 policy proposals casing 7 action fields [255].

At present no centralized registry for rare diseases exist in the country. NAMSE suggested for the setup of a web-portal of registries regarding rare disease in Germany. This will facilitate access to existing registries via a web portal - a "telephone book" of such registries. There were also recommendations for the establishment of "Disease-Specific Registries of Rare Diseases" which will be standardized for the inclusion of existing registries. In addition, no public central clinical trial registry dedicated to rare diseases are in place [255].

The Genetic Diagnosis Act (Gendiagnostikgesetz - GenDG) established guidelines for genetic testing which aims to prevent discrimination based on genetic characteristics, to protect human dignity and provides binding standards for good genetic testing practice. Since 2005, Germany instituted a mandatory screening program which included 14 conditions: phenylketonuria, biotinidase deficiency, galactosaemia, MCAD deficiency, VLCAD deficiency, LCHAD deficiency, CPTI, CPT2, CAT deficiencies, maple syrup urine disease, glutaric aciduria type 1, sivaleric acidaemia, congenital adrenal hyperplasia and congenital hypothyroidism. Newborn screening is a part of genetic testing. Germany has mandatory screening and genetic testing, however no specific rare disease policy exists.

Orphan drug designation status is available in Germany and orphan drugs get 10-year exclusivity. Orphan drugs are automatically reimbursed based on cost benefit analysis by the Institute for Quality and Efficiency in Health Care (IQWiG) in case of no availability of drug option. However, patients are required to make a co-payment of €10 per drug (limited to an annual threshold of 2% of individual yearly net income). As per HTA criteria, drugs are reimbursed based on their cost-effectiveness. Pre-licensing access is granted during the third phase of the clinical trial and when the product's safety and efficacy are guaranteed (257]. Various rare disease organizations are present in Germany, supported by Ministry of Education and Research. BMBF currently funds 12 research projects and €23 million is allocated for 3 years (154].

The German National Alliance for Chronic Rare Diseases (ACHSE) is a national level patient organization, a network of more than 100 patient organization for rare disease patients. Through ACHSE, network organization help each other and its patients to strengthen their influence in the political arena to improve the quality and duration of people living with a rare disease. ACHSE is an active member of EURORDIS and a member of its Council of National Alliances. Health-related groups and organisations are eligible for financial support from the statutory health insurance funds. With a legislative reform introduced on January 1, 2009 has made fund raising easier which was about €40 million in 2011 [255].

6.5 UNITED KINGDOM (UK)

In the UK rare disease is defined as affecting approximately 5 individual or fewer in 10,000 and they require exceptional and joint efforts for patients to be treated effectively. It is estimated that 1 in every 17 people will be affected by rare disease at some point in their lives. UK published its first national plan titled "UK Strategy for Rare Diseases" in 2013. The plan presented a high-level frame work which contained 51 commitments, with a set vision by 2020 to improve lives of patients living with rare diseases. The above strategy was applicable to all 4 countries of the UK: England, Scotland, Wales and Northern Ireland, namely. But it was up to the individual countries to have their own plan or adopt the above strategy by the end of February 2014. The main areas covered in the strategy includes:

- Empower people affected by rare diseases
- Identify and prevent rare diseases
- Diagnosis and early intervention
- Coordination of care
- The role of research

To meet the aims of the strategy it is imperative for various stakeholders to assume a collaborative approach which includes all the 4 UK health departments: The Department of Health and Social Care for England (DHSC), the Directorate for Healthcare Quality and Improvement at the Scottish Government, the Health and Social Services Group at the Wales Government and the Department of Health in Northern Ireland

The UK government issued its strategy for rare diseases in November 2013. The strategy includes 51 commitments to patients with rare diseases which includes diagnosis, information, healthcare, genomics, registries and research. A Stakeholder Forum has been established to monitor progress in implementing the strategy.

Table 29. Country plans based on the UK strategy

Country	Plans published	Year of issue	Issuing body
England	No formal plan published		
Scotland	It's Not Rare to have a Rare Disease	June 2014	Scottish government and other stakeholders
Wales	Welsh Implementation Plan for Rare Diseases	February 2015	National Implementation Group and other stakeholders
Northern Ireland	Providing High Quality Care for people affected by Rare Diseases	October 2015	Department of Health in Northern Ireland

Source: [261]

As a part of the UK Strategy, 100,000 (100K) Genome Project was launched by Prime Minister David Cameron in late 2012. Genomics England, company owned and funded by the Department of Health and Social Care of England (DHSC) was given the responsibility of this flagship project in collaboration with other partners. The focus of this project is aimed towards patients with rare disease and their families, as well as cancer patients and includes four main aims:

- To create an ethical and transparent programme based on consent
- To bring benefit to patients and set up a genomic medicine service for the NHS
- To enable new scientific discovery and medical insights and
- To kick-start the development of a UK genomics industry [261].

In fiscal year 2016-17, Genomic medicine centre was awarded Medical Research Council (MRC) and the Welsh government funding of flm and £ 2.4m respectively to support Wales' involvement in the Genomics England 100K Genomes project. Other countries also have received funding for the 100K genome project.

In 2016 the Secretary of State for Health announced investment of£ 816m in the NIHR (National Institute for Health Research) Biomedical Research Centers, for a period of 5 years from 1 April 2017. This funding has been awarded to 20 leading National Health Service (NHS) and university partners across England. These 20 research centers have led to the development of new, ground-breaking treatments, diagnostics, prevention and care for patients in a wide range of diseases including rare diseases.

The National Newborn Blood Spot Screening Programme is offered in all the four countries and eligible babies (test is not mandatory) are tested for 9 conditions here: homocystinuria (HCU), maple syrup urine disease (MSUD), glutaric aciduria type 1 (GAl), isovaleric aciduria (IVA), phenylketonuria (PKU), congenital hypothyroidism (CHT), sickle cell disease (SCD), cystic fibrosis (CF) and medium-chain acyl-coA dehydrogenase deficiency (MCADD) respectively [261]. The number of conditions for which screening is offered stands unfavorably when compared with other developed countries where screening is offered for 20 or above conditions.

Even with UK Strategy for Rare Diseases, UK has lagged behind other European countries in creating an appropriate framework for bringing the treatment for rare diseases to the patients. However, different countries are trying to abridge this gap with their individual efforts. For example, in England, the Advisory Group for National Specialized Services (AGNSS) process and the Highly Specialized Technology (HST) are responsible for the orphan drug appraisal. Drugs which are not selected through HST are left to the relevant budget holder like NHS England. In the UK, National Institute for Health and Care Excellence (NICE) established Highly Specialized Technology (HST) (NICE 2014d, 2014a) [262]. In Scotland, the Scottish Medicines Consortium (SMC) (2013b, 2014a) is the responsible body for appraising all medicines including orphan drugs. However, in past few years SMC has given "not recommended" status to many of the rare disease drugs. This raises concern amongst clinicians and patient organizations that the SMC may be denying access to orphan drugs based only on their cost even when the drugs have indicated clinical benefits for rare disease patients [263]. In Scotland and UK, NICE defined an incremental cost-effectiveness ratio (ICER) threshold of £30,000 per quality-adjusted life year (QALY) gained. In April 2017, NICE published an increased threshold of ICER of £100,000 per QALY gained for drugs for "very rare" diseases [264]. In Wales, drug reimbursement is taken care of by All Wales Medicines Strategy Group (AWMSG) (AWMSG 2014). It has been noticed that UK is fairly slow in making decision for orphan drug access and more likely to say no, than other countries such as Spain, Italy, Germany and France. At present, only half of licensed orphan medicinal products are available on the NHS.

6.6 CANADA

Canada does not have an official definition of rare disease. Health Canada estimates about 1 in 12 Canadian have rare disease. At international level, Canadian Institute of Health Research (CIHR) and Health Canada are developing programs based on the following definition "a rare disease is a life-threatening, seriously debilitating, or serious chronic condition that only affects a typically less than 5 in 10,000 people". The definition varies by jurisdiction. For Alberta's publicly funded drug plan, a rare disease is defined as a genetic lysosomal storage disorder that occurs at rate of< 1 per 50,000 individuals. Whereas, Ontario publicly funded drug plans' definition of rare disease is an incidence rate of< 1 in 150,000 live births or new diagnoses per year. Canada is one of the few developed countries without a national "orphan drug" program [265,266]. In 2012, Leona Aglukkaq, Canadian Minister of Health, announced Harper government's intention of Canada's orphan drug regulatory framework which was planned to be rolled out between 2017-19, but the initiative has been deleted. It is considered as a big blow to the rare diseases community as it will keep manufacturers away from applying for drug marketing authorization in Canada [267,268].

The Canadian Organization for Rare Disorders (CORD) is an established patient group, which works with patient, government, policy makers, clinicians and other stakeholders to address the issues faced by rare disease patients. To extend stakeholder engagement, CORD has proposed for the implementation of Canada's Rare Disease Strategy. The strategy aims to achieve five main goals:

- Improving early detection and prevention
- Providing timely, equitable and evidence-informed care
- Enhancing community support
- Providing sustainable access to promising therapies
- Promoting innovative research

Newborn screening is currently available in Canada however, state of newborn screening is patchy across country that leaves many newborns with rare diseases susceptible of going undetected before damage becomes disastrous and permanent. The number of tests newborn are tested varies across the country along with standard and criteria variation (269]. A list of number of conditions for which screening facility is available within various provinces is shown as in Table 28 and 29. In 2014, provincial and territorial health ministers realized the importance of newborn screening as critical tool to improve children health by early identification of rare disorders. Based on this recommendation was made by health ministers to continue to develop an evidence-based list of recommended primary newborn conditions for pan-Canadian use. Thereafter, the Canadian Agency for Drugs and Technologies in Health (CADTH) was conferred a grant to organize a task force to study and come up with recommendation for a national approach to newborn screening (266].

Table 30.List of screening condition available in various provinces

Province/Territory	No. of conditions screening facility
Newfoundland & Labrador	7
Prince Edward Island	19
Nova Scotia	20
New Brunswick	19
Quebec	16
Ontario	30
Manitoba	47
Saskatchewan	37
Alberta	19
British Columbia	31
Yukon	30
North Territories	18
Nunavut- Kitimeot region	18
Nunavut- Kivilliq region	24
Nunavut- Baffin region	29

Source: [270]

Table 31.Different primary, secondary and metabolic conditions for which screening is done in Canadian provinces and territories

Conditions (primary, secondary and metabolic}		
BIO: Biotinidase	CAH: Cystic fibrosis	GALT: Transferase deficient galactosemia (Classical)
HB S/C: Sickle-C disease	HEAR: Hearing screening	CAH: Congenital adrenal hyperplasia
CH: Congenital hypothyroidism	HB S/S: Sickle cell anaemia	HB S/A: S- eta thalassemia
SCID: Severe combined immunodeficiency	CCHID: Critical congenital heart disease	3-MCC: 3-Methylcrotonyl-CoA carboxylase
CUD- Carnitine uptake defect	LCHAD: Long-chain hydroxyacyl CoA dehydrogenase	PKU: Phenylketonuria
ASA: Argininosuccinate academia	GA-1: Glutaric academia type 1	MCAD: Medium-chain acyl-CoA dehydrogenase
PROP: Propionic academia	BKT: Beta ketothiolase	HCY: Homocystinuria
MCD: Multiple carboxylase	TFP: Trifunctional protein	CBL A,B: Methylmalonic academia
HMG: 3-Hydroxy 3-methylglutaric aciduria	MSUD: Maple syrup urine disease	TYR-1: Tyrosinemia type 1
CIT I: Citrullinemia type I	IVA: Isovaleric academia	MUT: Methylmalonic academia
VLCAD: Very long-chain acyl-CoA dehydrogenase	2M3HBA: 2-Methyl-3-hydroxy butyric aciduria	CACT: Carnitine acylcarnitine
GA-II: Glutaric academia type II	MAL: Malanie academia	2MBG: 2-Methylbutyrly-CoA dehydrogenase
CBL-C,D: Methylmalonic academia	GALE: Galactose epimerase	MCKAT: Medium-chain ketoacyl-CoA thiolase
3MGA: 3-Methylglutaconic aciduria	CIT-II: Citrullinemia type II	GALK: Galactokinase
MET: Hypermethioninemia	ARG: Arginemia	CPT-Ia: Carnitine palmitoyltransferase I
H-PHE: Benign hyperphenylalaninemia	SCAD: Short-chain acyl-CoA dehydrogenase	BIOPT-BS: Defects of biopterin cofactor biosynthesis
BIOPT-REG: Defects of biopterin cofactor regeneration	CPT-11: Carnitine palmitoyltransferase II	IBG: Isobutyryl-CoA dehydrogenase
TYR-11: Tyrosinemia type II	De-Red: Dienoyl-CoA reductase	M/SCHAD: Medium/short chain L-3-hydroxyl acyl-CoA dehydrogenase
TYR-111: Tyrosinemia type III		

Source: [270]

At present, Canada does not have a national registry for rare diseases however, different stakeholders have established several disease-specific registries. For example, the cystic fibrosis patient registry by patient groups, the Genzyme rare disease registry (includes Poml8le, Gaucher, MPSl and Fabry) by industry, and the Canadian Fabry disease initiative by researchers. Some of these registries are linked at international level, which increases their potential value. For example, the Canadian neuromuscular disease registry, which is a nation-wide registry for people diagnosed with a neuromuscular disease. This registry participates in the international translational research in Europe-Assessment and treatment of neuromuscular diseases neuromuscular network (TREAT-NMD) and contains data of *over* 2400 Canadians affected by *over* 40 different rare diseases. There is a pressing need for unification of these registries to allow a cooperative use of its benefits [266].

The rate of research in the area of rare disease is scarce in the country though through CIHR, the government of Canada is supporting research in this area and playing leadership role via joining important international research initiatives. Since the launch of orphan drug legislation in 2000 in the USA, CIHR experienced an increase in their annual budget from~ Can$350m to~ Can$1b in 2009-10. Nevertheless, it was not until 2011 that the first specific funding for rare disease was announced with an allocation of maximum Can$14.5m between 2012-17 (271]. Amongst other initiatives, CIHR is supporting the development of Canadian branch of Orphanet (world's online reference portal for rare diseases). The organization is also playing vital role in the International Rare Diseases Research Consortium (IRDiRC), whose agenda is to enable the introduction of 200 new rare disease therapies and a means to diagnose most of them by 2020 [272].

Canada does not have an orphan drug designation or an independent orphan drug market authorization program. However, accelerated review is possible in certain circumstances. No market exclusivity is offered for the orphan drugs. Although some financial assistance is offered for the drug developers such as, tax incentives and fee reduction for market authorization. In addition, pre-licensing protocol assistance and regulatory assistance is provided. Public Service Health Care Plan which is increased from 80% to 100% *covers* drug's cost after the patient has reached a co-payment of Can$3000 (154].

Once drugs are approved by Health Canada, the Canadian Agency for Drugs and Technologies in Health (CADTH) Common Drug Review (CDR) is responsible for the reimbursement recommendation. The CADTH pan-Canadian Oncology Drug Review (pCODR) reviews cancer-based drugs. Reimbursement decision is prerogative of the provinces and territories. All jurisdictions have common reimbursement processes, while five provinces (British Columbia, Alberta, Ontario, Saskatchewan and New Brunswick) have established their own Drug for Rare Diseases (DRD) reimbursement process.

Alberta has a publicly funded, Rare Disease Drug Program, developed for ethical and compassionate reasons to support affected patients who find it hard to cope with the exceptionally high costs of DRD. In addition to ORD-specific program, the Alberta government has a Short-Term Exceptional Drug Therapy Program, which allows funding consideration for therapies that do not have current public or private funding avenue (which includes orphan drugs with or without market authorization). A separate evaluation framework for assessing funding for orphan drugs has been developed by the Ontario Ministry of Health and Long-Term Care under publicly funded drug program. New Brunswick has its own program "New Brunswick Drugs for Rare Diseases Plan" which include drugs reviewed through Ontario's DRD framework (265]. Canada has provisions for Managed access programs (MAPs) which facilitates patient access to orphan drugs (266]. A brief overview of rare disease coverage or reimbursement in five provinces is shown in Table 30. Table 31 sh ows evaluation and reimbursement status of several orphan drugs approved in Canada.

Table 32.Provinces/territories with ORD specific plans and processes

Provinces/Territories	Plan/Coverage	Processes
Alberta	Alberta's rare disease drug program for genetic LSD affecting 1:50,000 individuals (Alberta Health 2012b)	Application on case-to-case basis, includes drugs only for Gaucher, Fabry, Hunter syndrome and Pompe
New Brunswick	Drugs for rare diseases plan (Government of New Brunswick 20141)	MPS I, MPS II, Cryopyrin-associated periodic syndrome, Pompe disease and Niemann Pick type C
Ontario	Drugs for rare diseases evaluation framework (DRDEF)	Non-cancer related with annual incidence of <1:50,000 individual; access for all patients for with the indication rather than access for an individual patient. Submission review by the Drugs for rare diseases working group (DRDWG)
British Columbia	Expensive drugs for rare diseases (EDRD) program	Application review on case-to-case basis, drugs to be considered should cost >$50,000/patient, non-cancer related with prevalence of <1.7:100,000 individuals
Saskatchewan	The Saskatchewan drug plan	Annual incidence of <1:50,000 individuals

Source: [273]

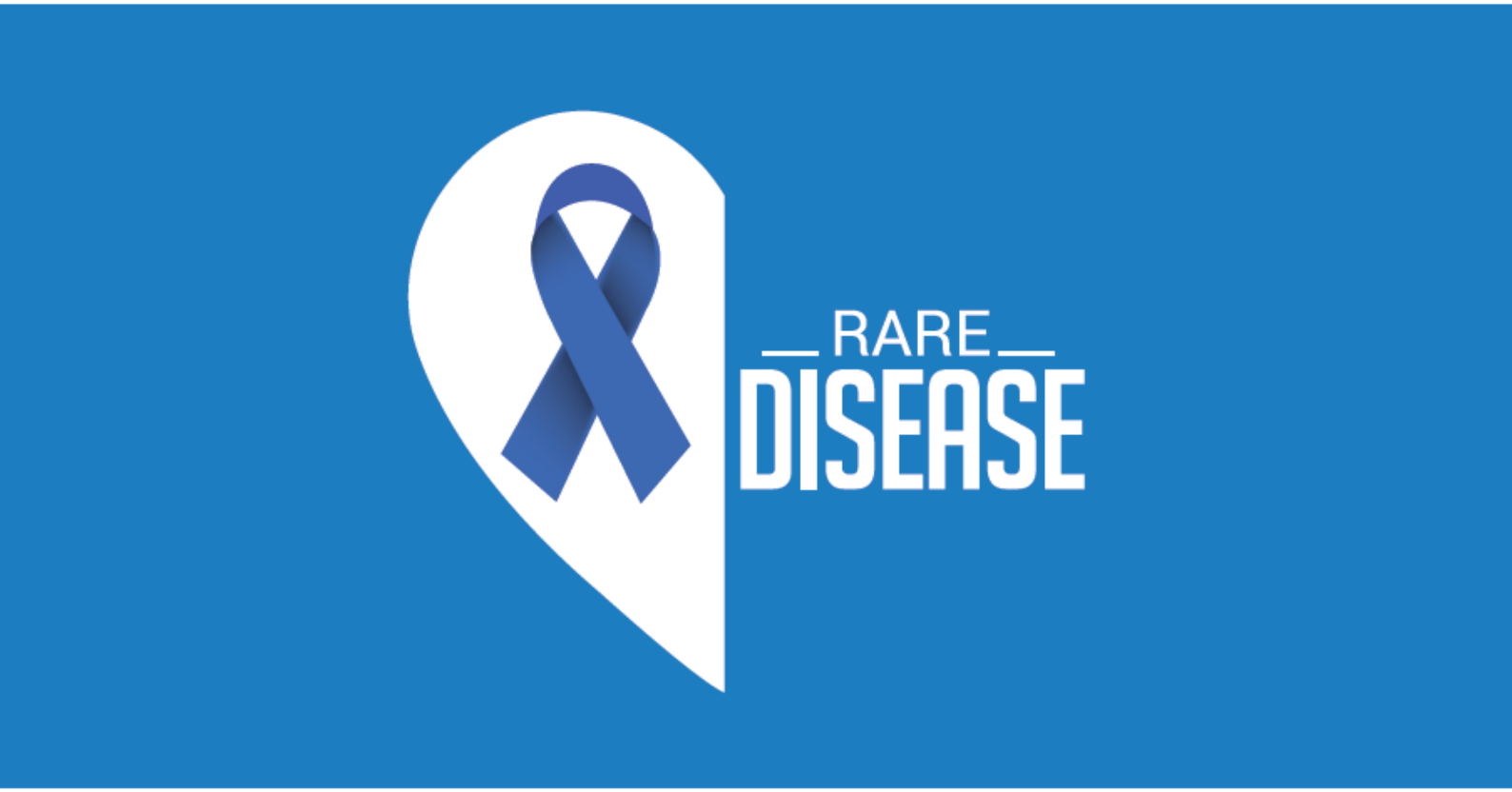


Table 33. Drugs evaluated using the Drugsfor Rare Diseases Working Group (DRDWG} framework.

Drug& Indication	DRDWG recommendation	Funding status	Price (Can$)	Average dose & annual drug cost/patient	Total drug expenditures (Can$)
Idursulfase (hunter syndrome)	Fund with criteria	EAP with criteria	$3,800/ 6mg vial	0.Smg/kg/week IV • 20 kg child - $400,000 • 70 kg adult - $1,200,000	$8,614,945 (Jun 2009-Jun 2012)
Alglucosidase: Adult & Infant-onset Pompe Disease	Fund with criteria	EAP with criteria	$840/ 50 mg vial	20 mg/kg/2 week IV • Adult-onset (70 kg): $600,000	$16,861,408 (Jun 2009-Jun 2012)
Miglustat: Niemann Pick, Type C	Fund with criteria	EAP with criteria	$109/ 100 mg capsule	12+ years old: 200 mg 3x/day PO under 12:100 mg/day to 200 mg 3x/day PO according to BSA $237,720	~$1,000,000 (Apr 2010-Jun 2012)
Laronidase: MPS I	Fund with criteria	IMD Program with criteria (Sep 2011)	$1,045/ 2.9 mg vial	0.58 mg/kg/week IV • 40 kg: $45,000 • 70 kg: $760,000	~$19,000,000 (Jan 2007-Apr 2012)
Galsulfase: MPSVI	Do not fund Unable to provide recommendation	IMD Program on case-by-case basis	$1984/ 5mg vial	1 mg/kg/week IV • 20 kg: $300,000 • 70 kg: $1,000,000	~$3,000,000 (Jul 2006-Jun 2012)
Vorinostat: Cutaneous T-cell lymphoma	Standard CED review Asked to reconsider & DRDWG recommended no funding due to lack of QOL data	Not funded	$75.50/ 100mg	400 mg/day PO $28,000 (based on median treatment duration of 147 days)	$0
Canakinumab: Cryopyrin-associated periodic syndrome	Fund with criteria	EAP with criteria	$16,000/ 150 mg vial	150 mg SC every 8 weeks $104,000	$0
Eculizumab: Paroxysmal nocturnal Hemoglobinuria	Standard CED review CED asked DRDWG assistance to develop model & funding criteria	EAP with criteria	$6,743/ 300 mg	600 mg weekly x 4 weeks; 900 mg on week 5 then 900 mg every 2 weeks IV $530,000	$8,678,053 (Aug 2011-Jun 2012)

Source: [274]

Abbreviation: EAP = Exceptional access program, CAD= Canadian dollars, BSA= Body surface area, MPS= Mucopolysaccharidosis, IMD = Inherited metabolic diseases, QOL = Quality of life, CED= Committee to evaluate drugs

6.7 JAPAN

In Japan, rare diseases originally were identified as "intractable diseases (Nambyo)". In 1995, Ministry of Health and Welfare revised the definition of Nanbyo as "a disease of unknown etiology with no effective treatment that presents a major financial and psychological burden and affects fewer than 50,000 of total patients. Currently, 330 disease groups are covered under Nanbyo programme by Ministry of health, labor and welfare (MHLW). Japan is the second country in the world to implement orphan drug legislation in 1993 [217]. However, no national plan is in place for rare disease.

In 2015, Japanese agency for medical R&D (AMED) along with Nanbyo researchers and Japanese university healthcare system launched "Initiative on rare and undiagnosed diseases (IRUD)". IRUD aims to construct an inclusive medical network and an internationally compatible data-sharing network [275]. So far IRUD has been successful in discovering 12 new diseases and diagnosing more than 800 patients who remained undiagnosed for several years but were identified within 6 months of registration within the program. The cons of this project is that it includes mainly doctors and researchers which leaves out the patient side involvement [276].

As per the amendment of the Pharmaceutical Affairs Act and Drug Fund for Adverse Reaction Relief and Research Promotion Act provides financial subsidies of up to 50% for research purposes and 10 years of market exclusivity [154,217]. In addition, Japan has independent orphan drug designation and market authorization, along with 15% tax credits, up to a 14% reduction in corporate tax and user fee waivers. In terms of the non-financial subsidy, priority review, fast track approval and free protocol assistance is provided to the drug manufacturers.

Fixed pricing which includes 10% cost plus and price-control is negotiated by Japanese National Health Insurance (NHI) and pharmaceutical industries. 100% reimbursement is ensured for approved orphan drugs which in part is covered with 30% coverage from insurance companies and 70% coverage by national/regional government [154].

Newborn screening (NBS) began in Japan in the year 1967. Cost of NBS is borne by Japanese government under its universal healthcare system. Conditions covered under NBS are congenital hypothyroidism (CH), phenylketonuria (PKU), galactosemia, Maple syrup urine disease (MSUD), congenital adrenal hyperplasia (CAH) and homocystinuria. Since 2012, NBS has been expanded to include other amino acid disorders, fatty acid disorders, organic acid disorders, LSDs and Pompe disease. However, LSDs and Pompeis currently rolled out for select population [277].

In the year 1997, Japanese government established the Japan intractable diseases information centre. The website contains general information on the 330 rare and intractable diseases, list of experts in the area of rare diseases and contact addresses of patients support group [278].

7. CHALLENGES ASSOCIATED WITH RARE DISEASE

Rare disease impacts not only the health and well-being of a patient but affects several aspects of their life including social facet. The condition many a times impact even the basic daily-routine tasks. Many of these conditions are life-long and debilitating and in severe cases can lead to death at a very young age. Patients often report that the effect of their rare condition stretch well beyond health and trespasses into their emotional and mental wellbeing. Depression, stress and anxiety are common conditions associated with rare disease patients owing to various reasons ranging from being unwell to years of misdiagnosis and difficulty in accessing correct treatment (279). On social front, patients are at disadvantage when accessing basic privileges as education and employment. This is not only due to their inability in attaining a job but in part due to insufficient facilities to support such patients (Figure 23). Integration of rare disease patients in society is a considerable. In addition, the financial wellbeing of rare disease patients and their family can be adversely and brutally impacted due to the long-lasting effect of these conditions.

It is comforting to see that rare diseases are slowly gaining attention worldwide to stimulate the research, development and marketing of medicinal products of rare diseases. Even with all the advancements, there are myriad challenges associated with rare diseases such as lack of knowledge/training, delayed diagnosis, limited understanding about the pathophysiology of diseases, lack of treatment, and lack/limited access to therapy or medical care (280).

Figure 23.Complex health and social challenges affecting rare disease patients

7.7.1. Lack of appropriate definition

Several countries across world have defined rare disease in their jurisdiction, which has helped them with the policy makings and designing national plans for rare diseases. This however, is not the case with most countries as seen in this report. Out of the 19 countries discussed in this report only 9 countries have official definition for rare diseases. Even advanced economies such as Australia, Hong Kong and Canada have failed to define rare diseases. Often countries with growing population face this issue of setting a static definition in a dynamic economy [279]. Recently, in a major setback after introducing national policy for the treatment of rare diseases in India in 2017, the Central government withdrew the policy. One of the reasons cited for this withdrawal is inaccurate definition of rare diseases.

7.7.2. Lack of Knowledge and Training

At present there are more than 6000 rare disease conditions currently known and this number is escalating continuously with an increase of more than 250 conditions every year. Many physicians are not knowledgeable about many of these conditions and cannot identify the symptoms correctly and are either not trained in rare diseases. A recent report by the UK think-tank "2020 health" confirms lack of experience in the medical specialists [261]. It has been observed that patients with same rare disease condition may present different symptoms and as such medical doctors and general practitioners cannot be expected to be familiar with many rare conditions. Lack of training becomes even grave in rural and lower economy countries. All this culminates into years of delay in diagnosis which is already complicated due to the complex etiology of rare conditions. Across countries lack of knowledge and sufficient training support has been identified as one of the major barriers for rare disease patients [62].

7.7.3. Scarcity of Information and Information Exchange

Availability and dissemination of information pertaining to rare disease is scarce at this point of time. It has been pointed as one of the major hurdles in the field of rare diseases. Lack of scientific knowledge and valuable information about the conditions make disease diagnosis challenging. In other words, dearth of information leads to less interest from research community, pharmaceutical industries, medical doctors, government and policymakers. According to several reports, patients often complain that there is lack of information either in early stages of diseases or after initial diagnosis [280].

7.7.4. Delay in Diagnosis and Prevention

Amongst other complicating factors, delay in diagnosis or misdiagnosis of rare diseases is a major contributor. Scarcity of medical experts, research gaps and information insufficiency, which leads to delay in diagnosis is one of the major issues as reported by rare disease patient community. This issue is further convoluted as signs and symptoms of rare disorders present differently in individual patients for same condition. Over the years, it has been observed that rare disease patients are frequently misdiagnosed, and in many cases, diagnosis may take up to 6-8 years or even longer. This is valuable period of time in the life of a rare disease patient as a big proportion of these patients only live up to 5 years of age due to their condition.

Currently, several metabolic disorder such as phenylketonuria, lysosomal storage disorders like Gaucher, Fabry, mucopolysaccharidosis and Pompe are preventable and treatable. Screening at an early age can help lot of children who may be affected by rare conditions and permanent disabilities or death.

7.7.5. Need of Specialized Care and Treatment

The population affected by rare diseases is often small, heterogeneous and the diseases are complex in nature. This warrants specialized care and treatment for these patients. Often time the symptoms of one patient varies significantly from other patient affected with same rare condition. Hence, patients may need personalized treatment. Normal clinics and hospitals are often lacking in the proper facilities needed to provide primary and palliative care to these patients. Establishing special clinics and rare disease expert centers will go miles to help these patients and their caregivers with timely and required attention.

7.7.6. Lack of Treatment

According to the current available information, only 5% of known rare diseases have some treatment options, which essentially means 95% of the patients are still desperately waiting to get treatment for their condition. As mentioned in earlier section, over the years diagnosis of rare disorders has improved with the advent of techniques such as tandem mass-spectrometry for oncology followed by metabolic disorders, and provisions for newborn screening. A fundamental issue with development of rare disease treatment is their complex pathophysiology or the natural history of the rare conditions, which remains a mystery in most cases. Amongst the available treatments, most therapies are aimed at managing the diseases as against to curing them. However, the accessible treatments have helped patients with improvement of their quality of life and extended their life span.

In a study by Heemstra et al., prevalent rare diseases receive more attention for research and drug discovery programme compared to less prevalent diseases [281]. This was further reinforced by a report by Yin, according to which "the US Orphan Drug Act" led to a substantial and steady growth in number of clinical trials for prevalent rare diseases, but not for less prevalent rare disorders [282].

7.7.7. Accessibility of the treatments

Another hurdle associated with delivery of orphan drugs to rare disease patients is unreliable access and reimbursement of orphan drugs after-market authorization. The accessibility is often hindered due to plethora of reasons ranging from: high cost of orphan drugs, pressure on national healthcare budgets, public policies, and reimbursement of orphan drugs [283]. Another reason for the accessibility of orphan drugs is the delay in market authorization. In advanced countries such as US and EU, drugs are generally approved in few years but in several others, it may take up to 8 years.

7.7.8. Public Health Priorities

According to health systems and policymakers, the number of patients suffering with rare diseases are scarce when compared to any common disease. This pushes the urgency to attend the needs of rare disease patients down on the list of respective governments. Albeit the outer picture being seemingly less intimidating, the reality remains that in aggregate the population of rare disease affected individuals is about 400-500 million worldwide. This is a huge number especially in the light of the fact that most of them are either life-threatening or may cause permanent disability [284]. Moreover, without appropriate definitions and identification it is difficult for policymakers to make rare diseases a priority.

7.7.9. Pricing and reimbursement

The cost of research and development of orphan drugs is substantially high, especially owing to the low prevalence of rare diseases. Pharmaceutical companies are dispassionate about focusing on this area of disease since the market is relatively small, highly specialized needs, development costs of orphan drugs are high, navigation of procedure for market authorization are intricate and the incentives from governments are not favorable or non-existent in different economies.

Some of the advanced economies such as the US and Europe have national plans and insurance coverage to cover the costs of these exorbitant drugs for the rare disease population. Orphan drugs that are not covered by insurance are realistically inaccessible to patients owing to their high cost [154]. Even with the costs-sharing the extent of coverage varies country to country and patients still have to share costs either as co-payment or coinsurance, which hinders orphan drug accessibility [286]. In many countries, for example, India and China, which currently do not have orphan drug legislations, these drugs are often self-funded and constitutes "out-of-pocket expenses" [154].

7.7.10. Lack of funding in research and clinical trials

A fundamental challenge in drug development for rare diseases is the lack of in-depth knowledge about the pathophysiology of the diseases. Even for the rare conditions which have some kind of treatment available or under research, face a major issue while navigating drug development and clinical development path. These issues are further complicated by lack of funding. The high cost associated with the research especially in terms of requirement of sophisticated method and machinery of drug development deters interests of venture capitalist and other investors from investing into R&D for orphan drugs.

Further down the line, during the clinical phase orphan drugs face numerous challenges such as: small patient population, clinical trial logistics, lack of acceptable preclinical model, insufficient know-how about the potential biomarkers of rare diseases, meaningful clinical endpoints, limited number of experts and ethical issues such as use of placebo.

7.7.11. Lack of common voice

Over the last several decades, with the institution of orphan drug legislation in the US and other countries, various advancements have been witnessed by the rare disease community. Based on our independent secondary research, we observed that countries across Asia and other continents, have many patient organizations pushing a particular rare disease cause forward within their jurisdiction. However, most of them have not been able to make any significant progress. It is imperative that different stakeholders which includes patients, families, caregivers, patient organizations, pharmaceutical companies and policymakers should come together, may be as an umbrella organization to make a unified voice. In this way, a more coordinated approach can be adopted by the concerned bodies to come up with solutions to solve the challenges associated with rare diseases.

Interest from different stakeholders has been seen in the field of rare diseases and efforts have been made to advance the causes of rare disease patients and families, in terms of access to treatment or social benefits. However, one thing that has been pointed by many patients and caregivers is that although stakeholders are advancing the cause, but they do so from their individual perspectives which often leads to futile efforts or means less benefit for the suffering community.

8. RECOMMENDATIONS FOR THE VARIOUS STAKEHOLDERS

Based on our secondary research and interaction with the experts in the area of rare disease, we are presenting recommendations for the improvement of issues associated with rare diseases. In simple terms, following are the areas that needs urgent attention and are main pain points for the rare disease community:

1. There is a strong need for harmonization amongst different stakeholders concerned with rare diseases. Figure 24 shows the key stakeholders involved with rare diseases and the need for collaborative efforts aimed at patient centric partnerships for the evolution of better treatment, quality life for rare disease patients and to mitigate the obstacles faced by these patients.

Figure 24.Partnerships and coordinated efforts essential between different stakeholders involved in the health and welfare of patients with rare disease

Source: [2]

2. To develop adaptive and inclusive definition for rare disease. This is essential in order to provide the necessary push to the policymakers to develop orphan drug legislation and national plan for rare diseases. In order to establish a policy framework, it is imperative to recognize that orphan drugs and rare diseases are altogether a different arena which means it requires a unique framework and funding mechanism and comparing them with other common diseases will only push the cause in reverse.

3. Information and knowledge about rare diseases is limited, which makes it difficult for rare disease patients, families, caregivers and clinicians to identify the signs and symptoms at an early stage of the disease. Hence, it is pragmatic that information about rare disease be made easily accessible and comprehendible for the patients and their caregivers. Limited number of specialists are available in most jurisdictions and often found only in urban areas, making it almost inaccessible for patients in rural areas to approach them due to associated logistics and high cost.

   It has been noticed that several countries have made considerable efforts in this direction. For example, several USA organization such as National Institutes of Health (NIH), National Organization of Rare Disorders (NORD) and Food and drug Administration (US FDA) and European Organization for Rare Diseases (EURORDIS), ORPHANET and European Platform for Patient's Organizations, Science and Industry (EPPOSI) have made progress to improve the collation and exchange of information regarding rare diseases. ORPHANET has been working on international level to provide better infrastructure and has succeeded in registering a total of 5954 rare diseases. Such organizations have been able to provide support to patients, facilitate information access to patients, allows information exchange and networking which can improve research and development on rare diseases [287].

4. R&D for common disease drugs is a complex process, which costs billions of dollars and many times end up in a dead end. The process of drug development for rare diseases is further perplex and is often more difficult to overcome. The problems are confounded with small number of population, lack of meaningful data points and logistical issues. According to a report by Shire, for clinical trials for idursulfase, a treatment for Hunter Syndrome, recruitment of 96 patients was done, which at the time made it the largest study for rare disease. In order for the recruitment of the aforementioned patients, Shire had to open 15 sites globally and yet entire families had to be relocated from one country to another [288]. This in turn demands the need to develop innovative drug trials, designed to address the small patient population of rare diseases and to be equipped with relevant clinical endpoints from limited data [288]. Additionally, better regulatory pathways unambiguously designed for rare diseases are required which can only be designed by the joint efforts from industries, policy-makers and regulatory authorities, such as Food and Drug Administration (FDA) and European Medicines Agency (EMA). These pathways will enable in early orphan drug registration, designation, faster and more drug approvals [288,289].

5. Despite development of orphan drugs, their access by patients in several countries and remote areas is still lacking. Every country need to develop their infrastructure for orphan drug access, which essentially should be done at two different levels:
   1) *Internally* i.e. with the government, hospitals, specialists and NGOs;
   2) *Externally* i.e. in collaboration with other countries and international patient organization (for example, NORD and EURORDIS) to be able to provide early access of orphan drugs to the suffering patients.

6. To progress the field of rare disease with sustainable progress, payers need to be engaged in a rare disease programme at an early stage to better understand and define appropriate measures for reimbursement and to further inculcate these measures into the clinical development plan.

7. Orphan drugs need to have a better economic evaluation method. With the introduction of Health Technological Assessment (HTA), these drugs are mostly evaluated based on cost-benefit ratio, which is not an effective method of assessment for orphan drugs. As discussed previously, currently 95% of the rare diseases do not have any kind of treatment option available for the patients. This when multiplied with the high costs of orphan drugs, which is usually higher >100,000 USD in most cases confounds the issue further. Based on cost-benefit ratio most orphan drugs will never be approved. High cost of orphan drugs is a highly debatable topic within most health systems around the globe. Health policy makers and governments are often torn between whether to help rare disease patients by allocating high budget which will help only few patients versus allocating it to help several thousand affected with common diseases. Although the budget allocated to rare diseases is a small hole in the pocket of government when compared with the total national health budget yet a discord exists between rare diseases patient community and policy makers. Moreover, health economics, should not only consider the cost of drug as a primary consideration but other factors such as socio-economic status of the patient, health and other benefits.

   In an exemplary example, Thailand in 2016, fixed the cut-off incremental cost-effectiveness ratio to be below THB 160,000 per quality-adjusted life year (QALY). Surprisingly, for type 1 Gaucher disease, there budget impacts and equity issues made funding for this disease a positive economic choice, irrespective of the high ICER ofTHB 6,300,000 per QALY or 40 times higher than the ICER cut-off. This is an encouraging idea for orphan drug funding and points to the fact that while making decisions for such drug funding's, cost-effectiveness is not the only parameter to be considered. Several other factors that should be considered should be participation of different stakeholders, strong government commitment for the cause, establishment of guiding methods and procedure and solid enforcement. The progress in Thailand's orphan drug market access will increase awareness in funding bodies across the SEA region [1].

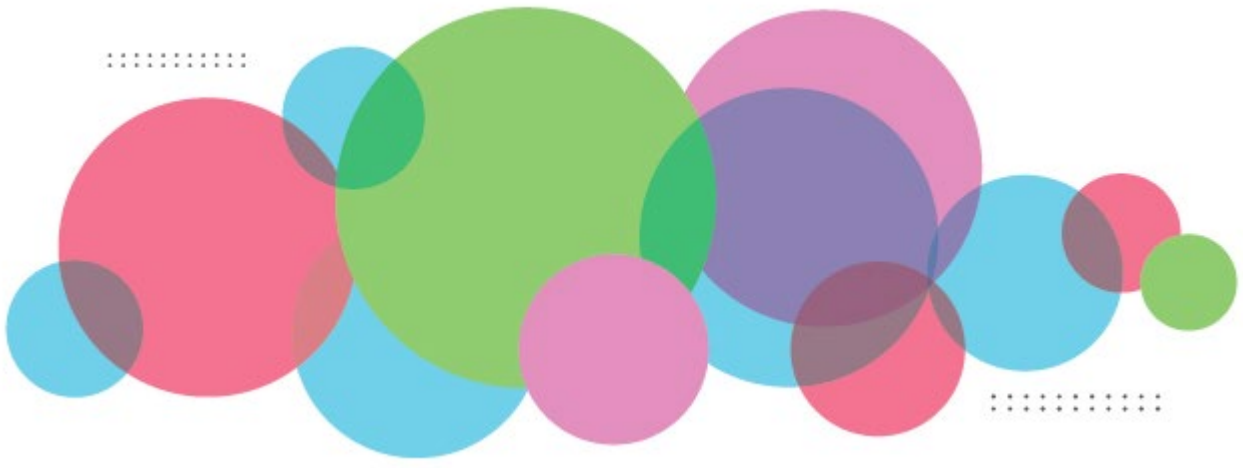
8. Healthcare is a human right and hence it should be provided to all citizens independent of their health status. More often than not rare disease affected patients face discrimination, inequity in terms of how society perceives them and unequal job opportunities. As such the burden of rare diseases is astonishingly high and these prevalent injustices adds to the already existing non-monetary issues.

9. As discussed in previous section, most physicians are unaware about the signs and symptoms of the rare diseases, not only in third-world countries but in developed economies as well. This issue is further escalated owing to the high number of rare diseases both known and unknown. It is equally urgent and essential that not only the specialists, physicians but also secondary workers who are involved in the treatment and care of rare disease affected population should be well-trained to provide efficient care and support to the needy. In addition, to take advantage of fast-evolving technologies, established networks, and available tools, it is indispensable to educate physicians and engage patients and families.

10. Many countries in the recent past have managed to issue national plan or are in the process of developing one. However, one thing that we have noticed is that most of these countries have failed to implement these plans at national levels and hence the rare disease community cannot reap the full benefits of such plans. A recent example is the India's failed policy for rare disease treatment. A better implementation and efforts to raise awareness is the need of the hour.

11. As discussed in earlier sections, one of the issues associated with rare disease is lack of national registries where all the information about such patients can be collated at a single place in a given demographical region. This will allow the government, hospitals, physicians, patients and caregivers easy access to the available information to provide better treatment and support. Currently, individual countries have several individual disease registries. However, they fail to attract the deserved attention from government, policy makers and pharma companies. It is therefore, quintessential that these local registries be unified under a national portal to provide better quality information and easy access [205].

12. Presently, rare disease advocacy organizations are either for a particular disease or for very specific and limited subset of prevalent rare conditions. They are quite disbursed, which dilutes their presence in making enough noise for the rare disease patients. Individually, these organizations are very small, but together they constitute a huge community [288]. These organizations aim to provide support and care for rare disease patients and their caregivers. However, on their own it is arduous and improbable for these organizations to provide sophisticated level of healthcare and support. And so, it is highly advisable that rare disease organizations unify within a given geographical region, which will help them obtain more funding, required attention and better support and care from the needed agencies.



9. APPENDIX

Table 34.List of rare diseases from the Notice on the First National List of Rare Diseases in China. The following list was jointly issue by five bodies including the National Health Commission

No.	Diseases	No.	Diseases
1	21- Hydroxylase Deficiency	23	Congenital Scoliosis
2	Albinism	24	Coronary Artery Ectasia
3	Alport Syndrome	25	Diamond-Blackfan Anemia
4	Amyotrophic Lateral Sclerosis	26	Erdheim-Chester Disease
5	Angelman Syndrome	27	Fabry Disease
6	Arginase Deficiency	28	Familial Mediterranean Fever
7	Asphyxiating Thoracic Dystrophy (Jeune Syndrome)	29	Fanconi Anemia
8	Atypical Hemolytic Uremic Syndrome	30	Galactosemia
9	Autoimmune Encephalitis	31	Gaucher's Disease
10	Autoimmune Hypophysitis	32	General Myathenic Gravis
11	Autoimmune Insulin Receptopathy (Type B Insulin Resistance)	33	Gitelman Syndrome
12	Beta-Ketothiolase Deficiency	34	Glutaric Acidemia Type I
13	Biotinidase Deficiency	35	Glycogen Storage Disease (Type I, II)
14	Cardic Ion Channelopathies	36	Hemophilia
15	Carnitine Deficiency	37	Hepatolenticular Degeneration (Wilson disease)
16	Castleman Disease	38	Hereditary Angioedema (HAE)
17	Charcot-Marie-Tooth Disease	39	Hereditary Epidermolysis Bullosa
18	Citrullinemia	40	Hereditary Fructose Intolerance
19	Congenital Adrenal Hypoplasia	41	Hereditary Hypomagnesemia
20	Congenital Hyperinsulinemic Hypoglycemia	42	Hereditary Multi-infarct Dementia (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalqpathy, CADASIL)
21	Congenital Myasthenic Syndrome	43	Hereditary Spastic Paraplegia
22	Congenital Myotonia Syndrome (Non-Dystrophic mytonia, NDM)	44	Holocarboxylase Synthetase Deficiency

45	Homocysteinemia	68	Medium Chain Acyl-CoA Dehydrogenase Deficiency
46	Homozygous Hypercholesterolemia	69	Methylmalonic Academia
47	Huntington Disease	70	Mitochondrial Encephalomyopathy
48	Hyperornithinaemia-Hyperammonaemia-Hhomocitrullinuria Syndrome	71	Mucopolysaccharidosis
49	Hyperphenylalaninemia	72	Multi-Focal Motor Neuropathy
SO	Hypophosphatasia	73	Multiple Acyl-CoA Dehydrogenase Deficiency
51	Hypophosphatemia Rickets	74	Multiple Sclerosis
52	Idiopathic Cardiomyopathy	75	Multiple System Atrophy
53	Idiopathic Hypogonadotropic Hypogonadism	76	Myotonic Dystrophy
54	lgG4 related Disease	77	NAGS Deficiency
55	Inborn Errors of Bile Acid Synthesis	78	Neonatal Diabetes Mellitus
56	Isovaleric Acidemia	79	Neuromyelitis Optica
57	Kallmann Syndrome	80	Niemann-Pick Disease
58	Langerhans Cell Histiocytosis	81	Non-Syndromic Deafness
59	Laron Syndrome	82	Noonan Syndrome
60	Lever Hereditary Optic Neuropathy	83	Ornithine Transcarbamylase Deficiency
61	Long Chain 3-hydroxyacyl-CoA Dehydrogenase Deficiency	84	Osteogenesis Imperfecta (Brittle Bone Disease)
62	Lymphangioleiomyomatosis (LAM)	85	Parkinson Disease (Young-onset, Early-onset)
63	Lysine Urinary Protein Intolerance	86	Paroxysmal Nocturnal Hemoglobinuria
64	Lysosomal Acid Lipase Deficiency	87	Peutz-Jeghers Syndrome
65	Maple Syrup Urine Disease	88	Phenylketonuria
66	Marfan Syndrome	89	POEMS Syndrome
67	McCune-Albright Syndrome	90	Porphyria

91	Prader-Willi Syndrome	106	Sitosterolemia
92	Primary Combined Immune Deficiency	107	Spinal and Bulbar Muscular Atrophy (Kennedy Disease)
93	Primary Hereditary Dystonia	108	Spinal Muscular Atrophy
94	Primary Light Chain Amyloidosis	109	Spinocerebellar Ataxia
95	Progressive Familial Intrahepatic Cholestasis	110	Systemic Sclerosis
96	Progressive Muscular Dystrophies	111	Tetrahydrobiopterin Deficiency
97	Propionic Acidemia	112	Tuberous Sclerosis Complex
98	Pulmonary Alveolar Proteinosis	113	Tyrosinemia
99	Pulmonary Cystic Fibrosis	114	Very Long Chain Acyl-CoA Dehydrogenase Deficiency
100	Retinitis Pigmentosa	115	Williams Syndrome
101	Retinoblastoma	116	Wiskott-Aldrich Syndrome
102	Severe Congenital Neutropenia	117	X-linked Agammaglobulinemia
103	Severe Myoclonic Epilepsy In Infancy (Dravet Syndrome)	118	X-linked Adrenoleuko Dystrophy
104	Sickle Cell Disease	119	X-linked Lymphoproliferative Disease
105	Silver-Russell Syndrome	120	Idiopathic Pulmonary Fibrosis
		121	Idiopathic Pulmonary Arterial Hypertension

Source.[11]

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