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To: panel_hs@legco.gov.hk

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Subject: 【補充資料】就4月11日立法會衞生事務委員會《有關罕病政 策及藥物》特別會議的補充文件

香港特別行政區立法會

衞生事務委員會

致衞生事務委員會成員：

自衞生事務委員會於2017年4月11日的特別會議上再次討論《罕見疾病的政策及藥物》後，罕盟得悉部分議員希望更切實了解香港以外各地罕見疾病政策或措施的落實及發展程度，故罕盟現特隨函附上一篇國際期刊《Review of 11 national policies for rare diseases in the context of key patient needs》的英文原文及中文譯文，予諸位委員作補充參考資料。

罕盟期望此期刊能協助　閣下了解罕病政策的普及性與各地針對罕病發展所進行的工作。並以此作借鏡，為香港罕見疾病政策定下策略性框架及時間表。若　閣下希望掌握更多有關罕見疾病議題的資料和現況以便跟進，歡迎隨時與罕盟聯絡（電話號碼：2708 9363）。

祝工作順利、生活愉快！

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香港罕見疾病聯盟
Hong Kong Alliance for Rare Diseases

從病人的核心需要審視 11 個國家的罕病政策

Saifyya Dharssi, Durhane Wong-Rieger, Matthew Harold and Sharon Terry

(Review of 11 national policies for rare diseases in the context of key patient needs 中譯本)

Dharssi et al. Orphanet Journal of Rare Diseases (2017) 12:63

概要：

罕病所表現出的嚴重程度與患者數目，均對全球的公共衞生系統構成負擔。對很多病人而言，他們往往面對沒有適當護理、延誤診斷、治療方案有限甚至缺乏等障礙。這些挑戰迫使罕病病人團體擔當重要角色，提升病人的聲音和推動立法，支持發展照顧罕病病人需要的計劃。

在這個過程中，美國於 1983 年訂立的《孤兒藥品法》(Orphan Drug Act)，成為里程碑，為其他國家提供了路線圖，引進和實施類似的孤兒藥立法。最近，歐盟進一步鼓勵採用和實施更廣泛針對罕病的規劃或策略，更充份正視罕病病人的全面需要。儘管有這些立法工作，甚或不少病人倡議組織已投入更大力度推動採納和實施罕病規劃，各國在落實罕病政策的程度或範疇上依然存有落差。為了更深入了解這些關卡和挑戰，我們必須抓緊機會，找出罕病病人的核心需要，故此綜觀現時不同地域以及不同經濟狀況的國家中的罕病立法情況和政策發展水平，便至關重要。

我們分析了 11 個國家的罕病政策：德國、法國、英國、加拿大、保加利亞、土耳其、阿根廷、墨西哥、巴西、中國和台灣。我們以五個病人最需要的方面評估每個國家的政策的實施及情況：改進護理的統籌、診斷的資源、治療的可及性、病人的認知和支援，以及促進創新研究。我們的研究結果顯示，病人群體在推動改善罕病護理的立法及規劃有著持續的角色。另外，我們發現即使全民罕病規劃為改善護理提供重要的指引，不同國家實施的情況不一。我們需要更多的研究，揭示某些罕病規劃的具體元素對病人的成效。

背景：

罕病是全球公共衞生議題

個別罕病在定義上只是影響少數人，但累積起來卻對公共衞生有著顯著的影響。即使不同國家對不同罕病有不同定義，一般的界定準則每 50 萬人中少於 1 人至每 2 千人中少於 1 人。美國 1983 年訂立的《孤兒藥品法》，以受影響人數來定義罕病；而根據此定義，實際罕病的流行程度根據不同人口數目有所不同。當一個疾病影響少於 20 萬人，便被視之為罕見，而其他國家則以流行比例作為準則。例如，歐洲的罕病定義是每 1 萬人中少於 5 人。巴

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西則類似世界衛生組織的界定，即每 10 萬人中少於 65 人。台灣的罕病界定準則為每 1 萬人中少於 1 人。

估計全球約有 5000 至 8000 種認定的罕病，影響約 6 至 8%的人口。不同罕病在病因學及臨床表現上有相當的差異，但大部份都會嚴重影響壽命、體能及精神能力。此外，不論國家的大小及人口，罕病造成明顯的經濟負擔，這源於增加的醫療開支及損失的生產力。

不少罕病病人在尋求護理時遭遇障礙，當中只有少於百份之十的人獲得對應性的治療。延誤治療、有限的資源及欠缺對應性的治療，往往令病人不能得到適當及時的護理。即使是診斷稍為延遲，已經對結果帶來強烈的影響。除此之外，超過 40%的罕病患者，更因錯誤診斷加劇了延遲治療的情況。即使病人獲得診斷，不少人亦難以得到所需資源，包括專科中心、適當統籌的護理、病人支援系統及有效的治療。對於很多罕病來說，不單止沒有有效的治療方法，甚至連病情進展的資料也非常有限。因此，必須進行自然歷史（natural history）及深層的病理生理學（pathophysiology）研究，才能為開發針對性藥物奠下基礎。

透過提升病人的聲音，以及在回應病人需要的計劃中成為伙伴，病人群體在應對挑戰上，扮演著重要的角色。大約三十五年前，在美國罕見疾病組織(National Organization for Rare Disorders)的旗幟下，形成對罕病的關注及支持的病人運動。在一位母親（阿貝·邁耶斯 Abby Myers）、一位國會議員（Henry Waxman）及一位演員（Jack Klugman）共同領導及推動下，罕病在一系列頭條事件(headline events)中，獲得全國公眾的注意，並且促使眾議院在 1983 年通過世界上第一項孤兒藥品立法。對於全國性的罕病政策的發展，這是奠基性的時刻，亦改變了罕藥發展的情況。從立法前的十年，只有十種新藥出現，立法後的三十年，已有超過 500 款新藥面世。《孤兒藥品法》的成功，令到其他國家相繼引入同樣的立法，包括日本、新加坡、韓國、澳洲及歐盟等。

當立法的工作較多集中在罕病創新治療的發展時，歐盟顯得更具前瞻性，他們認為有必要廣泛確保應對罕病患者的所有需要的全面性政策規劃。2009 年，歐洲議會採納了「罕病行動的建議」（Recommendation on an Action in the Field of Rare Diseases），以支持採納罕病的全民規劃及策略。歐洲理事會（European Council）建議發展全民規劃及策略來應對全面的需要，包括診斷、治療、護理及對罕病患者的支援。它鼓勵不同國家考慮不同的政策方面，包括增加對罕病的重視、支援相關研究、發展專科中心、病人組織的充權及實行健全的醫療基本架構。

一些國家在歐洲議會推出建議前，已有相關的政策。法國領先於其他成員國，在 2004 年採納全民罕病規劃。規劃創建了專科中心，用來統籌診斷及提供醫療及社會的照顧，編製關於診斷、護理、數據收集、進行臨床測試的全國性的方案。法國的全民規劃亦成為所有已發展或正在發展全民罕病規劃或策略的歐盟成員國的推動力及模範。在亞太地區，台灣有一套

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訂定的計劃，罕病被納入在全民的殘疾登記名冊，政府的社會服務計劃為罕病病人提供醫療津貼及扣稅、學校費用減免、就業支援及交通優惠。相似地，日本在 1972 年為罕見或難以對付的疾病（nanbyo）特別立法，約 130 項特別指定的頑疾（tokutei shikkan）或特別指定的罕病接受公共資助的護理。

當全民罕病規劃演進，病人及病人倡議者繼續擔當整全的角色，推進實施及採納計劃中的不同部份。歐洲就發展全民罕病規劃的專案（The European Project for Rare Diseases National Plans Development，EUROPLAN）曾經是一個由歐盟委員會（EU Comission）共同資助的項目，用作推動及實施罕病的全民規劃或策略，分享不同國家的相關經驗，在歐洲層面連結不同國家，得以有著共同策略。很重要地，以上專案有著有組織的病人參與，及曾在指導制訂及實施罕病的全國計劃或策略中，擔當重要的角色。為了達到目的，該專案包括了一個特定的角色 -- 予歐洲罕病聯盟（The European Organisation for Rare Diseases , EURORDIS）—— 一個包含歐洲不同罕病及病人的非政府組織的傘式組織（umbrella group）。歐洲罕病聯盟（EURORDIS）確保上述專案（EUROPLAN）的過程能夠反映病人的觀點，包括透過舉辦一系列的會議討論歐盟及國家政策的統籌。歐盟委員會成立一個罕病專家的委員會——歐盟罕病專家委員會（European Union Committee of Experts on Rare Diseases, EUCERD）聯合行動，去制訂及實施與罕病作戰的政策。EUCERD 聯合行動的期限在 2013 年 7 月完結，並以歐盟委員會的罕病專家組(EC Expert Group on Rare Diseases)來替代。該專家組繼續有病人組織的高度參與。透過由第三屆歐盟衛生計劃資助，名為「RD－Action」的 2015 年至 2018 年的共同行動，罕病政策的完整化及法典化的改善得以繼續。

歐洲罕病聯盟（The European Organisation for Rare Diseases , EURORDIS）繼續扮演一個不可或缺的角色，代表病人聲音及推動採納重要的罕病及孤兒藥立法。除此之外，國家層面的類似組織，如加拿大罕病組織（Canadian Organization for Rare Disorders, CORD），積極地扮演重要的角色推動政策發展。以上兩個組織制定了主要的立場書，列出公共決策者應最優先考慮的事項，以回應罕病病人的需要。每個國家的政策及計劃，均反映了他們醫療制度的優次及罕病病人的需要，歐洲罕病聯盟（EURORDIS）及加拿大罕病組織（CORD）的立場書就提供了一個通用但全面的框架，能夠適用於大部份的國家。因此，我們在這份文件根據歐洲罕病聯盟（EURORDIS）及加拿大罕病組織（CORD）的立場書所列舉的目標，分析 11 個不同國家的罕病的法例及相關政策、規管及計劃。這項審視是用來理解是否有機會進一步改善政策，檢查這些政策及計劃是否與罕病社群的五個方面的核心需要一致： 1. 改進護理的統籌、2. 診斷的資源、3.治療的可及性、4.病人的認知及支援及 5. 促進創新研究。我們亦考慮病人倡議組織的貢獻，及包括一些外在醫療規定的措施，作為現時罕病政策如何與醫療護理的形勢一致的起始考慮。這份研究的發現，將會啟發未來如何把罕病的全民規劃或策略的特定元素，轉化為護理罕病病人的規定。

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方法：

這項研究的資料從 11 個國家收集及分析，包括德國、法國、英國、加拿大、保加利亞、土耳其、阿根廷、墨西哥、巴西、中國及台灣。我們選取不同地域及社會經濟狀況的國家來分析，以代表更廣泛的罕病政策發展。我們沒有選取美國，因為它缺乏正式的全民罕病規劃及不同州份的政策差異，難以與其他國家作出比較。全民罕病規劃（National Rare Disease Plan, NRDP）這個名詞，是指透過全面及完整的方法，已經形成向罕病病人提供醫療及社會護理的策略及規劃。

我們以可公開查閱的官方文件及二手研究來評估全民罕病規劃（NRDP）。根據已公開的罕病政策的指引，我們評估以下全民罕病規劃中的元素：

- 國家政策
- 治療的可及性
- 診斷計劃
- 護理的統籌
- 研究
- 病人參與

我們以五項罕病社群的核心需要來評估資料： 包括：改進護理的統籌、診斷、治療的可及性、病人的認知及支援、研究。

結果：

表格一顯示了十一個國家的全民罕病規劃（NRDP）中的每一個政策元素的狀況。我們以整體醫療或經濟的狀況，即以人均本地居民總收入（Gross National Income, GNI）、醫療支出佔本地生產總值比例及全民罕病規劃（NRDP）的發展水平。法國及德國在國家層面已實施發展良好的全民罕病規劃（NRDP）。在調查的 11 個國家中擁有最高醫療支出及平均財富醫療（average wealth healthcare）， 法國及德國就罕病有集中的國家資金、良好的治療途徑、蓬勃的研究倡議、經統籌的網絡及跨境的合作。英國及加拿大有相似的醫療架構與全民罕病規劃（NRDP）， 兩者已在實施階段，並推行健全的計劃。保加利亞及土耳其有草擬中或全套的規劃，經批准的和類似程度的醫療經費，但是他們的計劃只是有限地實施。阿根廷、墨西哥及巴西有相似的醫療支出佔本地生產總值比例，但全民罕病規劃（NRDP）仍有待發展或仍在實施的前期。最後，中國及台灣沒有推行全民罕病規劃（NRDP）， 或已推出但沒有全面實施。

下文概括了每一國家不同病人組織的行動， 並分別分析五個方面，表達罕病群體的核心需要。

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第一方面：護理統籌

「護理統籌」一詞指善用資源，從而提供適時、公平及有實證依據的護理服務。各國採用的術語或計劃略有不同，但措施主要包括了針對罕病的專科中心 (center of expertise)、綜合醫護及行政資料庫和全民罕病名冊。雖然有一些國家以專科中心的方法來統籌罕病的護理服務，但是仍有很多國家因為還沒實施，或正採用其他策略的原因，而未曾嘗試專科中心的方案。

為罕病成立全面及專科中心的概念，是法國首次推行全民罕病規劃時所原創。其後，歐盟在十年前採用了法國的框架與概念。法國有超過六百個中心負責統籌研究、培訓醫療專家及協助診症（見表一）。雖然英國本身沒有專科中心，但英國罕病國家策略 (UK Strategy for Rare Diseases) 亦有建議創立類似的專科中心，提供具統籌和專業的護理，從而顧及到罕病患者的需求。伯明翰罕病中心 (The Birmingham Centre for Rare Diseases) 便是其中一例。再者，英格蘭國民保健處 (English National Health Service) 亦列出了 150 名高度專業化的醫療服務，部分更是針對治療罕病，例如肝臟移植、酵素替代療法、針對某些癌症病的質子治療等。此外，近期歐盟頒佈了指定歐洲參考資料網絡 (European Reference Networks) 的準則，用於罕病的治療，並於二零一六年十二月批准了第一輪共二十三個的醫療服務。

我們調查的亞洲國家中，沒有任何一個全民罕病規畫有正式落實專科中心。不過，台灣的衛生福利部全民健康署核定了一些醫療機構來診斷及治療罕病，及至少有十個認可的遺傳諮詢中心。可是，不同中心的護理統籌並未能完善地發展。台灣地理面積較小，病人因此無須遠行便可尋求治療。反之，面積較大的國家，統籌資源分配更是一個挑戰。這正是拉丁美洲目前就護理統籌面對的障礙。這些國家人口眾多卻四散各區，很多患者遠離專科醫療服務的集中地。為了拉近遠郊病患者與專科醫療服務的距離，很多國家利用創新科技解決此困境。阿根廷的衛生局近期發放了 Cibersalud，以電子衛生技術來強化專業人員間的網絡和轉介、診症及監察更為方便。Cibersalud 旨在推廣國內不同醫療專業人士之間的諮詢與溝通，並透過提供科技設備及研發影像會議的應用程式，協助並促進相關教育活動。最近，該局也推出了一項罕病的互動課程，意在提高及改善罕病的診症。課程針對小兒科、家庭醫學及普通科專業醫療人士，並以線上病例討論及每兩週舉行的遠程醫療會議作訓練模式。

在沒有為罕病設立正式專科中心的國家中，病人團體積極地支持護理統籌的工作。以阿根廷為例，垂體疾病協會 (Pituitary Diseases Association) 推行 “Hip Tour”，為專業人員提供醫療指引以便診斷。在墨西哥，溶酶體貯積病病人網絡 (Lysososmal Storage Disease Patient Network) 建立全面護理的模式，包括診症、治療及支援，並獲得高度的政治重視及認可。可是，此模式的位置集中，外展資源有限。總括而言，認定及創立專科中心或類似計劃，是鞏固現有罕病專門知識不可或缺的一步。

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第二方面：診斷

適時及準確的診斷，建基於提供方便和普及的篩檢服務。從調查的國家中發現，各國的政策與做法卻大相逕庭。當有效地介入時，新生嬰兒篩檢可以及早診斷及治療某類別的罕病，從而避免及減低病程或死亡。這是因為檢測一塊血斑，便可識辨多種身理情況。同時需要注意的是，不同地方採用不同的新生嬰兒篩檢的組合，取決於當地做法。一些新生嬰兒篩檢程序善用了 JMG Wilson 和 F. Jungner 於 1968 年定立的準則，判斷 有需要篩檢的人選。最近發表的歐盟新生嬰兒篩檢報告中表示，大部分管轄區都採用了科學協會的指引作考慮。可是，當中有不少主觀因素，令疾病篩檢的範圍難成共識。創新診斷科技的出現，亦為篩檢制度的發展方向帶來更多爭論。

很多國家地區已經實施了新生嬰兒篩檢核心計劃 (如台灣、巴西、英國、德國)。台灣已推行了涵蓋二十六種疾病的全民新生嬰兒篩檢計劃。同樣地，德國亦有包括十四種情況的全國性測試。因為現有能夠作新生嬰兒篩檢化驗的罕病有限，計劃涵蓋的疾病數目遠少於已識別的罕病總數。儘管加拿大有些省份已定期檢查三十多種疾病，但在 2016 年其衛生局亦正式認定了二十二種主要情況，以便各區各省進行新生嬰兒篩檢。這些要求的數目遠少於一塊血辦能夠檢查出的罕病數量，但這是全球普遍的情況（除了美國某些州份檢查超過五十多種）。受調查的國家大部分也缺乏正式的新生兒篩檢計劃，以及沒有合適的架構或資源來推行相關措施。以阿根廷、巴西、中國和台灣為例，他們各有其他計劃進行中，故此對於核心新生嬰兒篩檢的關注程度有限。例如，巴西政府雖然逐漸將基因研究轉化為臨床領域，而其衛生局亦於 2001 年設立全國性新生嬰兒篩檢計劃，但是尚有發展的空間。至今，此計劃只涵蓋了六種疾病，相對其他地方，如台灣共二十六種、德國十五種，巴西的情況可說是相形見絀。

嬰兒新生期過後，罕病診斷會變得更困難，導致診斷延誤及很多誤診。地域挑戰更會加劇此問題，因為長途尋求各地的專科醫療服務，可能妨礙診斷的準確性。在墨西哥，有些病人更將此比喻為"醫學朝聖"，因為旅途可長達五年多。2012 年歐洲罕病聯盟 （European Organization for Rare Diseases) 調查八種罕病中發現，代表的一萬二千位病人當中，百分之二十五需要輪候五至三十年才可得以確診，百分之四十在初期時被誤診（導致不恰當的醫療介入），百分之二十五需要去另一地區診症。同樣地，加拿大罕病組織發現，百分之二十的病人需要等候六至十四年才可確診，而百分之六十診斷前更需要諮詢三至二十多個專家。重要的是，一個可靠的診斷及篩檢計劃，可以大幅減低病人確診的時間，更可縮小診斷與病發時期之間的差距。這也是許多國家在護理的可及性方面的主要障礙。

除了認知以外，一項在許多國家推動的重要策略，是教育執業的醫護人員發展及擴大對罕病的專門知識。例如，阿根廷衛生部啟動了一項機制，促進全國各地機構的專業人員協

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作，旨在改進診斷。在很多新興醫療體系，病人組織在推動專業人員教育及協作扮演積極角色。在巴西，一個囊腫性纖維化病人組織在篩查什麼疾病的決策過程中起了重要作用；在墨西哥，病人組織發起建立早期診斷基金和病人名冊，並致力提昇對罕病的認知。亞太地區也朝這些方向進展，台灣罕病基金會(TFRD)與健康促進局協調，發送檢測樣本到境外及當地的檢驗所，以改進診斷，還資助當地醫院的罕病檢測。

第三方面：治療的可及性

罕病的治療，可以透過為促進孤兒藥的認定、批准及早期切入計劃而設的全國性規管及立法的政策予以解決。歐盟於 2000 年通過歐洲議會及歐盟理事會有關孤兒藥品的法規 (EC) 編號 141/2000)，涵蓋了歐盟所有成員國，亦包括此項調查裏的英國、德國、保加利亞和法國。再者，建立孤兒藥品委員會 (Committee for Orphan Medicinal Products) 是為了向歐盟委員會孤兒藥品指定作建議，協助後者作最終決定。根據歐盟孤兒藥品的規條，各類誘因包括規程支援，會提供給已指定的藥物。最近，按照優先藥品計劃，歐洲藥物管理局會提供及早和提升科技與規管的支援，以及加快治療測試，從而應對尚未滿足的醫療需要，為病人帶來重大的治療效益。不少國家也有加速孤兒藥物許可過程的措施，包括土耳其、墨西哥、中國、台灣及加拿大，不過各國審核準則與程序有異。在巴西，國家衛生檢查局 (Agência Nacional de Vigilância Sanitária) 於 2007 年訂立規例（RDC 議案 28 條）並於 2008 年 (RDC 16 條) 進一步澄清，指出孤兒藥品應優先審查及在七十五天內做出認可的決定。在實行上，認可程序可花費更長的時間，而該程序的時間表亦正被審視。墨西哥雖然沒有特定加快藥物認可的規例，但由美國食品藥物管理局或歐洲藥品局 (US Food and Drug Administration or the European Medicines Agency) 認受的孤兒藥品，可透過確認信來加速審查，使過程縮短至約六個月。阿根廷的全國藥物食品及醫療科技局 (Argentinian National Administration of Medicines, Food, and Medical Technology) 亦有類似成功例子，該計畫將已由美國或歐盟認受的孤兒藥簡化認可過程及條件。在加拿大，用來應對未滿足的需求及緊急情況的藥品，也會批准加速審核。

至於已受認可的藥品，有些國家亦有政策來確保病人能夠及早接受治療。英國國家醫療暨臨床卓越研究所 (National Institutes for Health and Clinical Excellence) 針對超級孤兒病（人口小於一萬分之一），為"高度專門治療"設立了另外的審查程序。在英國的其他地方，蘇格蘭藥品局 (Scottish Medicines Consortium) 製訂了新的審查罕病藥物方法，旨在增加病人與臨床醫生在評核過程的影響力，「病人與臨床醫生參與團隊」會被傳召到會議，陳述在慣常臨床和經濟評估過程中可能未有提及的額外好處。蘇格蘭還設立了新藥品基金，近期擴展至每年八千萬英鎊，分配給孤兒藥品，確保罕病病人能夠得到最先進的治療。同樣地，在保加利亞，罕病治療的醫療科技評估(HTA)亦有特別考慮。再者，阿根廷使用了一個獨特的退款制度，處理對社會健康服務項下特定藥品的財政支援。

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第四方面：病人認知與支援

究竟罕病病人與其家人得到什麼程度的教育與支持？我們以三個指標分析每個國家：公眾對於識辨與支持罕病的認知，病人對於參與、倡議與獲取資源的教育，醫護人員就著提昇診斷、治療與護理的培訓。在調查的國家中，有誰參與？做了什麼？有什麼成績？都相差頗大。公眾認知大則可由專門的國家或國際機構推廣，小則可由獨立組織推行當地認知計劃。這些活動無論在什麼層面，都有病人組織的積極參與。在英國、法國和德國，專注特定疾病或跨疾病的病人倡議團體亦有籌辦不同活動，包括教育及推廣認知的會議、為病人提供罕病研究指引、支持立法的倡議活動以及與政府人員會面。一些較少相關持份者的國家，強大的罕病病人團體網絡在認知、政策與醫護制度的回應上則有顯著的影響。不同地區的例子也可見一斑。比如在保加利亞，病人團體推行了獎勵計劃來支持罕病，很重要地教育及鼓勵了罕病病人群體。這不只令他們更容易獲得治療及了解醫療體制，更可倡議他們爭取的目標，包括要求立法以支援罕病病人需要，以及為十三個疾病流行病學登記名冊的設立扮演了很重要的角色。同樣地，在阿根廷和加拿大，全民協作促使政府實施罕病相關的立法與計劃。

這項研究涵蓋的亞太地區樣本中，中國與台灣都有罕病病人支援和倡議團體，可是他們的影響有別，反映了兩地政治、經濟、地緣與醫護上之差異。在台灣，非政府組織台灣罕病基金會特地專注為罕病病人與家人獲取政府支持。為此，台灣罕病基金會在罕病政策制定與倡議上扮演很重要的角色。該基金會於約二十年前成立，一直帶領著教育、增強意識及倡議的工作。透過與政府機構的統籌行動，最終於 2000 年協助通過《罕病防治及藥物法》。至於中國，在病人倡議團體有限的情況下，本地化及專注特定疾病的罕病團體將工作集中於教育方面。這些團體近期亦嘗試將不同持分者的聯繫變得更緊密。在 2011 年，中國醫療人員為罕病呼籲更多支持、研究、藥物研發及流行病學研究。病人團體、慈善機構與醫藥公司每年在國際罕病日（二月二十九日）及中國預防出生缺陷日（九月十二日）共同主辦病人支援計劃及學術會議，從而提高公眾意識及推廣立法。更近期，數個機構合併成中國罕病發展中心，代表著四十種罕病，並籌辦了幾個創新及具影響力的認知與教育計劃。

中國與台灣的境內網絡在工作重點與倡議方針都別樹一幟。台灣普遍專注境內提升認知及遊說工作，卻忽略了國際活動。反之，中國罕病發展中心則在國際領域廣泛地參與，亦有邀請外地病人倡議者和其他專家支持國內的工作。此分別歸咎於不同因素，台灣地理面積與人口較小，但擁有強健的經濟與高質和資源豐富的醫療制度，故此病人亦能合理地獲取護理服務。相比之下，中國擁有更大的地理面積及人口，以及一個新興的經濟和演變中的醫護制度。因此，中國罕病發展中心便尋求國際重視，良好操作及倡議工作。為此，該中心成了亞太罕病組織聯盟的發起人，並在 2014 年主持了國際罕病聯盟 (Rare Disease International) 的創立會議。此組織為一個罕病病人與倡議者的全球聯盟，旨在提升認知，交

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流資訊和加強罕病的支援。參與國際罕病聯盟是一個新的突破，因為這是一個國際性及病人主導的倡議團體，令中國有機會主辦在 2014 年舉辦的罕病國際會議和 2017 年的罕病國際大會。

有些國家有以醫療專家教育與培訓為重點範疇的特定計劃（阿根廷，德國），而另一些國家不注重醫護專業人材的發展（墨西哥，中國），反映了醫療專家在個別病人組織的參與程度之不同。德國罕病治療與研發中心 (Treatment and Research Centre for Rare Diseases) 透過德國醫療持續培訓學院 (German Academy for Further Medical Training On Rare Diseases) 提供醫療教育，讓醫生、相關專家與病人組織能夠互動和交流。在巴西，一項新的國家整體關注罕病病人政策 (National Policy of Integral Attention to People with Rare Diseases)包括了醫護人員專業訓練，從而建立了專業團隊為罕病病人診症。

第五方面：研究

罕病的研究與國家整體生產總值及在創新、科學與醫療保健的投入相輔相成。這些研究在有些國家得到政府充足的資助（法國、德國、英國、加拿大），有些則沒有得到正式的支持（土耳其、墨西哥）。在區域層面，歐盟透過歐盟研究與創新框架方案 (EU Framework Programme for Research and Innovation) 展示了對罕病研究的堅決承擔。第七屆框架方案 (2007-2013)將多於六億二千萬歐元的資金給予一百二十多個罕病合作研究項目。此資助促使來自各國大學、研究組織與病人組織形成多學科團隊。近期，視野 2020 (Horizon 2020) 由 2014 年至 2020 年致力資助歐盟的罕病研究。在國家層面，法國現今資助三百多個臨床研究項目，這些項目並與國內及國際研究所合作，為此法國被譽為這研究領域的領袖。在德國，聯邦教育及研究部從 2012 年為十二個研究合作組織在三年間資助了多於二千三百萬歐元，以及透過不同計劃提供額外資助，如國家基因組研究網絡 (National Genome Research Network)。中國罕病防治聯盟 (China Alliance for Rare Disease Prevention and Treatment) 成立首個國家預防及治療罕病研究計劃，旨在整合罕病病態生理學及自然史的基本數據，發展和應用醫學指引，以及推廣罕病分子測試。加拿大政府亦致力透過加拿大健康研究所 (Canadian Institutes for Health Research) 資助新興的研究團隊及機構，並資助罕病模擬的維護以及轉譯研究（基因識辨、疾病名冊、先導診所）。

有些國家（保加利亞、土耳其、阿根廷、墨西哥、巴西）只有很少甚或沒有國家計畫來推行罕病創新及研發工作。阿根廷的研究項目常以私人計劃、研究撥款或從病人組織來獲取資助。同樣地，巴西沒有長期的全國性計劃來推行罕病研究。不過，巴西議會正審視相關法例，確保與被忽略和罕見疾病相關的研究資助。

病人名冊是收集疾病、人口及治療數據的很重要方法。法國的國家罕病資料庫 (Nationale de Donnees Maladies Rares) 從專科中心收集及處理數據，此統籌模式可為其他國家作借鑑。當

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法國病人接受治療時，他們的資料便會存於病人名冊。相反，英國、保加利亞和阿根廷在計劃的不同階段才有病人登記程序，可是此措施尚未實行。為了支持不同病人名冊的罕病資訊分享和統一化，歐洲委員會在歐盟社區行動 (EU Program of Community Action) 在公共衛生方面成立了歐洲罕病病人名冊平台 (European Platform for Rare Disease Registries)，應對資訊分享及統一化的挑戰。此平台仍在發展階段中。Orphanet 協助整理罕病病人名冊、數據庫及生物資料庫，從而提供資訊給相關持分者。

整體來說，罕病病人名冊正朝向國際層面發展。例如，土耳其沒有完善的國家罕病病人名冊，但該國參與了歐盟病人名冊，如 TREAT-NMD (針對神經肌肉疾病) 和 EUROCARE CD (針對囊性纖維化)。在保加利亞，病人團體正為病人名冊的法例做出更改。巴西缺乏國家罕病病人名冊，但病人協會仍能收集某中疾病的資訊。有些國家如墨西哥和中國都有病人名冊，可是分佈在不同地區，各做法有異，故此沒有統一的架構促進特定病人或人口分析。台灣雖然有全民殘障登記冊，但卻沒有針對罕病；可是，台灣血栓暨止血學會正為血友病推行病人名冊。

討論：

這份研究評估了在經濟、政治和醫療衛生等因素存在差異的抽樣國家的罕病狀況，同時評估病人組織在制定國家政策和計劃時所擔任的角色，包括罕病立法、全民罕病規劃和為罕病提供的統籌和全面服務。大部份抽樣的國家都已經製訂或有意製訂全民罕病規劃（法國、德國、英國、加拿大、保加利亞、阿根廷、巴西、墨西哥和台灣）。雖然政府正式認可，但除了法國，其他國家都沒有統籌的策略和政策，以全面推行。的確，實施的範圍和能力差異可以很大。整體而言，有較高醫療保健支出及人均國民總收入，以及有全國性醫療衛生服務系統的國家（法國和德國），會有設計良好的早期切入治療／罕藥資助／診斷計劃／統籌護理和有較強的研究動力。相比之下，英國和加拿大在財政指標和地區的醫療衛生服務系統上很相似，卻仍未設立國家專科中心、國家篩查及診斷指引、提供罕病治療的全國性準則等。蘇格蘭、北愛爾蘭和英國有獨特的藥物測試部門。在英國，國家醫療及臨床卓越研究所 (National Institute for Healthcare and Clinical Excellence, NICE)另設機構，評估治療極罕見疾病的高度專門藥物。蘇格蘭設立了罕藥專用基金，北愛爾蘭考慮為罕藥設立專項資助。

土耳其、墨西哥和中國沒有罕藥法例，這些國家的人均國民總收入和醫療衛生支出均較低。發展較落後和醫療衛生資源及人均國民總收入較少的國家，較難通過和實施全民罕病規劃。一些未有正式全民罕病規劃的國家，依然透過立法／政策／監管以改善罕藥的可及性（例如墨西哥的罕藥分類及加速審查的政策）。

明顯地，政策與實施之間存在差異。有些國家有特定對罕藥的管制以加速授權過程，但精簡的程序不一定能促進／保證藥物得到許可。在巴西，確立的藥物批准時限是 75 天，但正

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式獲得批准的時間需要 13 至 30 個月。在抽樣調查的國家中，只有保加利亞和蘇格蘭會分配特定的資助予罕藥。然而，保加利亞的罕藥牌照發放經常延遲一至六年。

儘管未有正式的全民罕病規劃，一些國家有能力改善罕病政策制定的過程。雖然加拿大在 2015 年 9 月之前未有全民規劃，但卻有強有力的新生兒篩查政策及優良的診斷中心，優於其他國家。在亞太地區，台灣提供了很好的參考，它缺乏特定政策，卻正在發展改進中的篩查和診斷計劃，並由倡導小組作主導和由台灣政府提供資金援助。另外，儘管全民罕病規劃延遲實施，土耳其界定早期治療的途徑、指定統籌護理的專門中心，與及提供篩查和診斷計劃。

在歐洲進展的感染下，一些國家採納了 EUROPLAN 計劃所設計的諮詢程序及核心指標，用以支援罕病策略及計劃的發展和實施。在加拿大，加拿大罕病組織在全民罕病規劃的策略發展和實施上，擔當有效的角色。該規劃借鑒超過 30 個全民罕病規劃，主張的目標與英國罕病策略一致。與歐洲罕病組織在罕病研究基本架構、發展和管治的立場一樣，基於全面及平等的夥伴關係吸納病人參與，是加拿大罕病組織的核心建議。

在其他國家，包括墨西哥，病人倡導組織積極參與國家衛生部門的小規模工作小組，在建構討論、教育決策者和推動支持全民罕病策略的政治議程上，擔任重要的角色。在一些沒有正式全民罕病規劃的國家，經協調和具影響力的疾病倡導組織，在回應落差和推行支援社區核心需要的計劃中，發揮領導作用。其中一個例子是阿根廷，在缺乏正式專科中心的情況下，病人組織在支援統籌護理上擔當主動角色，當地腦下垂體疾病聯盟周遊全國，向專業人士提供藥物的最新情報，分辨和診斷疾病。保加利亞的病人組織致力修改法例，設立中央病人名冊，從而與國際性的資料庫接軌。在中國，中國罕病防治聯盟已經成立了第一個全國性的罕病預防及治療研究計劃。

這顯示儘管各國有政策優次，病人支援組織可以成功推動實施有助罕病病人核心需要的計劃。然而，即使成功採納這些計劃，為確保病人得到全人的護理和治療，整合和統籌的策略是必要的。

為了獲得更多的幫助，病人可以透過建立組織間的聯盟去推動政策的發展。西葡語美洲國家罕見疾病聯盟(The Iberoamerican Alliance for Rare Diseases) 在西葡語美洲地區成立了一個系統，協作及分享與罕病有關的構思。最近成立的亞太地區罕病聯盟組織，是罕病的協作同盟（APARDO，中國、日本、印度、澳洲和新加坡），旨在改善罕病的護理和治療的可及性。重要的是很多在這份研究分析的國家，是國際罕病聯盟(Rare Disease International)的成員，提供清晰的時間表，建立和改善倡議、認知、資訊共享和網絡、研究及合作。由於罕病政策持續發展，罕病組織的聯合，透過共享資源推動創新研究及良好操作，是不可或缺的；還要在計劃發展過程中擴大病人聲音的角色，以正視罕病群體的需要。

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總結

根據歐洲罕病聯盟(EURORDIS)和加拿大罕病組織(CORD)立場書勾勒出的目標，這份研究透過分析罕病病人的核心需要，探討不同國家的罕病立法、相關政策、監管和規劃。與之前的報告一樣，這份研究揭示了不同國家在罕病的基本架構有很大差別，然而調查的國家有限，亦非旨在評估具體政策和架構產生的病人成效。我們需要進行持續的研究，將政策和現行計劃相互關連，以及最終對病人護理帶來的效果。重要的是，這些資料可以提供策略性框架，以建構國家內和國家之間的持續對話，從而界定最好的罕病管理方法，統籌國際間為改善罕病護理所作出的努力。

－全文完－

備註：

1. **中譯本省略了章節內容中的參考文獻註腳，如欲查閱，請參考英文原文版本。**
   （*Dharssi et al. Orphanet Journal of Rare Diseases (2017) 12:63*）。
2. **原意及內容以英文原文為準，中譯本謹供輔助閱讀。**
3. **中譯本由香港立法會張超雄議員辦事處及香港罕見疾病聯盟共同翻譯，並徵得原文作者同意。**

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香港罕見疾病聯盟
Hong Kong Alliance for Rare Diseases

表一. 十一個國家的罕病政策和管理體系總結

	台灣	中國	巴西	墨西哥	阿根廷	土耳其	保加利亞	加拿大	英國	德國	法國
國家政策	已接納； 正在實施	無	處於早期實施階段	無統一計劃	已許可； 正等候實施	指引的草稿已通過； 計劃的實行延遲	已許可； 有限的實施	已接納； 正在實施	計劃已全部被 4 個英國組成國家接納；正在實施	已接納； 正在實施	兩個計劃已實施； 第三個計劃的展開進行中
授權過程	可以加速審查 罕藥的分類程序已就緒	儘管計劃迅速，罕藥的認可延遲 普通藥和罕藥並無區別	可以加速審查； 時間線會改變 罕藥無特別註冊程序	可以加速審查 罕藥分類程序已就緒	由 ANMAT 管理藥物許可的條件 美國和歐盟許可的藥物可以簡化授權程序 罕藥註冊程序已就緒	無明確的罕藥地位的申請	歐盟中央授權 罕藥產品委員會為罕藥命名和界定地位	可以加速審查	歐盟中央授權 罕藥產品委員會為罕藥命名和界定地位	歐盟中央授權 罕藥產品委員會為罕藥命名和界定地位	歐盟中央授權 罕藥產品委員會為罕藥命名和界定地位
早期切入治療的計劃	無正式的國家政策，但政策已經實行 未註冊的藥物可以申請後入口	未批准的罕藥可能可以透過捐贈提供	無法例和計劃存在 未註冊的藥物可以申請後入口	無任何計劃	免費可及海外藥物的計劃	有計劃提供予不滿足的醫療需要的病人，但需要合乎某些條件	無法律上的規定要提早可及	無計劃會有早期切入；病人在特別情況下可以申請到特別可及計劃	早期與藥物計劃切入是許可的，但罕見病不是特定的	第三階段的臨床試驗和當產品的安全與功效是得到保證時會得到撥款	準備罕藥可以有／沒有市場授權

現行治療渠道	特別的可及渠道會考慮 數種藥物最近得到許可 有分列的預算而不包括在NHI	無特別的可及渠道會考慮 無特定予罕藥的資助	透過公共健康系統會有有限制的治療可及 無特定予罕藥的資助	只有少量資料可以提供 無特定予罕藥的資助	全面的罕見病病人保護: 行動 26.689 尚未實施 某些已選擇的藥物有退款制度，提供財政支援予社會健康服務	可及的途徑已經界定 無特定予罕藥的資助	罕藥的可及已經改善，特別是過去的 4 年間 HTAs 的罕藥有特別考慮 10%的 NHIF 年預算會分配予罕藥	可以獲得罕藥的渠道與其他藥物一樣都是透過 HTA 外國藥物 罕藥供給的特別計劃	NICE HST 重新檢視超罕藥的過程 蘇格蘭的新藥物資助分配了 80,000,000 英鎊予罕藥	有數個新措施用以改善獲得罕藥的渠道 無特定予罕藥的資助	市場的許可是需要的 罕藥只能處方予罕見病認證中心 (RD competence centres；在法國超過 500 個) 無特定予罕藥的資助
診斷方案	改善的篩查和診斷正在發展 超過 26 種疾病的全民新生兒篩查計劃	無國家檢查和/或診斷計劃可以提供	提供六種新生兒罕病的檢查 主要罕病的研究中心位於巴西南里奧格蘭德州聯邦大學以進行診斷	無早期診斷的新措施 有限的新生兒檢查 早期診斷的診所正在發展	立法已通過但無已準備的計劃	少量的公共診斷中心 透過衛生部門進行 3 種罕病的新生兒檢查 於大學進行基因測試 海外測試是	為早期診斷而設的國家計劃預計會於 2016 年前獲全數資助和實行	外地的新生兒篩查計劃隨數量和情況改變 衛生部長為 22 種情況實行篩查計劃	英國罕病策略無專門地包括早期診斷計劃 新生兒罕病測試的擴展於 2015 年開始	提供 14 種情況的新生兒檢查 強制性檢查和基因測試，但無特定的罕病政策	提供 4 種新生兒的病理測試(兩種罕病) 不平等的測試接駁

						可行的					
護理統籌	無全面的專科中心 10 種以上的罕病遺傳諮詢中心已經許可 部份政府政策已經實行但護理統籌沒有全面發展	在北京和上海無為特定的罕病設立全面的專科中心 大部份成熟的治療是與血液有關的罕病	專業健康認證中心展開的國家政策正在進行	無已發展的中心，但有功能上活躍的 12 個公民組織網絡 *Lysosomal Storage Disease Network*. 診斷、治療、支援	已計劃: 行動 26.689 電子醫療 已展開以加強專業人員網絡 "Hiptour" 病人主導的新措施為 HCPs 提供醫療指導	少量中心有專業服務；大部份是大學醫院和研究中心	尚未就緒 罕病委員會尚未運作	為特定罕病而設的專科中心； 部分與不同地點的成人診所研究有關 無為全部罕病專科中心而設的國家統籌機構	英國罕病策略要求專科中心提供護理資源的調節, 150 個高級專業服務的提供者	罕病專科中心和網絡已為跨境研究準備	131 個參考資源中心和 501 個認證中心就緒
研究	無罕病病人名冊 全民殘疾病人名冊已經準備和血友病的病人名冊正在發展	2003 年 CARDPT 國家研究計劃 跨境的措施獲得推動力 無國家中央的病人資料庫或病人名冊 名冊 2003	只有少量誘因； 無長期的措施； 2014 年由 CNPq 提出新措施用以檢查和資助 15 個研究罕病的計劃(診斷和治療) 用以獲得罕病研究資助	無資助的研究、計劃或者新措施 罕病病人的資料庫發展正在進行	無全國性的新措施已經準備 部份研究在病人組織、研究資助和私人倡議的協助下進行 立法已經通過但病人名	無新措施、網絡或者跨境合作 無國家病人名冊，但土耳其參與在歐洲病人名冊 全面的國家流行病調查正在進行	正在提高的意識但只有少量的新措施研究是準備就緒 中央化的病人名冊得到許可但尚未運作	加拿大研究所的健康研究資助基本的和翻譯的研究 提出將罕病研究正式包納在 CIHR, Genome Canada 和 IRDiRC	與製藥廠合作的以病人為中心的研究已經存在 英鎊 10000 的有關基因罕病的計劃 英國公共健康打算建立國家罕病病人名冊	28 種罕病組織得到教育部和 BMBF 研究支援 12 個研究計劃； 23,000,000 歐元分配予 3 年跨境研究計劃 無中央統一協調的罕病	超過 300 份資助的臨床研究計劃 資助被分配予基本和臨床的研究 *Banque Nationale de Données Maladies Rares* 國家

		年於地方層面推行 病人團體的資料庫發展正在進行	的議案正在審議 無國家的病人名冊；由病人團體收集數據 DORA 計劃和 FEMEXER 罕病資料庫正在發展		冊依然未發展					病人名冊	的資料庫已經推出 歐洲和國際合作已經發展
病人參與	強而有力的病人支援/倡議小組在罕病的政策上活躍 TFRD 幫助通過 2000 年的罕病控制和 ODA	有限的病人支援組織但本地的罕病團體提高了意識/推廣立法 罕見疾病的中國組織在 RDI 上活躍	病人組織罕扮演一個重要的角色	病人組織罕扮演一個重要和活躍的角色	病人組織參與活躍 與政府的合作有助罕病的立法推行和計劃	只有少量資料可以提供	病人組織參與活躍 已實施的支援和教育計劃在 13 種罕病的登記上扮演一個角色	病人團體支持和促進擁護 CORD 國家策略與加拿大罕病聯盟一起展開	已設立的病人組織扮演一個活躍的角色 持份者參與在英國罕病和專業醫療健康聯盟	已設立的病人組織在罕病的政策中有參與和扮演一個角色	已設立的病人組織在罕病的政策中有參與和扮演一個角色
人均國民總收入 (2105)	22,723	7820	9850	9710	13,640	9950	7220	47,500	43,340	45,790	40,580

醫療衛生支出（國內生產總值 %)	6.6	5.5	8.3	6.3	4.8	5.4	8.4	10.4	9.1	11.3	11.5
平均財富醫療衛生排行	8.8	5.0	6.5	7.3	7.0	6.5	7.8	2.8	2.3	2.3	1.8

備註：

1. **中譯本省略了章節內容中的參考文獻註腳，如欲查閱，請參考英文原文版本。**
   Review of 11 national policies for rare diseases in the context of key patient needs（*Dharssi et al. Orphanet Journal of Rare Diseases (2017) 12:63*）
2. **原意及內容以英文原文為準，中譯本謹供輔助閱讀。**
3. **中譯本由香港立法會張超雄議員辦事處及香港罕見疾病聯盟共同翻譯，並徵得原文作者同意。**

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Review of 11 national policies for rare diseases in the context of key patient needs

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Abstract

Rare diseases collectively exert a global public health burden in the severity of their manifestations and the total number of people they afflict. For many patients, considerable barriers exist in terms of access to appropriate care, delayed diagnosis and limited or non-existing treatment options. Motivated by these challenges, the rare disease patient community has played a critical role, elevating the patient voice and mobilizing legislation to support the development of programs that address the needs of patients with rare diseases.

The US Orphan Drug Act of 1983 served as a key milestone in this journey, providing a roadmap for other countries to introduce and implement similar orphan drug legislation; more recently, the European Union (EU) has gone further to encourage the widespread adoption and implementation of rare disease plans or strategies designed to more adequately address the comprehensive needs of patients with rare diseases. Despite these legislative efforts and the growing contributions of patient advocacy groups in moving forward implementation and adoption of rare disease programs, gaps still exist across the policy landscape for several countries. To gain deeper insights into the challenges and opportunities to address key needs of rare disease patients, it is critical to define the current status of rare disease legislation and policy across a geographically and economically diverse selection of countries.

We analyzed the rare disease policy landscape across 11 countries: Germany, France, the United Kingdom, Canada, Bulgaria, Turkey, Argentina, Mexico, Brazil, China, and Taiwan. The status and implementation of policy was evaluated for each country in the context of key patient needs across 5 dimensions: improving coordination of care, diagnostic resources, access to treatments, patient awareness and support, and promoting innovative research.

Our findings highlight the continuing role of the patient community in driving the establishment and adoption of legislation and programs to improve rare disease care. Further, we found that while national rare disease plans provide important guidance for improving care, implementation of plans is uneven across countries. More research is needed to demonstrate the effect of specific elements of rare disease plans on patient outcomes.

Keywords: National rare disease plan, Policy, Legislation, Patient advocacy, Europe, Asia, North America, South America

Background

Rare disease is a global public health issue

Individual rare diseases by definition affect few people, but cumulatively have a major impact on public health. While the definition of rare disease varies by country, prevalence-based definitions range from 1 in 500,000 to 1 in 2000 [1, 2]. In the United States, the Orphan Drug Act of 1983 defined a rare disease by the number of affected people; by this definition, the actual prevalence of rare diseases varies with population numbers [3]. A disease is considered rare if it affects fewer than 200,000 individuals, whereas other countries define a rare disease based on prevalence rates [1, 3–6]. For example, in Europe, diseases are considered rare when they affect fewer than 5 individuals in 10,000 [7]. In Brazil, the definition is similar to the World Health Organization definition, as those affecting less than 65 out of 100,000 individuals [8]. In Taiwan, a rare disease is defined as a disease that is prevalent in fewer than 1 in 10,000 individuals [9].

An estimated 5000 to 8000 rare diseases have been identified worldwide, affecting approximately 6 to 8% of

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the population [10]. While rare diseases exhibit considerable diversity in etiology and clinical presentation, most are severely disabling with serious effects on life expectancy and physical and mental abilities [11]. Further, rare diseases constitute a major economic burden independent of a country's size and demographics; these costs arise from increased healthcare spending and lost productivity [1, 12–14].

Many rare disease patients experience barriers in access to care, and fewer than 10% receive disease-specific treatment [15]. Delayed diagnoses, limited access to resources, and absence of specific therapies often preclude patients from receiving proper, timely care. Even brief delays in diagnosis may have profound effects on outcomes; for over 40% of rare disease patients, treatment delays are precipitated by misdiagnoses [11, 16]. When patients are diagnosed, many are unable to access resources such as centers of expertise, coordinated care, patient support systems, and effective treatment. For many rare diseases, there are no effective treatments and information on disease progression is limited. Therefore, research into the natural history and underlying pathophysiological mechanisms of rare diseases is necessary to develop a foundation for discovering targeted medicines.

The patient community plays a critical role toward addressing these challenges, by elevating the patient voice and partnering in the development of programs to address the needs of patients with rare diseases. Approximately three and a half decades ago, the patient movement to create awareness and support for rare diseases took shape in the United States under the banner of the National Organization for Rare Disorders. Joint efforts under the leadership of a mother (Abby Myers), a congressman (Henry Waxman), and an actor (Jack Klugman) garnered the national stage in a series of headline events that captured the public imagination and mobilized Congress to pass the world's first orphan drug legislation in 1983. This was a seminal event in the development of national rare disease policy and transformed the landscape for rare disease drug development; from 10 new drugs in the decade preceding the Orphan Drug Act to over 500 new drugs in the succeeding three decades [3, 17]. The success of the Orphan Drug Act informed efforts to introduce orphan drug legislation in other countries [18] such as Japan, Singapore, South Korea, Australia, and the European Union.

While these legislative efforts were more focused on the development of innovative treatments for rare disease patients, the European Union went one step further, broadly ensuring that comprehensive policy programs addressed all needs of rare disease patients. In 2009, the European Council adopted the "Recommendation on an Action in the Feld of Rare Diseases," which supports the adoption of national plans and strategies for responding to rare diseases. The council recommended the development of national plans or strategies to address comprehensive needs, including diagnosis, treatment, care, and support of citizens with rare diseases [10]. Countries were encouraged to consider in these plans aspects such as the improvement in the awareness of rare diseases, the support for research into rare diseases, the development of centers of expertise, the empowerment of patient organizations, and the implementation of a robust healthcare infrastructure.

A number of countries preceded the European Recommendation and France was already ahead of other member states, adopting the First National Plan for Rare Diseases in 2004 [19]. The plan created centers of expertise that were responsible for coordinating diagnosis and provision of health and social care, writing national protocols for diagnosis and care, collecting data, and conducting clinical trials. France's National Plan served as the impetus and model for all European Union countries, which have developed or are in the process of developing National Plans or Strategies for rare diseases [19]. In the Asia Pacific region, Taiwan had a set of established programs, where rare diseases are included in the National Disability Registry and government social services programs for patients with rare diseases that include health-related subsidies and tax deductions, school fee reductions, employment supports, and transportation discounts. Similarly, Japan had enacted special legislation in 1972 to address "nanbyo," or rare and intractable diseases, with about 130 "tokutei shikkan" or special designated rare diseases receiving public subsidized care [20].

As national plans for rare diseases evolve, patients and patient advocates continue to play an integral role in moving forward the implementation and adoption of the programs outlined in the plan. The European Project for Rare Diseases National Plans Development (EUROPLAN) was a project co-funded by the EU Commission to promote and implement National Plans or Strategies to tackle rare diseases, to share relevant experiences within countries, linking national efforts with a common strategy at a European level [21]. Importantly, EUROPLAN formally included organized patient input and has played a key role within the European Union in guiding the establishment and implementation of National Plans or Strategies for rare diseases [21]. To this end, EUROPLAN included a specific role for the European Organization for Rare Diseases a European umbrella group of non-governmental associations of patients with rare diseases. The European Organization for Rare Diseases ensured that EUROPLAN processes were reflective of patient viewpoints, in part by organizing a series of conferences to discuss coordination of the European Union and national policy [16]. A committee of rare disease experts, the European Union Committee of Experts

on Rare Diseases (EUCERD) Joint Action, was set up by the European Commission to formulate and implement policy to combat rare diseases [22, 23]. The mandate of EUCERD Joint Action ended in July 2013 and been replaced by the EC Expert Group on Rare Diseases in 2013 [24]. The EC Expert Group continues to have a strong presence of patients' organizations in the field of rare diseases. The elaboration of policies in the field of rare diseases and improvement of the codification of rare diseases has been continued through the scope of RD-Action, a Joint Action co-funded via the 3rd EU Health Programme for the years 2015–2018. The European Organization for Rare Diseases (EURORDIS) continues to play an integral role representing the voice of patients and driving forward the adoption of important rare disease and orphan medicine legislations at the European level. In addition, similar organizations at a national level, such as the Canadian Organization for Rare Disorders (CORD), actively play an instrumental role in driving forward policy development. Both organizations have developed key position statements that outline top priorities that public decision makers should consider when addressing the needs of rare disease patients. While each countries policies and programs reflect the priorities of their health care system and needs of rare disease patients, the EURODIS and CORD position statements provide a general, but comprehensive framework that could be applicable to a majority of countries. As such, in this paper, we analyzed the rare disease legislation and associated policies, regulations, and programs across a diverse sample of 11 countries according to the goals outlined in the European Organization for Rare Diseases and Canadian Organization for Rare Disorders position statements. The objective of the review is to understand where there are opportunities for further policy development by examining how these policies and programs might align with key needs of the rare disease community, which are summarized in five dimensions: 1. improving coordination of care, 2. diagnostic resources, 3. access to treatments, 4. patient awareness and support, and 5. promoting innovative research. We also considered the contributions of patient advocacy groups and included some external measures of healthcare provision as an initial consideration for how current rare disease policy might align with the healthcare climate. The findings from this study will inform future studies evaluating how specific elements for National Plans or Strategies for rare diseases translate to provision of care for rare disease patients.

Methods

Information for this study was collected and analyzed from 11 countries: Germany, France, the United Kingdom (UK), Canada, Bulgaria, Turkey, Argentina, Mexico, Brazil, China, and Taiwan. Countries included in the analysis were selected to be geographically and socioeconomically diverse, and represent a wide range of rare disease policy development. The US was excluded since it lacks a formal National Rare Disease Plan and policy variation across states confounds comparisons with other countries. The term National Rare Disease Plan (NRDP) was used to refer to strategies and plans that have been developed to support a comprehensive and integrated approach to the delivery of health and social care for rare disease patients.

NRDPs were assessed using publically available official documents and secondary research. Based on guidance published [25] for rare disease policy, the following elements of NRDPs were evaluated for each country:

- National policy
- Access to treatment
- Diagnosis programs
- Coordination of care
- Research
- Patient engagement

The data were then assessed on the basis of our five keys needs of the rare disease community: coordination of care, diagnosis, access to treatments, patient awareness and support, and research.

Results

The status of National Rare Disease Plan (NRDP) policy elements for each of the 11 countries is presented in Table 1. Countries were arranged in the table according to overall healthcare/economic status, defined by gross national income (GNI) per capita and healthcare spending (relative to gross domestic product [GDP]), and the level of NRDP development. France and Germany have well-developed NRDPs that are being implemented at the national level. With the highest healthcare spending and average wealth healthcare ranks of the 11 countries surveyed, France and Germany have centralized national funding, good access to treatments, robust research initiatives, coordinated networks, and cross-border collaborations in place for rare diseases. The UK and Canada have similar healthcare structures and NRDPs that are both in the implementation stage with a number of robust programs in place. Bulgaria and Turkey have draft or full plans approved and comparable levels of healthcare spending, but their plans have had limited implementation. Argentina, Mexico, and Brazil have similar healthcare spending relative to gross domestic product (GDP) but NRDPs are awaiting development or are very early in implementation. Finally, the NRDPs of China

Table 1 Summary of rare disease policy and regulatory frameworks across 11 countries

	France	Germany	UK	Canada	Bulgaria	Turkey	Argentina	Mexico	Brazil	China	Taiwan
National Policy	Two plans implemented; Launch of third plan underway	Adopted; implementation underway	Plan adopted for all 4 UK nations; implementation underway	Adopted; implementation underway	Approved; limited implementation	Draft guideline passed; implementation delayed	Approved; awaiting implementation	No uniform plan	In early implementation stage	None	Adopted; implementation underway
Authorization Process	Central EU authorization COMP OD Designation	Central EU authorization COMP OD Designation	Central EU authorization COMP OD Designation	Accelerated review available	Central EU authorization COMP OD Designation	No defined OD designation	ANMAT regulates conditions for drug approval Streamlined authorization available for US or EU-approved drugs OD registration process in place	Accelerated review available Process in place for OD classification	Accelerated review available; timelines vary No special registration process for ODs	Delays in OD drug approval despite fast-track program No distinction between ODs and regular drugs	Accelerated review available Process in place for OD classification
Early Access Programs	Processes in place for ODs with and without market authorization	Granted during the third phase of the clinical trial and when the product's safety and efficacy are guaranteed.	Early Access to Medicines scheme approved, but not specific to RD	No plan for early access; Patients may apply to the Special Access Program in special circumstances	No legal provision for early access	Program available for patients with unmet medical needs meeting defined criteria	Program for free access to drugs from other countries in place	No programs in place	No legislation or programs in place Unregistered medicines can be imported upon request	ODs yet to be authorized may be available through donation programs	No formal NP in place, but policies implemented Unregistered medicines can be imported upon request
Current Access to Treatment	Market authorization required ODs can only be prescribed in RD competence centers (+500 in France) No OD-specific funding	Several initiatives exist to improve access to ODs No OD-specific funding	NICE HST review process for ultra-orphan drugs Scotland's New Medicine Fund allocated £80 M for ODs	ODs assessed through same HTA process as other drugs Provincial Drug Plans-special provisions for ODs	Access to ODs improved markedly over last 4 years Special considerations for HTAs of ODs 10% of annual NHIF budget allocated to ODs	Pathways for access are defined No OD-specific funding	Comprehensive RD patient care: Act 26.689 not yet implemented Refund system provides financial support to Social Health Service for select drugs	Limited information available No OD-specific funding	Limited access through public health system No OD-specific funding	No special access considerations No OD-specific funding	Special access considerations Several drugs approved recently Separate budget not covered by NHI
Diagnosis Programs	Neonatal screening available for 4 pathologies (2 RDs) Inequality in access to tests	Newborn screening available for 14 conditions Screening and genetic testing mandatory, but no specific RD policies	The UK Rare Disease Strategy does not specifically contain early diagnosis programs Expansion of RD testing in newborns as of 2015	Provincial newborn screening programs vary in number and conditions Health Ministers to implement screening programs for 22 conditions	National program for early diagnosis expected to be fully funded/ operational by 2016	Few public diagnosis centers Neonatal screening for 3 RDs through Ministry of Health Genetic testing at universities; testing abroad possible	Legislation passed, but no programs in place	No early diagnosis initiatives Limited newborn screening Early Diagnosis Clinic under development	Newborn screening available for 6 RDs Main rare diseases research centers is located in the Federal University of Rio Grande do Sul,for diagnosis	No national screening and/or diagnostic programs available	Improved screening and diagnosis in development Nation-wide newborn screening program for 26+ diseases
Coordination of Care	131 centers of reference and 501 centers of competence are in place	RD expert centers and networks for cross-border research in place	UK Strategy for Rare Diseases Calls for specialist centres to deliver coordinated care, 150 providers of highly specialized services	Centers of Expertise in specific rare diseases; some linked to research across sites with adult clinics No national coordinating body for all RD Centers of Expertise	Not in place RD committee not yet operational	Few centers with specialized services; mostly university hospitals and research centers	Planned: Act 26.689 Cibersalud launched to strengthen specialist networks "Hiptour" patient-lead initiative provides medical guidance to HCPs	No developed centers, but functionally active network of 12 civil organizations Lysosomal Storage Disease Network: diagnosis, treatment, support	National policy initiated with accreditation of specialized health centers in progress;	No comprehensive specialist centers Centers for specific RDs located in Beijing and Shanghai Most mature treatments for hematologic RDs	No comprehensive specialist centers 10+ RD genetic counseling centers approved Some NPs implemented but coordinated care not fully developed
Research	300+ funded clinical	28 RD organizations supported by	Collaborative initiatives with	Canadian Institutes for Health	Growing awareness but few	No initiatives, networks, or	No national initiatives in place	No funded research	Few incentives; no long-standing initiatives; Initiative in 2014 by the National Council of		No RD-specific national registry

Table 1 Summary of rare disease policy and regulatory frameworks across 11 countries *(Continued)*

	research projects Funding allocated for basic and clinical research Banque Nationale de Données Maladies Rares national database launched European/ international collaborations developed	Ministry of Education and Research BMBF funding 12 research projects; €23 million allocated for 3 years Cross-border research projects No central coordinated RD registry	pharmaceutical companies for patient-centered research exist UK10K project on RD genetics Public Health England intends to build national RD registry	Research funds basic and translational research Proposed formal inclusion of RD research in CIHR, Genome Canada, and IRDiRC	research initiatives in place Centralized patient registry approved but not yet operational	cross-border collaborations No national registries, but Turkey participates in European registries Comprehensive national epidemiological survey underway	Some research conducted with support from patient organizations, research grants, or private initiatives Legislation passed, but registries still under development	projects or initiatives Development of RD patient database in progress	Scientific and Technological Development (CNPq), which screened and funded 15 research projects devoted to rare diseases (diagnosis and treatment) Bill to secure RD research funding under review No national registries Patient groups collect data DORA program and FEMEXER RD database in development	CARDPT national research program initiated in 2013 Cross-border initiatives gaining momentum No national centralized patient database/ registry Registry launched at local level in 2013 Patient group-developed database in progress	National disability registry in place and hemophilia registry in development
Patient Engagement	Established patient organizations are engaged and play a role in RD policy	Established patient organizations are engaged and play a role in RD policy	Established patient organizations play active role Stakeholder engagement by Rare Disease UK and Specialized Healthcare Alliance	Patient group support and advocacy facilitated by CORD National Strategy launched with Rare Alliance Canada	Patient organizations actively engaged Implemented support and education programs and played a role in the launch of 13 RD registries	Little information available	Patient organizations play active role Collaborations with government aided implementation of RD legislation and programs	Patient organizations play an important, active role	Patient organizations play an important role	Patient advocacy groups limited but localized RD groups raise awareness/ promote legislation Chinese Organization for Rare Disorders active in RDI	Strong patient support/ advocacy groups active in RD policy TFRD helped pass 2000 Rare Disease Control and ODA
Gross National Income per Capita (2015)	40,580	45,790	43,340	47,500	7220	9950	13,640	9710	9850	7820	22,723
Healthcare Spending (% GDP)	11.5	11.3	9.1	10.4	8.4	5.4	4.8	6.3	8.3	5.5	6.6
Average Wealth Healthcare Rank	1.8	2.3	2.3	2.8	7.8	6.5	7.0	7.3	6.5	5.0	8.8

Abbreviations Administración Nacional de Medicamentos, Alimentos y Tecnología Médica; *BMBF Bundesministerium für Bildung und Forschung*, Federal Ministry of Education and Research; *CARDPT* China Alliance for Rare Disease Prevention and Treatment; *CIHR* Canadian Institutes of Health Research; *CORD* Canadian Organization for Rare Disorders; *EU* European Union; *DORA Doenças Raras,* rare diseases; *FEMEXER Federación Mexicana de Enfermedades Raras*, Mexican Federation for Rare Disorders; *HTA* Health technology assessment; *IRDiRC* International Rare Diseases Research Consortium; *NHI* National Health Insurance; *NHIF* National Health Insurance Fund; *NICE* National Institute for Health and Care Excellence; *NP* national plan; *OD* orphan drug; *RD* rare disease; *RDI* Rare Diseases International; *TFRD* Taiwan Foundation for Rare Disorders

and Taiwan are not proposed or are proposed but not fully implemented.

The patient organization actions for each country are presented within each of the five dimensions representing key needs of the rare disease community, summarized below.

Dimension 1: Coordination of care

The term "coordination of care" was used to describe resources designed to improve the provision of timely, equitable, and evidence-informed care. Programs and terminology vary by country but include Centers of Expertise (COEs) on rare diseases, integrated healthcare administrative databases, and national registries for rare diseases. While some countries attempt to coordinate their approach to rare disease management using centers of expertise, many countries do not, either because they have not yet adopted this approach or are employing different strategies.

The concept of dedicated and comprehensive centers for rare diseases was originally developed by France for its first National Rare Disease Plan (NRDP), and then adopted by the EU upon the request for national plans nearly a decade ago. France has over 600 centers that coordinate research, train healthcare professionals (HCPs), and facilitate diagnoses (Table 1) [26]. Although centers of expertise do not exist, per se, in the United Kingdom (UK), the UK Strategy for Rare Diseases recommended the creation of specialist centers to deliver coordinated and expert care required to support the needs of rare disease patients [27]. The Birmingham Centre for Rare Diseases is an example of the way one hospital has created a specialist center for treating patients with rare diseases. In addition, the English National Health Service lists about 150 providers of highly specialized services, some of which are directed at rare diseases, such as liver transplant services, enzyme replacement therapy, and proton beam therapy for specific cancer treatments [28]. Further, the European Union recently issued criteria for designating European Reference Networks (ERNs) across the European Union for treating rare medical conditions and in December 2016 approved the first wave of 23 European Reference Networks (ERN)s [27, 29].

In the Asian countries surveyed, no formal NRDPs for Centers of Expertise are in place. The Taiwanese Bureau of Health Promotion has approved medical institutions to serve as centers for diagnosing and treating rare diseases, and Taiwan has at least 10 approved genetic counseling centers [30]. However, the coordinated care across centers is not fully developed. Given the relatively small geographic size of Taiwan, patients may not have to travel far to access treatment, but, in larger countries, dispersal of uncoordinated resources is a challenge. To this point, barriers in the coordination of care in Latin American countries are due to large population sizes spread across vast landscapes, with many patients located far from urban centers where centralized expertise tends to be located. However, to support access to expertise in rural areas, many countries are employing technology to address this issue. In Argentina, the Health Ministry recently launched Cibersalud, an innovative tool to strengthen the network of specialists in the country and facilitate referrals, diagnosis, and monitoring. Cibersalud seeks to promote consultations among healthcare professionals from different establishments in the country and to assist teaching activities, through the provision of technological equipment and the development of applications that allow videoconferencing between establishments. More recently, the Ministry of Health launched an interactive course on Rare Diseases aimed at strengthening the diagnosis of rare diseases. The course is intended for healthcare professionals, including pediatrics, family medicine and general practitioner residents of public hospitals and training is conducted through on online discussion on clinical cases and biweekly telemedicine meetings (i.e. Cibersalud) [31, 32].

In countries without formal centers for rare diseases, patient groups are playing an active role in supporting coordinated care. For example, in Argentina, the Pituitary Diseases Association implemented "Hiptour" to provide medical guidance to professionals for the diagnosis of pituitary diseases in new patients. In Mexico, the Lysosomal Storage Disease Patient network has helped to create a model of comprehensive care starting with diagnosis and including treatment and support that has garnered high-level political attention and endorsement. However, it is centrally located and also limited in outreach resources. Overall, identifying and creating Centers of Expertise or comparable programs represent an important step toward consolidating existing rare disease expertise.

Dimension 2: Diagnosis

An accurate and timely diagnosis is predicated on availability of universal or highly accessible screening and diagnostic programs and services. Across the surveyed countries, policies and practices varied significantly. Neonatal screening has the potential to contribute to an early diagnosis and management of a fraction of rare diseases when there is an effective intervention which can avoid or mitigate severe consequences and/or death if provided early enough Multiple conditions can be identified from a single bloodspot collected at birth. However it is important to note that the composition of a newborn screening panel can vary between regions, depending on local prevalence. A number of newborn screening

programs commonly utilize criteria established by JMG Wilson and F. Jungner in 1968 to decide whether a particular condition is a suitable candidate for screening [33]. A recent report on the practices of newborn screening implemented in EU member states noted that most jurisdictions also take guidelines of scientific societies in consideration [34]. However, many aspects are subjective and there is not always agreement about which disorders should be part of the panel. With the advent of new diagnostic technologies, debates have currently arisen as to how screening programs should adapt.

Many countries have implemented core programs of neonatal screening (eg, Taiwan, Brazil, UK, Germany). Taiwan has implemented a nation-wide newborn screening program that covers at least 26 diseases [30]. Similarly, Germany tests for 14 conditions nationwide [35]. While this number is far removed from the total number of identified rare diseases, only a limited number of neonatal screening assays are currently available. In 2016, Canada announced that the Health Ministers had agreed to a list of 22 core conditions for newborn screening programs across all provincial and territorial jurisdictions, although some provinces were already routinely testing for 30+ diseases [36]. These requisites are all considerably lower than the number of rare diseases that could be tested with a single bloodspot, and this is true of most countries globally (except for the United States, where some states test for 50 or more diseases). In most of the countries surveyed, there was a distinct lack of formal programs for newborn screening and/or infrastructure/resources to support implementation, and this was apparent across geographic regions, with Argentina, Brazil, China, and Taiwan as leading examples where other rare disease initiatives are in place or in planning but limited attention has been given to core newborn screening as an essential component of the rare disease program. For example, in Brazil despite the progressive translation of genetic research into a clinical field and efforts by the Ministry of Health to establish the National Newborn Screening Program (Programa Nacional de Triagem Neonatal – PNTN) in 2001, progress still remains to take place. Currently, only six diseases are included in the formal newborn screening program [8, 37]. The panel still is modest when compared with the screening programs of other countries, including Taiwan with 26 diseases and Germany with 15 diseases.

Beyond the neonatal stage, diagnosis of rare diseases can be even more difficult, resulting in long delays in diagnosis and many misdiagnoses. Geographical challenges exacerbate this problem since long journeys to visit specialists in different regions can impair accurate diagnosis. In Mexico, some patients describe “medical pilgrimages” to different doctors so as to reach a diagnosis, which can take 5 years or longer to achieve. A 2012 European Organization for Rare Diseases survey of eight rare diseases representing 12,000 patients found that 25% of patients had to wait between 5 and 30 years for a diagnosis, 40% received an initial erroneous diagnosis (leading to wrong medical interventions), and 25% had to travel to a different region to obtain a diagnosis [38]. Similarly, a survey conducted by the Canadian Organization for Rare Disorders found that about 20% of patients waited between 6 and 14 years to get a diagnosis and 60% consulted 3 to 20+ specialists on the way to a diagnosis. Importantly, the availability of robust diagnosis and neonatal screening programs can significantly reduce the patient diagnostic odyssey and bridge the gap between disease onset and diagnosis that, for many countries, represents a major barrier in access to care.

Beyond awareness, an important strategy that is being promoted in many countries is education for health care practitioners to develop and expand expertise in rare diseases. For example, the Argentinian Health Ministry launched a tool to promote collaboration between professionals from different institutions across the country with the goal of improving diagnosis. In many emerging healthcare systems, patient groups have taken an active role in promoting professional education and collaboration. The mobilization of a cystic fibrosis patient group was important in shaping decisions on what diseases are screened in Brazil, while, in Mexico, patient groups have spurred the development of early diagnosis funding, patient registries, and efforts to raising rare disease awareness. Progress in these directions has also occurred in the Asia-Pacific region, as the Taiwan Foundation for Rare Disorders (TFRD) coordinates efforts with the Bureau of Health Promotion to send specimens for testing in both foreign and domestic labs for improving diagnosis and subsidizing costs for rare disease testing at local hospitals.

Dimension 3: Access to treatments

The availability of rare disease treatments is addressed in a number of national regulatory and legislative policies designed to facilitate orphan drug designation, authorization, and early access programs. The European Union passed regulation (EC) No 141/2000, on orphan medicinal products in 2000, which covers all of the countries in the EU, including the UK, Germany, Bulgaria and France represented in this survey [39]. Further, the Committee for Orphan Medicinal Products (COMP) was established with the responsibility to recommend orphan designation of medicines for rare diseases to the European Commission for final decision [40]. In the European Union under the Regulation on Orphan Medicinal Products, medicines designated as orphan medicinal products are provided incentives, including protocol assistance. More recently, under the new Priority Medicines (PRIME) scheme, the European Medicines Agency (EMA) will offer early and enhanced scientific and

regulatory support and enable accelerated assessment for therapies that address significant unmet medical need and offer the potential to bring a major therapeutic advantage to patients [41]. Several other countries have expedited review processes for orphan medicines, namely, Turkey, Mexico, Brazil, China [42], Taiwan, and Canada [43], but the criteria and process vary across the countries [44, 45]. In Brazil, the Agência Nacional de Vigilância Sanitária (ANVISA), enacted a regulation (Resolution RDC 28) in 2007 that was further clarified in 2008 (RDC 16), stating that orphan drugs should receive priority review and a decision on approval within 75 days [8]. In practice, the approval can take much longer and regulatory developments are underway to improve review timelines. In Mexico, despite no specific regulation for expedited approval, orphan medicinal products that have been approved by other Agencies, such as the US Food and Drug Administration or the European Medicines Agency, can be expedited via a letter of recognition, and this mechanism has shortened the authorization timeline to approximately 6 months [45]. Argentina has had similar success with a program administered by the Argentinian National Administration of Medicines, Food, and Medical Technology that streamlines authorization requirements for orphan drugs approved in the United States or the EU [45]. In Canada, drugs for unmet needs or urgent situations are eligible for expedited review.

For approved drugs, several countries have policies in place to ensure timely patient access to treatment following regulatory approval. The UK's National Institutes for Health and Clinical Excellence (NICE) have established a separate review process for "Highly Specialised Therapies" which address ultra-orphan diseases (population of less than 1 in 10,000) [46]. Elsewhere, within the UK, The Scottish Medicines Consortium has also developed a new approach for reviewing rare disease medicines designed to increase the influence of patients and clinicians in the appraisal process. This "Patient and Clinician Engagement group" can be convened to address additional benefits that may not be represented in the conventional clinical and economic assessment process. Scotland also has a New Medicine Fund that was recently expanded to £80 million a year allocated to orphan drugs to ensure patient access to the most advanced therapies for diseases with unmet needs [47]. Similarly, in Bulgaria, special considerations are made for health technology assessments for rare disease treatments [48]. Further, Argentina employs a unique system of refund that administers financial support to the Social Health Service for certain drugs.

Dimension 4: Patient awareness and support

To what degree do patients and families get the education and support for their rare disease? For each country, we looked at three key indicators: public awareness directed toward better identification and support, patient education toward, among other things, engagement, advocacy and access to resources, and healthcare professional development to enhance diagnosis, treatment, and care. The countries within our sample varied considerably regarding who was involved, what was done, and how much was achieved. Public awareness ranged from comprehensive campaigns organized by dedicated national or international organizations to local awareness initiatives implemented by stand-alone groups. In all types of activities at all levels, patient organizations were actively engaged. In the United Kingdom, France, and Germany, established patient advocacy organizations, both disease-specific and cross-disease, organized and delivered a range of programs including education and awareness conferences, patient guides to rare disease research [49], and advocacy that spanned from support for legislative acts to receptions with government leaders [50]. In other countries where few other stakeholders were active, strong national rare disease patient networks had the strongest influence on awareness, policy, and health system response. Examples come from disparate regions in our sample. For instance, in Bulgaria, patient organizations implemented award-winning programs and support for rare diseases and, as importantly, educated and motivated the rare disease patient community not only to better access and navigate the healthcare system but also to advocate for their cause, including a call for legislative action to support their needs and playing an integral role in the launch of 13 epidemiological registries for rare diseases [51]. Similarly, national rare disease collaborations in Argentina and Canada [52] have prompted governments to implement legislation and rare disease programs.

In the Asia-Pacific region where our sample consists of China and Taiwan, rare disease patient support and advocacy groups have been active but the scope and impact of their involvement have varied, reflecting differences in political, economic, geographic, and healthcare contexts. In Taiwan, the non-governmental organization Taiwan Foundation for Rare Disorders (TFRD) deliberately focused on obtaining government support for patients and families with rare diseases. To that end, Taiwan Foundation for Rare Disorders has had a key role in shaping rare disease policy and advocating for rare disease patients. Established nearly two decades ago, the organization leads education, awareness, and advocacy efforts. Through coordinated efforts with governmental organizations, Taiwan Foundation for Rare Disorders helped pass the Rare Disease Control and Orphan Drug Act of 2000. In China, where patient advocacy groups are limited in number, localized and disease-specific, medical rare disease groups have focused their efforts

primarily on implementing educational initiatives. Recent efforts have been made to bring together different members of the stakeholder community. In 2011, Chinese medical professionals issued a call to support healthcare, research, drug development, and epidemiological studies for rare diseases [53]. Patient groups, charitable organizations, and pharmaceutical companies have co-hosted patient assistance programs and academic meetings on International Rare Disease Day (February 29) and China Birth Defects Prevention Day (September 12) each year to raise public awareness and promote legislation for rare diseases. More recently, the Chinese Organization for Rare Disorders, formed from an amalgamation of several groups and now representing approximately 40 rare diseases, has conducted several highly innovative and impactful awareness and education programs.

The Chinese and Taiwanese national networks are distinct in their focus and advocacy. Taiwan has more generally focused on within-country awareness raising and lobbying, eschewing most international activities, while the Chinese Organization for Rare Disorders has participated extensively in international arenas and also invited many foreign patient advocates and other experts to support their efforts in China. The differences are due to context. Taiwan is geographically and population-wise a small country, with a relatively strong economy and a high-quality and well-resourced healthcare system that is reasonably accessible to most patients. China, by contrast, is huge in both land mass and population with an emerging economy and evolving healthcare system. The Chinese Organization for Rare Disorders has sought to attract international attention, best practices, and advocacy support. To that end, the Chinese Organization for Rare Disorders is a founding member of the Asia-Pacific Alliance of Rare Disease Organizations and in 2014 was host to the founding meeting of Rare Disease International (RDI), a global alliance of rare disease patients and advocates, to raise awareness, exchange information, and increase the support of the rare disease cause. Participation in the Rare Disease International meeting breaks new ground in that it is an international, patient-led advocacy group and the Chinese Organization for Rare Disorders has the opportunity to host the International Conference on Rare Diseases along with the Rare Disease International meeting in 2017.

Some countries had plans that specifically included health care professional education and training as a key area of focus (Argentina, Germany), while other countries did not emphasize health care professional development (Mexico, China), and this difference reflects, to some degree, the differential involvement of HCPs in the respective patient organizations. The Treatment and Research Centre for Rare Diseases in Germany provides continuing medical education through the German Academy for Further Medical Training on Rare Diseases program, which facilitates interactions and communications between physicians and relevant experts as well as patient organizations [54]. In Brazil, a new National Policy of Integral Attention to People with Rare Diseases includes health care professional training to create specialized teams of professionals to treat patients with rare diseases.

Dimension 5: Research

Research for rare diseases is commensurate with overall GDP as well as investment in innovation, science, and healthcare; it has been relatively well funded with government investment in some countries (France, Germany, UK, Canada) and not officially supported in other countries (Turkey, Mexico). At a regional level, the European Union has demonstrated a strong commitment to rare disease research through the EU Framework Programme for Research and Innovation. Under the Seventh Framework Programmes for research (2007–2013), over €620 million in support was granted to over 120 collaborative research projects on rare diseases. The funding facilitated the formation of multidisciplinary teams from universities, research organizations, industry, and patient organizations from across Europe and beyond [55]. More recently, Horizon 2020, which runs from 2014 to 2020 continues the European Union's strong commitment to funding rare disease research [56]. At a country specific level, France, which currently funds over 300 clinical research projects with collaborations across national and international institutions, is seen as a leader in the research space [26]. In Germany, the Federal Ministry of Education and Research (BMBF) is currently funding 12 research consortia since 2012, with more than €23 million for three years and has supported additional funding through initiatives such as the National Genome Research Network [54, 57]. In China, the China Alliance for Rare Disease Prevention and Treatment (CARDPT) has established the first ever national research program of prevention and treatment for rare diseases, which intends to compile basic data on rare disease pathophysiology and natural history, develop and apply medical guidelines, and promote molecular testing for rare diseases [58]. In Canada, the government has committed funding through the Canadian Institutes for Health Research for emerging teams and consortia of researchers, as well as funding to maintain rare disease models and funding for translational research (gene identification, disease registries, and pilot clinics).

In several countries (Bulgaria, Turkey, Argentina, Mexico, Brazil), there appear to be few or no national initiatives to promote research and/or innovation in the treatment of rare diseases. Research projects in

Argentina are often conducted and funded through private initiatives, research grants, or support from patient organizations. Similarly, there is no long-standing initiative to promote research on rare diseases at the national level in Brazil; however, a bill intending to secure funding for rare and neglected disease-related research is currently being reviewed by Congress.

Registries are important means of collecting disease, demographic, and treatment data. France is a model for national coordination of registries with their Banque Nationale de Données Maladies Rares, a national organization collecting and organizing data from centers of expertise [59]. French patients enter the registry via the center at which they receive care. In contrast, the UK, Bulgaria, and Argentina, have national patient registries in various stages of planning, but not implemented as of yet. To help support the standardization and sharing of information across rare disease registries, the European Commission, within the EU Program of Community Action in the field of Public Health, has initiated the establishment of a European Platform for Rare Disease Registries to address the challenge of standardizing and sharing information across rare disease registries. [60]. This platform is still in development. Orphanet tracks rare disease registries, databases, and biobanks so as to provide access to this information to all stakeholders

Overall, a movement toward international registries is evolving; for example, national rare disease registries are not well developed in Turkey, but the country has participated in European registries such as TREAT-NMD (for neuromuscular disease) and EUROCARE CF for cystic fibrosis. In Bulgaria, patient groups are working to modify legislation addressing patient registries. In Brazil, no national registries exist for rare diseases, but patient associations have been able to collect information in disease-specific areas. Some countries such as Mexico and China have registries that are geographically dispersed and locally based, but lack standard structures to facilitate patient-specific or whole-population analyses. While a national disability registry exists in Taiwan, registries specific to rare disease are lacking; however, the Taiwan Society of Thrombosis and Hemostasis is currently implementing a patient registry specific to hemophilia.

Discussion

This study assesses the status of rare diseases in a sample of countries varying across economic, political, healthcare factors and, at the same time, examines the role of patient organizations in shaping national policy and programs, including rare disease legislation, national rare disease plans, and coordinated comprehensive services directed to rare diseases. Most of the countries represented in our sample (France, Germany, the UK, Canada, Bulgaria, Argentina, Brazil, Mexico, and Taiwan) have developed or announced intentions to develop a National Rare Disease Plan, some of which are officially recognized by the government but none, except for France, are experiencing coordinated strategies and policies toward comprehensive implementation. Indeed, the scope and capacity vary considerably. In general, countries that had higher healthcare spending and GNI per capita, as well as national healthcare delivery systems (France and Germany), also had well-developed national plans that encompass early access to treatments, funding for orphan drug access, diagnosis programs, coordinated care, and strong research initiatives. In contrast, the UK and Canada are similar in their financial metrics as well as regionalized healthcare delivery structures, which have challenged the development of national centers of expertise, national guidelines for screening and diagnosis, and national criteria for access to therapy. Scotland, Northern Ireland, and the United Kingdom have unique drug assessment agencies. In the United Kingdom, the National Institute for Healthcare Excellence (NICE) has developed a separate body to assess "highly specialized drugs" primarily for ultra-orphan indications [61], while Scotland introduced a dedicated Rare Conditions Medicines Fund [62] and Northern Ireland considers some form of "ring fenced fund" for orphan drugs [63].

Turkey, Mexico, and China do not have orphan drug legislation; analysis of external financial metrics revealed that these countries also had the lowest GNI per capita and healthcare spending. Countries that were lesser developed and/or had low healthcare spending and GNI per capita were more likely to have National Rare Disease Plans (NRDP) that were not endorsed or implemented. Still, some countries lacking formal NRDPs had legislation/policies/regulations in place to improve access to orphan drug treatment (eg, orphan drug classification and accelerated review policies exist in Mexico).

Clearly, gaps exist between policy and practice. While a number of countries have regulations specific to orphan drugs that are designed to accelerate the authorization process, streamlined processes do not necessarily expedite or guarantee drug approval. In Brazil, the established time frame for responding to authorization requests is 75 days, but authorization times have varied from 13 to 30 months. Bulgaria and Scotland were the only countries across those surveyed to have specific funding allocated to orphan drugs. However, orphan drug licensing in Bulgaria is often delayed from 1 to 6 years.

Despite the lack of formal NRDPs in place, several countries have been able to make great progress in improving processes in the rare disease landscape. Though Canada did not have a national plan in place until September 2015, it has a very strong newborn screening policy and well-established diagnostic centers that exceed what is available in many other countries [36]. In

the Asia-Pacific region, Taiwan provides a model for good programs that exist in the absence of specific policy; improved screening and diagnosis programs are in development, led by advocacy groups and funded by the Taiwanese government. Further, Turkey has defined pathways for early treatment, designated specialized centers for coordinated care, and provides screening and diagnosis programs despite delayed implementation of its NRDP.

Several countries, inspired by the progress in Europe, have adapted the consultation process and the core indicators developed by the EUROPLAN project to support the development and implementation of rare disease plans and strategies [64]. In Canada, the Canadian Organization for Rare Disorders played an instrumental role in the strategic development and implementation of the Canadian NRDP, which was distilled from 30+ other NRDPs and asserts goals that are closely aligned with those of the UK Strategy for Rare Diseases [65, 66]. Consistent with the position of the European Organization for Rare Diseases (EURODIS) on rare disease research infrastructure, development, and governance, the inclusion of patients as full and equal partners is a central recommendation set forth by the Canadian Organization for Rare Disorders (CORD) [65, 67].

In other countries, including Mexico, the patient advocacy community is playing a large role in shaping discussions, educating policy makers and driving the political agenda to support national rare disease strategies by actively participating in small working groups with their national Health Commissions. In several countries without formal NRDPs, coordinated and influential disease-specific advocacy groups have provided leadership in addressing gaps and implementing programs to support key needs within the community. One such example of the active role patient groups are playing in supporting coordinated care in the absence of formal centers of expertise is seen in Argentina, where advocates from the Pituitary Diseases Association in Argentina travel around the country and provide medical updates on pituitary diseases to professionals to help identify and diagnose patients. Similarly, patient groups in Bulgaria have been working to modify legislation addressing patient registries to create a centralized registry that is more compatible with international databases. In China, the China Alliance for Rare Disease Prevention and Treatment has established the first ever national research program of prevention and treatment for rare diseases. This demonstrates that despite national prioritization, patient advocacy organizations can drive successful implementation of programs that can help support the key needs of rare disease patients. However, despite the successful adoption of these programs, integrated and coordinated strategies are necessary to ensure holistic access to care and treatment for patients.

To further garner support, patients can further policy development by creating alliances between/among organizations. The Iberoamérican Alliance for Rare Diseases (ALIBER) has established a system across Ibero-American countries to collaborate and share ideas surrounding rare diseases. The recently formed Asia-Pacific Alliance of Rare Disease Organizations (APARDO) represents a collaborative unification of national rare disease groups aimed at improving access to care and treatment of rare diseases in China, Japan, India, Australia, and Singapore. Importantly, many countries analyzed in this study are members of Rare Disease International (RDI), which provides a clear framework for establishing and improving advocacy, awareness, information sharing and networking, research, and partnerships. As the landscape of rare disease policy continues to evolve, the unification of rare disease patient organizations will be essential to driving innovative research with shared resources and best practices, and amplifying the role of the patient voice in the development of programs to address the needs of the rare disease community.

Conclusion

According to the goals outlined in the EURORDIS and CORD position papers, our study explored the rare disease legislation, associated policies, regulations, and programs across a diverse sample of countries through the perspective of the key needs of the rare disease community. Consistent with previous reports [25, 68, 69], our analysis revealed substantial differences in rare disease infrastructure across countries; however, it was limited in the scope of the countries considered and was not designed to assess the effect of specific policies and structures on patient outcomes. Subsequent analyses should be conducted to correlate policy with the presence of actual programs and, ultimately, their effects on patient care. Importantly, this information will provide a strategic framework that can structure ongoing dialogues within and between countries so as to define best practices in rare disease management and harmonize efforts across the globe in improving patient care.

Abbreviations

ALIBER: *Alianza Iberoamericana de Enfermedades Raras,* Iberoamérican Alliance for Rare Diseases; ANVISA: *Agência Nacional de Vigilância Sanitária*, National Health Surveillance Agency; APARDO: Asia-Pacific Alliance of Rare Disease Organizations; BMBF: *Bundesministerium für Bildung und Forschung*, Federal Ministry of Education and Research; CARDPT: China Alliance for Rare Disease Prevention and Treatment; COE: Centers of Expertise; COMP: Committee for Orphan Medicinal Products; CORD: Canadian Organization for Rare Disorders; EMA: European Medicines Agency; ERN: European Reference Networks; EU: European Union; EUROPLAN: European Project for Rare Diseases National Plans Development; EURORDIS: European Organization for Rare Diseases; GDP: Gross domestic product; GNI: Gross national income; HTA: Health technology assessment; NICE: National Institute for Health and Care Excellence; NORD: National Organization for Rare Disorders (NORD); NRDP: National rare disease plans; ODA: Orphan Drug Act; PRIME: Priority

Medicines; RDI: Rare Diseases International; TFRD: Taiwan Foundation for Rare Disorders; UK: United Kingdom

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Authors' contributions
Conceived and designed the review: SBD, DWR, ST, MH. Compiled and analyzed the reviewed material: SBD, DWR, MH. Wrote the paper: SBD, DWR, ST, MH. All authors read and approved the final manuscript.

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