

# INTERNATIONAL JOINT RECOMMENDATIONS

## TO ADDRESS SPECIFIC NEEDS OF

## UNDIAGNOSED RARE DISEASE PATIENTS

October 2016

On behalf of patients living with undiagnosed and rare diseases across Europe, North America, Australia and Japan; SWAN UK (the support group run by Genetic Alliance UK), the Wilhelm Foundation, EURORDIS (Rare Diseases Europe), Rare Voices Australia (RVA), the Canadian Organization for Rare Disorders (CORD), the Advocacy Service for Rare and Intractable Diseases' stakeholders in Japan (ASrid) and the National Organization for Rare Disorders (NORD) jointly submit the following list of recommendations to address the specific needs of patients without a diagnosis. We urge all stakeholders to recognise undiagnosed patients as a specific population within the rare disease community.

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### The 5 Recommendations to address specific needs of undiagnosed rare disease patients

- 1. Undiagnosed Rare Disease Patients should be recognised as a distinct population** with specific unmet needs by national authorities to enable development of personalised health and social care. Although some undiagnosed diseases are common, the vast majority are rare. Hence, in this paper we refer to undiagnosed patients as "undiagnosed rare disease patients".
- 2. National sustainable programmes** dedicated specifically for undiagnosed diseases should be developed and supported by appropriate authorities in each country to enable rapid and equitable access to diagnosis and social support.
- 3. Knowledge and Information sharing should be structured and coordinated** at national and international levels to optimise use of existing resources and facilitate access for all undiagnosed rare disease patients.
- 4. Patients should be equally involved** with other stakeholders in the governance of undiagnosed diseases programmes and international networks to adequately address the priorities of undiagnosed rare disease patients and contribute to improved healthcare.
- 5. Ethical and responsible international data sharing should be promoted** through existing initiatives to support diagnosis, increase clinical collaboration, facilitate research, and accelerate treatment of undiagnosed and rare conditions.

Undiagnosed rare disease patients require the availability of a complete health and social care pathway in advance of receiving a diagnosis. Such care should promote their chances of receiving an accurate diagnosis in as efficient and timely way as possible, while ensuring that, until a diagnosis is made, they nevertheless receive the best possible health and social care. These recommendations also highlight the importance of promoting ethical and responsible international data sharing to help inform a clinical diagnosis, accelerate research into novel conditions and provide insights into disease mechanisms. Furthermore, knowledge and information sharing among all stakeholders should be optimally coordinated and fostered so that patients can access appropriate resources in a timely and efficient manner.

The term **diagnosis** can be defined as an understanding of disease pathogenesis, linking genetic and clinical findings and informing prognosis and therapy<sup>1</sup>. The following recommendations refer to this definition.

An important distinction to consider, for the undiagnosed population, involves the different groups of undiagnosed patients, as based upon the various reasons for difficulties in obtaining a diagnosis:

- **'Not yet diagnosed'** refers to a patient who lives with an undiagnosed condition that should be diagnosed but hasn't been because the patient has not been referred to the appropriate clinician due to common, misleading symptoms, or an unusual clinical presentation of a known rare condition<sup>2</sup>.
- **Undiagnosed ("Syndromes Without A Name" or SWAN)** refers to a patient for whom a diagnostic test is not yet available since the disease has not been characterised and the cause is not yet identified. This patient can also be misdiagnosed as his/her condition can be mistaken for others. These conditions are also likely to be rare.

Patients or families in either of these groups might never receive a diagnosis, and it is not possible to tell *a priori* which group any specific family or patient might be in. However, the measures necessary to improve the outcomes for each group are distinct:

- To improve outcomes for the 'not yet diagnosed' group, both the route to, and the quality of, diagnostic tools and also access to extensive genomic data need to be improved.
- To improve outcomes for the 'undiagnosed'/'SWAN' group, more diagnostic testing methods, including genomics, need to be integrated within clinical practice, and underpinned by genomic data sets, to facilitate the diagnosis of novel conditions.

*"To help people with rare diseases, we need more than technological advances – we need global cooperation."* Paul Lasko, Scientific Director, Institute of Genetics, Canadian Institute of Health Research and former chair of the International Rare Diseases Research Consortium.

## 1. Undiagnosed rare disease patients should be recognised by national authorities as a distinct population with specific unmet needs to enable development of personalised health and social care

Many people throughout the world are struggling in search of a diagnosis<sup>3,4,5</sup> which often serves as the key to unlock access to effective medical and social care as well as treatment. Some patients live for extensive periods, in many cases their entire lives, with an undiagnosed condition; obtaining a diagnosis can be a long and difficult journey<sup>6,7,8,9</sup>. For example, a EURORDIS survey of eight relatively common rare diseases in Europe showed that 25% of patients waited from 5 to 30 years for a diagnosis, and during that time, 40% received an incorrect diagnosis<sup>10</sup>. Similarly, in Australia, a survey of adults living with rare diseases found that 30% waited 5 or more years for a diagnosis and 50% received an incorrect diagnosis<sup>5</sup>.

Late diagnoses delay the beginning of specific treatments and can have irreversible and life threatening consequences, including worsening of clinical status, significant psychological distress of the patient and families, and, death in cases that are progressive and degenerative. Undiagnosed rare disease patients and families also face added social and daily life challenges, incurrent from the lack of knowledge on the condition and its consequences on health, functioning and wellbeing. The length of delay in diagnosis can vary greatly depending on the disease and on the country, as well as on individual factors<sup>10</sup>, such delays have negative influences on scarce national health resources, since they are expensive and represent an inappropriate waste of highly specialised healthcare funding.

Living in uncertainty is debilitating for families affected by undiagnosed conditions. A significant consequence revolves around the heartache and stress patients and their families experience, compounding feelings of isolation and exclusion that worsen with the chaotic journey through numerous referrals, investigations, and disease evolutions. In situations where diseases are inherited, many families have several affected siblings. For these families, the absence of a diagnosis denies them an informed reproductive choice and access to genetic counselling, and increases the risk and worry of having another child suffering from the same undiagnosed condition<sup>11</sup>.

Those with undiagnosed conditions, whether occupying that status temporarily or life-long, express common concerns as to what matters most to them, including:

- Pursuing a consistent and organised approach to understanding the condition – the search for a diagnosis should not stop, but should not be chaotic;
- Working in collaboration with healthcare professionals who respect and listen to the family;
- Not delaying healthcare provision until diagnosis, as this may not occur;
- Addressing the issues associated with access to social services, education, occupation, and rehabilitation support;
- Getting assistance with care coordination that includes communication and information sharing among professionals and the family.

Being undiagnosed is not always a temporary phase, so there is an urgent need to recognise this population as a distinct group with differing and specific needs that differentiate them as a population from those with diagnoses. The undiagnosed community is continuously struggling to access health and social care because our modern societies use systems that still rely on a diagnosis to design their approach to patient care.

In most countries, undiagnosed rare disease patients remain an invisible and highly vulnerable population whose specific needs have not been identified or assessed. An urgent priority is for national healthcare and social welfare authorities to begin by analyzing the volume and the needs of their undiagnosed population; this should be highlighted in commissioning arrangements to adequately allocate national resources.

Physicians caring for patients whose complex and rare conditions are particularly difficult to diagnose must accept that their isolated efforts will frequently fail. Indeed, healthcare practitioners cannot be expected to recognise or identify all of the 6000 to 7000 known rare genetic diseases<sup>12</sup>, let alone diseases that have not been identified and characterised. This is why it is crucial to raise awareness among healthcare professionals about rare as well as undiagnosed diseases. Educating healthcare and social care professional about the impact of being undiagnosed on family life and about the need for support and care pathways prior to diagnosis is essential to improve the current situation for undiagnosed rare disease patients on a long and complicated medical odyssey.

## 2. National sustainable programmes dedicated specifically for undiagnosed diseases should be developed and supported by appropriate authorities in each country to enable rapid and equitable access to diagnosis and social support.

National coordinated systems designed to support health and social care professionals and undiagnosed rare diseases patients should be developed and implemented to provide clear access to relevant expertise, enabling faster diagnosis and optimum health and social care management.

National and/or regional health and social care authorities are responsible for identifying and assessing the needs of undiagnosed rare disease patients. This should lead to integrated clinical and social pathways specifically designed to answer those needs. Local and regional clinical services should be able to apply 'red flag indicators' in situations where a diagnosis is unlikely to occur for suspected "syndromes without a name" and undiagnosed patients to facilitate timely referral to specialised undiagnosed disease programmes and access to adequate social support.

Several dedicated programmes<sup>13,14,15,16</sup> have been designed specifically to meet the needs of patients for whom medicine has failed to provide a diagnosis despite extensive investigation. Some programmes focus on advancing clinical genetic practice whilst others rely on a phenotype informed approach combined with genomic testing.

By bringing together a multidisciplinary and coordinated team of experts and providing access to the latest technologies, these programmes offer patients and their families the hope of a diagnosis and, importantly, the possibility to develop therapeutic strategies and access to treatment. In return, patients provide researchers the opportunity to explore the human genome, inform new aspects of cell biology and gain new insights into disease mechanisms.

All diagnoses require thorough clinical evaluations, specialised medical expertise, and collaborative consultations<sup>17</sup>. Nevertheless, not all undiagnosed disease patients will receive the answers they need, despite optimally coordinated efforts and use of the latest technologies. Therefore, it is critical to provide clear and detailed information that enables meaningful informed consent and that manages patients' expectations. Genetic counsellors and other healthcare professionals should be able to communicate effectively the potential outcomes and implications of genetic sequencing and other investigations intended to find a diagnosis<sup>18</sup>.

Specific undiagnosed diseases programmes have been initiated in several countries often as part of research projects funded only for a predetermined period. Consequently, there is a limited capacity to evaluate patients in need of a diagnosis and, due to funding models, several programmes are unsustainable over time. However, the progress made by many of these research teams demonstrates the valuable gains possible with national coordinated efforts to diagnose and support patients with undiagnosed rare diseases. Unfortunately, the lack of sustainability of some of these programmes is likely to impair long lasting efforts that could result in better diagnostic tools - unless these tools, together with the skills and knowledge gained, are adopted and implemented by national health authorities<sup>14</sup>.

The various national projects<sup>13,14,15,16</sup> illustrate the diverse nature of collaborations between researchers and clinicians aiming to diagnose patients with rare and undiagnosed conditions using similar and sometimes complementary approaches ranging from genomic, phenomic and/or metabolomic technologies to functional studies. All these approaches are invaluable in the response to the unmet medical needs of undiagnosed disease patients, aiming to provide patient-relevant clinical outcomes and maximise the potential for research.

National undiagnosed diseases programmes should be developed in every country to enable a more efficient use of scarce resources, pooling national healthcare resources, expertise and funding and refocussing these into specific programmes to target undiagnosed diseases. Certain key principles are needed to implement national healthcare pathways that are vital to ensure the opportunity for diagnosis and treatment of patients with rare diseases in every country. These include:

- The implementation of a 'red flag system' to facilitate referral to national undiagnosed disease programmes and easier and faster access to special expertise and technology such as next generation sequencing;
- Long-term and sustainable funding of national programmes ;
- International collaboration of national centres of excellence sharing best practices, ethical guidelines, common protocols and genetic and phenotypic data (see 5).

### 3. Knowledge and Information sharing should be structured and coordinated at national and international levels to facilitate access to relevant resources for all undiagnosed patients

There are a number of undiagnosed patient associations and families that are very active online, sharing information and communicating largely through social media. An international online community specifically for undiagnosed patients has been developed on the RareConnect platform<sup>19</sup> in 8 languages. This virtual community enables people living with an undiagnosed rare disease to meet others with similar experiences, share their stories and learn from each other wherever they live around the world. The RareConnect community was built in partnership with leading patient groups for the undiagnosed that provide resources such as moderators, relationships with specialists and validated information. Patient representatives and advocates from all countries should encourage their members to participate in this international, multilingual online community to expand available information and centralise relevant knowledge for the benefit of everyone affected by undiagnosed rare diseases.

Umbrella patient organisations and national helplines for rare diseases, often the first point of contact when signs of the disease start to develop, play a significant role in supporting undiagnosed disease patients and their families. It is of paramount importance to implement a systematic approach by which requests and needs from undiagnosed rare disease patients are recorded through common standards and data sets and robust protocols are in place.

Such approach will enable to manage demands in the most efficient and appropriate manner, and to link with and support dedicated patient organisations for rare and undiagnosed diseases. It will also ensure that these vulnerable patients do not go unnoticed by the healthcare systems.

Currently, most countries do not have resources dedicated to responding to requests from undiagnosed rare disease patients, severely limiting what the voluntary sector can do, even with defined protocols and patient registries. It is essential that these organisations and helplines are adequately resourced to be effective “first line” responders as these programs are being developed.

Although organised, structured and valuable national initiatives exist in several countries to support undiagnosed rare disease patients secure a diagnosis, there is a huge disparity in accessing these resources both among and within different countries. Dedicated programmes for undiagnosed patients should be established in each country and become the spokes of an international network. An international network of clinical centres was initiated in 2014 to address unmet needs of undiagnosed patients at a global level. The Undiagnosed Diseases Network International (UDNI)<sup>20,21</sup> was established following three international conferences (2014-2016) supported by the Common Fund, within the Office of the NIH Director, along with the Wilhelm Foundation, Sweden<sup>22</sup>. However, there is currently no specific support provided to clinical centres wishing to be part of this consortium and participation is entirely on a voluntary basis.



To enable more equitable and faster access to specialist care and relevant information, it is necessary to develop a framework to support partnerships among the different stakeholders for a more efficient flow of information. Increased visibility of existing resources (such as information about ongoing undiagnosed programmes and relevant research projects, specialised expertise, social support, dedicated patient organisations, financial help) would also facilitate access and maximise efforts at many different levels. For example, a unique partnership has recently been established between the French association for undiagnosed diseases<sup>28</sup>, the national rare disease helpline and the French reference network (“AnDDi-Rares”) for rare developmental abnormalities and intellectual disabilities. The objectives of this partnership include offering undiagnosed rare disease patients and their families different solutions to access relevant information and increasing the visibility of existing resources<sup>23</sup>.

Direct and regular communication among patient organisations, national alliances for rare diseases, helplines, healthcare and social care professionals, centres of expertise and specialised programmes would enable a much more efficient use of existing resources. Developing partnerships will also add to the collective knowledge of the rare disease community, enable the development of new management approaches and benefit from health savings. Patients and their associations are essential pillars for fostering knowledge sharing, identifying research priorities, and promoting and helping to maintain undiagnosed disease programmes and should be lead partners in global health networks to further support clinical training and clinical translational research<sup>24</sup>.

#### 4. Patients should be equally involved with other stakeholders in the governance of undiagnosed diseases programmes and international networks to adequately address the priorities of undiagnosed rare disease patients and contribute to improved healthcare

Engagement of health and social care professionals with patients and their families is crucial for their mental, emotional and social wellbeing. In addition, failure to gain patient insights at the right time can lead to misplaced priorities and costly late-stage failures<sup>25</sup>. To aid in comprehensive management, care pathways must enrol the help of the many active patient organisations. For example, the UDNI recognises that patients’ participation and experiences contribute to improved healthcare. Therefore, active patient engagement within the UDNI will be integral to the success of the network in achieving its objectives. Hence, an international Patient Advisory Group (iPAG) will be developed to ensure that the patient’s voice is heard within the network and throughout various activities<sup>20</sup>. The iPAG will bring together elected undiagnosed rare disease patient representatives from dedicated patient organisations across the globe (see below) and is expected to play an increasing role in UDNI activities in collaboration with national undiagnosed diseases programmes.

Patient organisations specifically dedicated to support undiagnosed disease patients and their families have been established in several countries around the world<sup>22,26,27,28,29,30,31,32,33</sup>.

Often initiated by patients themselves or parents of undiagnosed children, these organisations have at least one objective in common, which is to enable families to share their stories and break the feelings of isolation and guilt. Equitable and fast access to diagnosis and specialised healthcare must be considered a basic right for the undiagnosed population.

For example, obtaining fair and fast access to high throughput next generation sequencing is often advocated by undiagnosed patient organisations as a key priority in addressing the needs of families on a diagnostic odyssey.

A recent initiative by SWAN UK aims to formalise a network of patient associations specifically supporting patients living with syndromes without a name and rare conditions within the different European countries. The planned objectives for this network include:

- The Networking and sharing approaches to supporting families of children/young people with undiagnosed genetic conditions;
- Disseminating knowledge about genomic technologies;
- Facilitating access to genomic technologies for families within the undiagnosed community;
- Building a platform for the undiagnosed community to have a voice in policy development in Europe;
- Providing a forum to enable peer support between families of children/young people with undiagnosed genetic conditions;
- Acting as a point of contact for members of the research community to build connections

- Linking to international networks and more specifically, a Patient Advisory Council within the UDNI.

Patient organisations clearly have an important role in the initiation and maintenance of undiagnosed rare disease pathways, and will bring a much needed, valuable insight into patients' experiences and expectations. Consequently, all undiagnosed diseases programmes across the globe should include patient representatives in their governance to maximise the impact of patients' involvement and contribute effectively to the successful delivery of their objectives.

## 5. Ethical and responsible international data sharing should be promoted through existing initiatives to increase collaboration, improve diagnosis, facilitate research and accelerate treatment of undiagnosed and rare conditions

It is now widely accepted that large-scale data sharing is necessary to facilitate research progress into the aetiology of difficult to diagnose and complex and/or rare diseases. Clinical academic research groups, patient organisations, clinical diagnostic service providers, health care professionals, industry, payers, regulators and policy makers, all acknowledge the strong need for the implementation of a strategy that **protects and assists clinicians in sharing information to help patients achieve a diagnosis and that respects the rights of this vulnerable population and the specific sensitivity of their data, through cross-border and international collaborative efforts**<sup>34</sup>.



The importance of international data sharing is even more evident for rare and uncharacterised diseases for which there are no validated diagnostic tools. Ethical and responsible data sharing should be enabled through implementation of the international charter of principles for sharing bio-specimens and data (that includes the ethical foundations on which data-sharing should be based)<sup>35</sup>, whilst taking into consideration the expectations of rare disease patients on large-scale data sharing<sup>36</sup>.

A promising approach in the discovery of novel causative disease genes is based on "Matchmaking". Several databases have been established by genetic communities through which participants submit genomic and phenotypic data with the goal of identifying previously uncharacterised disease-associated genes by "matching" to comparable cases.

For example, DECIPHER<sup>37</sup> is an interactive web-based database that incorporates a suite of tools designed to aid the interpretation of genomic variants and enhance clinical diagnosis<sup>38</sup>. DECIPHER enables a flexible approach to data-sharing within an international consortium of collaborators. Following a similar goal, scientists at the University of Toronto in Canada developed PhenomeCentral, an international portal that connects clinicians who are trying to diagnose and treat unknown rare diseases patients who have similar symptoms<sup>39</sup>.

A further international knowledge platform for undiagnosed diseases is Patient Archive<sup>40</sup>, delivered through partnerships including the Garvan Institute of Medical Research, the Office of Population Health Genomics Western Australia and Genetic Services of Western Australia.








DECIPHER, PhenomeCentral and Patient Archive, in concert with others, are participating in Matchmaker Exchange<sup>41,42</sup> which represents the largest effort to enable linking of several databases to allow communication of specific case details within larger shared environments. This project is funded by the Global Alliance for Genomics and Health<sup>43</sup> and the International Rare Disease Consortium<sup>44</sup> and is supported by a growing number of teams and projects working toward a federated platform (exchange) to facilitate the matching of cases with similar phenotypic and genotypic profiles (matchmaking).

The Platform for Engaging Everyone Responsibly or PEER<sup>45</sup> is another participant in Matchmaker Exchange; it is unique in that it enables patients and their caregivers, to share clinical information and biological specimens and allows participants to set their own sharing, privacy and data access preferences. Indeed, providing patients the opportunity to enter their own phenotypic and genetic data into a platform with the appropriate support<sup>46</sup> and guidance should significantly facilitate data collection on rare diseases with scarce knowledge and should contribute to a better understanding of disease causes and mechanisms and the development of therapeutic strategies.

Global participation in the Matchmaker Exchange project should be encouraged, supported and facilitated by national authorities, dedicated undiagnosed diseases organisations together with umbrella organisations to enable improved diagnosis of complex and undiagnosed cases and provide patients with answers regarding the prognosis of their conditions.

# Co-signatories & Acknowledgments

## Co-signatories (Patient Organisations)

	SWAN UK	United Kingdom
	Wilhelm Foundation	Sweden
	EURORDIS	Europe and International
	Rare Voices Australia	Australia
	Canadian Organization for Rare Disorders (CORD)	Canada
	Advocacy Service for Rare and Intractable Diseases' stakeholders in Japan	Japan
	National Organization for Rare Disorders (NORD)	USA

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- <sup>27</sup> Spanish Association - Objetivo Diagnostico: <https://www.facebook.com/objetivodiagnostico/>
- <sup>28</sup> French Association - Sans Diagnostic et Unique : <http://www.asdu.fr/>
- <sup>29</sup> Italian Association - Fondazione HOPEN: <http://fondazionehopen.org/home>
- <sup>30</sup> Dutch Association – Platform ZON: <http://www.ziekteonbekend.nl/>
- <sup>31</sup> Syndromes Without A Name, Australia: <http://www.swanaus.com.au/>
- <sup>32</sup> Syndrome Without A Name, USA: <http://swanusa.org/>; RUN (Rare and Undiagnosed Network), USA: <http://rareundiagnosed.org/> and U. R. Our Hope, USA: <http://urourhope.org/>
- <sup>33</sup> Syndromes Without A Name, New Zealand: <http://www.swannz.org.nz/>
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