



Llywodraeth Cymru
Welsh Government

Welsh Implementation Plan for Rare Diseases

Annual Update 2018

Mae'r ddogfen yma hefyd ar gael yn Gymraeg.
This document is also available in Welsh.

1. Introduction and overview:

This Welsh Implementation Plan for Rare Diseases Annual Update 2018 provides a brief narrative of progress made against the Welsh Implementation Plan for Rare Diseases and its yearly priorities. The update provides an exposure to a range of rare disease case studies and updates from a range of viewpoints; including charities, academic, research and clinical.

The *Welsh Implementation Plan for Rare Diseases*¹ was updated in July 2017 and re-affirms the Welsh Government's commitment to both, empowering those with a rare disease and ensuring those affected by any kind of rare disease have timely access to high quality pathways of care. The Rare Disease Implementation Plan puts in place a framework to deliver the Welsh Government's commitment to the vision in the UK Strategy for Rare Diseases.²

The Welsh Rare Diseases Implementation Group (RDIG) supports the implementation and the management of the plan. The RDIG includes broad representation from each health board in Wales, Welsh Health Specialised Services Committee (WHSSC) and Public Health Wales; additionally the Group has representation from the Rare Disease and Genetics Alliance and a patient representative. The Group is chaired by Dr Graham Shortland, Medical Director, Cardiff and Vale University Health Board.

Progress has been made to increase awareness of rare diseases, health care professionals and genetics have led the way to speeding up diagnosis. However, substantial challenges have been encountered to increasing the profile of rare diseases outside of treating clinicians.

¹ [Welsh Rare Diseases Implementation Plan \(July 2017\)](#)

² [UK Strategy for Rare Diseases](#)

2. Progress on priorities for 2018/19/key achievements:

The key priorities identified for 2018-19 Welsh Implementation Group included:

- a. Identify and improve the pathway for patients with unknown or delayed diagnosis;
- b. Ensure better use of patient feedback, best practice and evidence to improve pathways for primary, secondary and specialist services;
- c. Improve reporting of rare disease information including epidemiology, significant event analysis and shared learning.

a. Identify and improve the pathway for patients with unknown or delayed diagnosis:

Following the publication of a Statement of Intent³ in March 2016 and subsequently wide consultation with multiple stakeholders within and outside of Wales, the then Cabinet Secretary for Health and Social Care, Vaughan Gething AM, launched the Genomics for Precision Medicine Strategy⁴ in July 2017. This strategy sets out the Welsh Government's plan to create a sustainable, internationally-competitive environment for genetics and genomics to improve health and healthcare provision for the people of Wales. The strategy supports the principles laid out in other Welsh Government Strategies, such as "A Healthier Wales"⁵, and adopts the values of Prudent Healthcare.

As part of establishing appropriate governance arrangements to support the implementation of the strategy, '*Partneriaeth Genomeg Cymru*' - *Genomics Partnership Wales* was formed as an umbrella organisation to nurture a united approach to genomics in Wales. The Partnership represents a number of organisations across several disciplines, each with their individual strengths and international reputation, coming together to deliver a programme of work that will enable the ambition and commitment laid out in the Genomics for Precision Medicine Strategy to be realised. The vision of Genomics Partnership Wales is: "*Working together to harness the potential of genomics to improve the health, wellbeing and prosperity of the people of Wales*". Key partners include the All Wales Genomics Service, Public Health Wales' Pathogen Genomics Unit and the Wales Gene Park, along with higher education institutions in Wales, NHS Wales and Welsh Government.

£6.8 million was initially invested in the implementation of this strategy, and subsequent investment of £2.3 million has been made in 2019-2020 to support the expansion of the testing provision, carried out by the All Wales Genetics Laboratory, in light of major restructures to genomic services in NHS England. This funding by Welsh Government, through WHSSC, enabled a much larger group of patients with rare diseases to access genetic testing. The partnership has also purchased a NovaSeq sequencer to support the provision of whole genome sequencing and this will become an asset for Wales across the NHS and academic sectors.

³ Statement of Intent for Genomics and Precision Medicine – March 2016:

<http://www.assembly.wales/ministerial%20statements%20documents/statement-intent-genomics-precision-medicine/160323genomicsen.doc>

⁴ Genomics for Precision Medicine Strategy: <https://gov.wales/sites/default/files/publications/2019-04/genomics-for-precision-medicine-strategy.pdf>

⁵ A Healthier Wales: our Plan for Health and Social Care:

<https://gweddill.gov.wales/docs/dhss/publications/180608healthier-wales-mainen.pdf>

In February 2018, Wales joined the 100,000 Genomes Project placing rare disease patients at the heart of the genomic medicine revolution. The project, now a UK-wide initiative, seeks to transform patient care, encourage genomic discovery and drive a thriving genomics sector.

In an agreement between Cardiff and Vale University Health Board (CVUHB), Cardiff University and Genomics England (the company leading the Project across the UK), 420 whole genome sequences (WGS), have been commissioned for patients with rare diseases and their families in Wales.

The 100,000 Genomes Project aims to sequence 100,000 genomes from 70,000 people with rare diseases and their families, as well as those with cancer. To date, more than 50,000 whole genomes have been sequenced with the ultimate 100,000 WGS milestone due to be reached by the end of 2018.

Welsh rare disease patients and their families who choose to participate in the 100,000 Genomes Project, may be provided with a diagnosis and spared years of uncertainty and distress (often known as the diagnostic odyssey). With more precise and rapid diagnosis, there is also the potential to reduce pressure on Welsh health and social care budgets.

In this **case study** from the **100,000 Genome Project** it describes how last year a six year old child and their mother and father gave blood samples to be analysed in the 100,000 genome project. DNA was then extracted from the blood samples and sent away so that their genome sequences could be determined.

There were approximately 6 million differences in the six year old's DNA compared to a reference DNA sequence and by looking for a rare change that wasn't in their mother or father that had a functional effect on a protein. Thus the number of changes were reduced down to two.

The team looked carefully at these two changes and found that one change in a gene called KMT2A was linked to symptoms similar to those found in the child. The KMT2A gene makes a protein that binds to DNA and affects expression of other genes. Mistakes in the KMT2A gene causes Wiedemann-Steiner syndrome which has only been found in a few hundred patients worldwide.

This 100,000 genome project result has suggested some extra tests that can be carried out, these were:

- An echocardiogram and renal tract ultrasound to rule out congenital abnormality that may occur in some patients;
- Checks of immune function if there is evidence of recurrent infections;

As this change was not present in his mother and father it reduces the chances of them having another affected child and reassures other family members. A diagnosis of Wiedemann-Steiner syndrome enables the family to contact others in a similar

situation for example the Wiedemann-Steiner syndrome foundation that provides support for individuals and families affected by the syndrome.⁶

b. Ensure better use of patient feedback, best practice and evidence to improve pathways for primary, secondary and specialist services:

In this update from the **Genetic Alliance UK**, it sets out the patient and public involvement in rare disease research. Wales Gene Park works with patients and the public to involve them in rare disease and genetic research. In addition to representation on their governance boards, patient and public involvement is a key aspect of their work across all work programmes particularly health professional education and engagement and participation in research.

The rare disease patient network has opportunities throughout the year to take part in relevant research opportunities. Opportunities are advertised through a newsletter and directly to patients and carers who are required for condition specific studies. They also support the recruitment of patients and the public to steering committees and governance structures for research projects.

Following a consultation workshop with patients and the public at their annual meeting, they have developed a Rare Disease Research Portal which will host relevant studies in the field of rare diseases on the Wales Gene Park website. The Portal will promote Health and Care Research Wales studies in addition to projects from researchers who sit outside the infrastructure. It will link to training opportunities for patient and public involvement representatives via the Health and Care Research Wales training programme.

The design and development phase of the portal is complete, however, they will be consulting with patients and the public regarding its usability before launching later in 2019. They will be engaging with researchers through our Professional Network to increase the number of rare disease research opportunities available following its launch.

Professor Keir Lewis (Swansea University and Hywel Dda University Health board (HDUHB)) provides an **outline** on the establishment of a new rare diseases charity.

Wales Orphan and Rare Lung Disease (WORLD) was created in March 2018 by health and Research and development staff in HDUHB. Its goals are for *“The preservation and protection of good health for the public benefit, by promoting the awareness and understanding of rare lung disease in West Wales”*.

WORLD promotes discussion, engagement, support, knowledge and research:

- Providing a forum for rare lung disease patients, families and carers to meet and share experiences
- Raising awareness and engaging health professionals to help improve diagnosis and management of rare lung disease
- Offering emotional and educational support to rare lung disease patients, families and carers including signposting to other relevant bodies
- Gathering information on patient numbers and outcomes and supporting research into rare lung disease

⁶ Credit to the 100,000 genomes project, including Dr Sharon Whatley and Dr Arveen Kamath.

Currently the Group consists of over 70 members from the HDUHB area consisting of patients, their carers and/or family. The charity's Trustees meet quarterly and include a patient (and her husband). WORLD have had two very successful meetings in Parc Y Scarlets attended by local health delivery managers, council and other third sector organisations. Patient involvement has led to the creation of social media and web presence.

Supported by some local businesses and an active fundraising group the Group has become financially viable and have several more events planned. With additional resources the Group hopes to expand their membership across Wales to improve patient involvement in shaping future services.⁷

c. Improve reporting of rare disease information including epidemiology, significant event analysis and shared learning.

In this **case study** from the Congenital Anomaly Register and Information Service (**CARIS**) it reviews the epidemiology of a rare disease in Wales with comparisons to European data.

Sirenomelia, sometimes called 'mermaid syndrome', is a congenital condition in which the legs of a baby become partly or completely fused together in the womb. Problems with the development of the spine, the digestive tract and other organs are also common. It is very uncommon for a baby with sirenomelia to be born alive.

A review of sirenomelia in Wales revealed that 17 cases were recorded between 1998 and 2016: approximately one per year. Previous research would suggest that one case is expected approximately every three years. This finding led the CARIS to consider whether this unexpectedly high number of cases was due to chance or whether the cases were linked in some way that public health action could prevent. CARIS requested figures on reported cases of sirenomelia from EUROCAT (European Surveillance of Congenital Anomalies), which gathers data from national/regional congenital anomaly registers around Europe. Data from 24 registries was available with the most complete figures reported from 1998.

A total of 97 case were identified over 9,637,494 births. The rate across all EUROCAT data was 1 case per 100,000 births; the rate in Wales was 2.2 per 100,000 births with statistical analysis suggesting the difference between the rate in Wales and the overall rate was greater than might be expected by chance alone. With the support of statisticians and environmental health professionals, a detailed analysis of the Welsh data considered whether there was any evidence that common features between cases might be linked to the occurrence of sirenomelia. CARIS includes a wide range of data including maternal age, health and residence. Statistical methods were not able to identify any factor that might link the cases.

However, CARIS continues to collect these data and may review this evidence again in the future. This review of sirenomelia illustrates how CARIS can identify and

⁷ WORLD can be contacted through email at joinusatworld@outlook.com.

respond to higher-than-expected rates of congenital anomalies through using a Europe-wide evidence base and expertise from across Public Health Wales.⁸⁹

In this additional **case study** from the Congenital Anomaly Register and Information Service (**CARIS**), it demonstrates using linked population data to identify children in Wales with Cystic Fibrosis.

CARIS data was used as part of a joint project to assess whether Cystic Fibrosis (CF) children could be identified across routine electronic health record (EHR) data in Wales, and how effective the method was. 352 cases were identified in the hospital admissions data for Wales (PEDW dataset), primary care General Practice (GP) consultations from the Welsh Longitudinal General Practice (WLGP) dataset and the Congenital Anomaly Register and Information Service (CARIS) data over an 18-year period 1998-2016.

The data was linked using a unique person identifier within the Secure Anonymised Information Linkage (SAIL) Databank. 158 of these cases matched across all three sources. Since CF is a severely debilitating condition, a greater match was expected. This prompted further investigation of those cases, which did not appear in all data sources, as these seemed least likely to be true cases.

In conclusion, the 158 cases that appeared in all three datasets were least likely to be misclassified, with the 50 cases in both CARIS and PEDW data, the next least likely. The 19 cases in PEDW that had not been picked up by Newborn screening were still likely to be CF cases (possibly moving into Wales after birth). However, the 43 cases found only in WLGP seemed to display symptoms of CF but had no test results to confirm the condition.

Further work has now linked the UK CF Registry within the SAIL Databank. This allows more accurate identification of CF cases, thus improving understanding and the potential to reduce misclassification, whilst enabling researchers and projects to address a much richer range of research questions using multiple data sources including EHR, CARIS and the UK CF Registry data.¹⁰

⁸ Further details on CARIS's work on sphenomelia are available here:

<http://www.caris.wales.nhs.uk/anomalies-of-possible-concern#sire>

⁹ Credit to Chris Emmerson, David Tucker and CARIS.

¹⁰ Credit to Rowena Griffiths and Ashley Akbari (Swansea University Medical School), Daniela K Schlüter (Centre for Health Informatics, Computing and Statistics (CHICAS)), Rebecca Cosgriff (Cystic Fibrosis Trust), David Tucker (CARIS/Public Health Wales) and , David Taylor-Robinson (Department of Public Health and Policy, University of Liverpool).

3. UK policy board/forum:

a. UK Policy Board

Wales is a member of the UK Policy Board, representation comes from Welsh Government, including policy and genomics representatives.

The Policy Board meets four times a year and its membership allows collaboration across the four nations. Welsh Government has previously raised concerns with the Department of Health on the re-organisation of genetic testing services in England and its potential implications for Wales.

Wales hosted a meeting of the UK Policy Board at Welsh Government in Cardiff on 16 October 2018.

b. Rare Diseases UK Forum 2018

Wales hosted the Rare Diseases UK Forum 2018 conference, it took place on 17 October 2018 at the Temple of Peace, Cardiff. It was jointly chaired by Drs Graham Shortland and Mark Walker; it was hosted and funded by Welsh Government. The purpose of the event was to:

- To provide updates to attendees of developments and case studies in rare diseases across the UK.
- To provide attendees with the chance to provide first hand feedback to rare disease clinicians, health service commissioners and government officials.
- To promote discussion on the care and treatment of rare diseases and to shape future policy.

The day was split into presentations and breakout sessions. There were six presentations covering, the UK Forum, Wales, Northern Ireland and England. Drs Shortland and Walker provided the audience their experiences both as clinicians and as personally involved.

For Wales, Dr Rachel Butler and Prof Keir Lewis gave presentations, one on evaluating clinical exome sequencing for the benefit of the management of patients with rare diseases (aka SIGNAL) and Wales Orphan and Rare Lung Disease (WORLD).

The two breakout sessions covered three themes, these were:

- Identifying and preventing rare diseases, and data collection, sharing and storage in the rare disease context;
- Diagnosis and genomics, early intervention, care pathways and care coordination;
- Participation, prioritising and funding research, maintaining links with international partners, and European Reference Networks.

Common outcomes from the breakouts were:

- Challenges:
 - Data sharing, too many limitations, either through potential legal aspects (GDPR), willpower or methods of securing sharing. Rare disease data often shows patient identifiable regardless of anonymising due to low numbers of patients suffering from particular diseases.

- Coordination of care, including the transition between children and adult care, also patients that suffer from multiple conditions.
- Funding.
- Opportunities:
 - Data sharing, huge potential to speed up diagnosis and help patients, many rare disease patients would consent (data opt in) for their data to be shared if it ultimately helped them.
 - Increase awareness of rare diseases for clinicians and to allow for signposting for additional information as required.
 - Better use and creation of rare disease registers and random control trials, improving rare disease data.

Feedback from the day, through questions asked and the feedback forms, highlighted that the Rare Disease Forum's membership could be expanded and opened up. A larger audience could have been invited to the event and a stronger pan UK representation, with a desire for the UK's nations to work together more for the benefit of rare disease patients. Increased transparency from the Rare Diseases Policy Board was also indicated. While these learning points were for the UK Forum, valuable lessons could be learned for Wales.

4. Priorities for 2019/20:

The priorities for the RDIG from 2018-2019 will continue to be used for the year 2019-20:

- a. Identify and improve the pathway for patients with unknown or delayed diagnosis;
- b. Ensure better use of patient feedback, best practice and evidence to improve pathways for primary, secondary and specialist services;
- c. Improve reporting of rare disease information including epidemiology, significant event analysis and shared learning.

The continued use of these priorities will ensure continuity and demonstrate the slow but steady progress of improving the care, treatment and awareness of rare disease.

5. Conclusion:

The update highlighted that whilst the last 12 months has seen some progress in improving care for people with a rare disease in Wales, there are a number of areas where we have not made as much progress as we would have liked and further work is required. Work is still required to ensure there are clear referral and treatment pathways, improve awareness and education to aid early diagnosis and improved management and strengthen collaborative working with national work programmes.

Throughout 2018 and into 2019, the RDIG sought a partnership with industry that could be mutually beneficial. The aim of the RDIG was to secure paid coordination and clinical session time. These paid and dedicated roles could push forward the priorities of the Group and drive improvements for rare disease patients. Unfortunately the call to industry, while received and replied to, no worthwhile partnership could be secured that would suit both parties and collectively the majority of rare disease patients. However, working relationships with industry have been cemented and potential collaboration is still being explored.

Cross border working is essential within Wales, the United Kingdom and often, Europe. Representatives from Wales will continue to attend regular meetings of the UK Rare Diseases Advisory Group, the Rare Diseases Policy Board and participate in the Forum. Changes in England to the Genetic Testing Network and the new seven centres will be closely monitored to ensure Wales is not negatively affected.

We have made some progress in improving the care of people with a rare disease in Wales as highlighted in this update, yet there is still more to do. All stakeholders must continue to work together to build on the progress to date and deliver improved care.

The Rare Disease Implementation Group and its Chair, Dr Graham Shortland, is grateful to everyone who has participated in the implementation of the plan so far and will be working closely with colleagues across Wales over the next 12 months to drive forward this agenda.



Dr Graham Shortland, Chair of the RDIG, speaking at the Rare Diseases Day event in the Senedd on 14 February 2019. Credit: Genetic Alliance UK/ Michael Hall Photography