

Introduction



Welcome to the NeurOmics project newsletter.

This is the second edition and comes after the project has been underway for just over a year. This means that whilst we still have lots of work to do in pursuit of the overall research aims to revolutionize diagnostics and develop new treatments for ten major neuromuscular and neurodegenerative diseases, lots of progress has been made already. This newsletter will focus on those achievements and explain some of the techniques used to analyse the samples donated by patients. We will also describe some of the plans for the next year.

We hope that you will find it useful and we do encourage you to get in touch with any questions or comments you may have about what NeurOmics is doing.

Thanks for your interest in the NeurOmics project!

The NeurOmics team

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The NeurOmics team at a recent project meeting

What is NeurOmics?

Neurodegenerative and neuromuscular diseases (NDD/NMD) form one of the most frequent groups of rare diseases, affecting the life and mobility of over 500,000 patients in Europe and millions of their caregivers, family members and employers.

NeurOmics is a research consortium which brings together the leading research groups in Europe, highly innovative companies and other experts across the world. These groups will work closely together using the most sophisticated technologies and techniques in order to improve diagnosis and develop new treatments for ten major neurodegenerative and neuromuscular diseases affecting the brain and spinal cord, peripheral nerves and muscle.

Specifically, NeurOmics hopes to discover more genes which *cause* NDDs and NMDs and other genes which *modify* the diseases and determine how or why they might affect individual patients

differently. The discovery of new causative or modifying genes will improve diagnosis and may point to potential novel targets for drug therapy.

The NeurOmics project will take place over 5 years and is funded by the EU until September 2017. The project works closely with RD-Connect which was funded at the same time. RD-Connect will link together databases, registries, biobanks, complete clinical profiles, genetic sequencing data and sample availability for rare disease research worldwide. NeurOmics is one of the first projects to work with and provide data to RD-Connect and so is helping to shape the new platform.

More about RD-Connect: an integrated platform connecting databases, registries, biobanks and clinical data for rare disease research

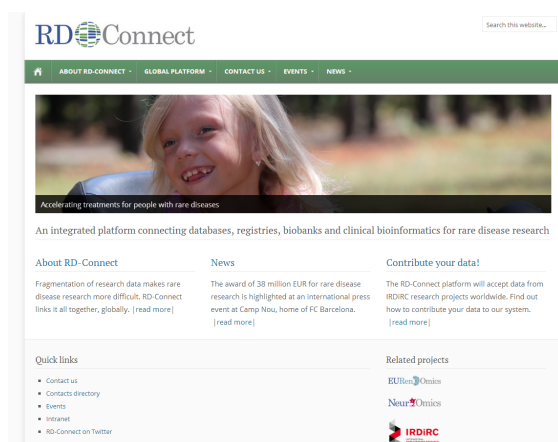
Rare disease research has historically been highly fragmented and disjointed, with groups of researchers carrying out excellent work but often in isolation from one another. These individual efforts often have little compatibility with each other, even when they may be looking at similar questions. This can make it almost impossible to connect the detailed clinical information held in one database with the genetic information held in another, or to make information accessible on whether a biomaterial sample or data from a clinical research study is available.

Linking up this data at the level of an individual patient enables researchers to gain a better overview of the disease they are studying without having to collect all the information again from scratch. Providing access to data by other researchers in a secure fashion with adequate data protection allows researchers in other institutions and studying other rare diseases to compare results and gain new insights.

Initiated in 2012, RD-Connect is a €12 million project funded by the European Union's Seventh Framework Programme. It is developing an integrated platform in which huge amounts of ('omics') data will be combined with clinical symptom (phenotype) information and biomaterial availability. This will be accessible online and queryable by researchers via a suite of analysis tools.

The infrastructure developed by RD-Connect provides support to research in rare disease to find new genes, biomarkers and potential new targets for therapy more quickly and efficiently. Its ultimate goal will be to improve outcomes for rare disease patients via major improvements in diagnosis and therapy.

Further information about RD-Connect can also be found at: www.rd-connect.eu



The RD-Connect homepage

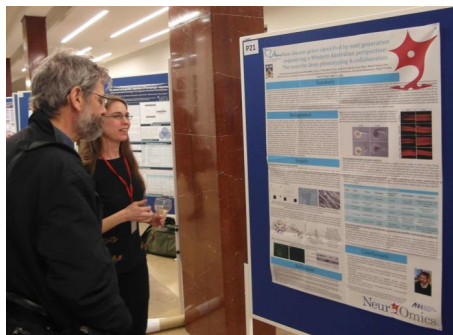
NeurOmics annual meeting in Heidelberg, Germany

Partners in the NeurOmics project met recently in Heidelberg, Germany for an annual meeting shared with RD-Connect and another research project, EUREnOmics which is investigating rare genetic kidney disease. Summaries of progress so far in all three projects were presented and discussions took place about the next steps needed to move the NeurOmics research forward.

Having the meeting alongside RD-Connect meant that partners could discuss how data generated by our research can be best linked up with the RD-Connect platform.



Members from NeurOmics, RD-Connect and EUREnOmics taking part in a joint session as part of the annual meeting in Heidelberg, Germany



Ana Topf (Newcastle) and Nigel Laing (University of Western Australia) discussing one of the NeurOmics posters at the annual meeting in Heidelberg

During one of the sessions, partners from all 3 projects displayed and presented posters detailing their particular area of research and work within the projects. Around 90 individual posters were included and those from NeurOmics covered such a range of topics as: identification of biomarkers in spinocerebellar ataxia; a protein mutation which causes a new form of hereditary spastic paraplegia; the results of whole exome sequencing on samples from patients with limb girdle muscular dystrophy and congenital myasthenic syndrome; functional pathways affected in Huntington's disease and ataxia; and data sharing in NeurOmics. A full list of poster titles will be made available soon on the project website.

NeurOmics, data and patients

Patient consent

To ensure that patients who have donated samples of their blood or other tissue for analysis in NeurOmics are fully informed and have consented to this kind of research, the project has provided consent form templates to all partners which specifically include large scale genetic sequencing techniques (such as whole exome sequencing, described below). They also ask donors' permission to share the results of this genetic analysis, as well as information about symptoms, with other researchers in rare disease in order that different groups can work together or at the same time on the same data. It is hoped that this will speed the progress of the research.

Collection of clinical data

To enable the effective sharing of information about patient symptoms, NeurOmics has built a clinical database with RD-Connect and their associated partner, PhenoTips. This database allows researchers to enter clinical information about a NeurOmics patient's disease into a standardised system which can then be searched to locate people with similar symptoms or with a particular set of clinical features.

The screenshot displays the 'Patient information' form in PhenoTips. The form is organized into several sections, each with a title and a list of radio button options. The 'Identifier:' section has a text input field and a '+ NEW ENTRY' button. The 'Sex:' section has radio buttons for 'Male' and 'Female'. The 'Clinical status' section has a dropdown menu with 'Y' and 'N' options. The 'Global mode of inheritance:' section has a list of inheritance patterns: 'Unknown', 'Sporadic', 'Autosomal dominant inheritance', 'Sex-limited autosomal dominant', 'Male-limited autosomal dominant', 'Autosomal dominant somatic cell mutation', 'Autosomal dominant contiguous gene syndrome', and 'Autosomal recessive inheritance'. The 'Global pace of progression' section has a list of progression rates: 'Unknown', 'Nonprogressive disorder', and 'Slow progression'. The 'Global age of onset:' section has a list of onset ages: 'Unknown', 'Congenital onset', 'Embryonal onset', 'Fetal onset', 'Neonatal onset', 'Infantile onset', and 'Childhood onset'. The 'Indication for referral:' section has a text input field. The right side of the form shows a list of inheritance patterns and onset ages, each with a radio button and a small icon.

Patient information

Identifier:

LABEL

+ NEW ENTRY

Sex:

MA Y N Clinical status

Global mode of inheritance:

- ☒ Unknown
- ☐ Sporadic
- ☐ Autosomal dominant inheritance
 - ☐ Sex-limited autosomal dominant
 - ☐ Male-limited autosomal dominant
 - ☐ Autosomal dominant somatic cell mutation
 - ☐ Autosomal dominant contiguous gene syndrome
- ☐ Autosomal recessive inheritance

Global pace of progression

- ☒ Unknown
- ☐ Nonprogressive disorder
- ☐ Slow progression

Global age of onset:

- ☒ Unknown
- ☐ Congenital onset
- ☐ Embryonal onset
- ☐ Fetal onset
- ☐ Neonatal onset
- ☐ Infantile onset
- ☐ Childhood onset

Indication for referral:

☐ Male ☐ Female

- ☐ Gonosomal inheritance
- ☐ X-linked inheritance
 - ☐ X-linked dominant inheritance
 - ☐ X-linked recessive inheritance
- ☐ Y-linked inheritance
- ☐ Multifactorial inheritance
- ☐ Digenic inheritance
- ☐ Oligogenic inheritance
- ☐ Polygenic inheritance
- ☐ Mitochondrial inheritance

- ☐ Progressive disorder
- ☐ Rapidly progressive
- ☐ Variable progression rate

- ☐ Juvenile onset
- ☐ Adult onset
- ☐ Young adult onset
- ☐ Middle age onset
- ☐ Late onset

Some of the information collected for all NeurOmics patients, across the 10 disease groups

A standard set of terms, taken from the Human Phenotype Ontology (HPO) has been used in this database so that the same symptoms are always referred to in the same way. Partners have also agreed what kind of data they will collect and record from patients – this means that data from two different disease groups within NeurOmics are easily comparable:

▼ OCULAR SIGNS

- ▶ ☐ NA ☒ Y ☐ N Structural eye abnormalities
- ▶ ☐ NA ☒ Y ☐ N Ptosis
- ▶ ☐ NA ☒ Y ☐ N Ophthalmoparesis
- ▶ ☐ NA ☒ Y ☐ N Cataract
- ▶ ☐ NA ☒ Y ☐ N Congenital cataract
- ▶ ☐ NA ☒ Y ☐ N Juvenile cataract

Other
(enter free text and choose among suggested ontology terms)

▼ BULBAR SIGNS

- ▶ ☐ NA ☒ Y ☐ N Speech problems
- ▶ ☐ NA ☒ Y ☐ N Swallowing problems
- ▶ ☐ NA ☒ Y ☐ N Other bulbar signs

Other
(enter free text and choose among suggested ontology terms)

▼ COGNITIVE DYSFUNCTION

- ▶ ☐ NA ☒ Y ☐ N Intellectual disability
- ▶ ☐ NA ☒ Y ☐ N Speech delay
- ▶ ☐ NA ☒ Y ☐ N Speech never acquired

Other
(enter free text and choose among suggested ontology terms)

▼ MUSCLE BULK

- ▶ ☐ NA ☒ Y ☐ N Muscle atrophy
- ▶ ☐ NA ☒ Y ☐ N Atrophy of proximal upper muscles
- ▶ ☐ NA ☒ Y ☐ N Atrophy of proximal lower muscles
- ▶ ☐ NA ☒ Y ☐ N Atrophy of distal upper muscles
- ▶ ☐ NA ☒ Y ☐ N Atrophy of distal lower muscles
- ▶ ☐ NA ☒ Y ☐ N Muscle hypertrophy
- ▶ ☐ NA ☒ Y ☐ N Other muscle signs

Other
(enter free text and choose among suggested ontology terms)

▼ SKELETAL DEFORMITIES

- ▶ ☐ NA ☒ Y ☐ N Scoliosis
- ▶ ☐ NA ☒ Y ☐ N Scapular winging
- ▶ ☐ NA ☒ Y ☐ N Contractures
- ▶ ☐ NA ☒ Y ☐ N Contractures of the joints of the upper limbs
- ▶ ☐ NA ☒ Y ☐ N Contractures of the joints of the lower limbs
- ▶ ☐ NA ☒ Y ☐ N Spinal rigidity

Other
(enter free text and choose among suggested ontology terms)

▼ WEAKNESS

- ▶ ☐ NA ☒ Y ☐ N Muscle weakness
- ▶ ☐ NA ☒ Y ☐ N Progressive muscle weakness
- ▶ ☐ NA ☒ Y ☐ N Generalized muscle weakness
- ▶ ☐ NA ☒ Y ☐ N Proximal upper
- ▶ ☐ NA ☒ Y ☐ N Proximal lower
- ▶ ☐ NA ☒ Y ☐ N Distal upper
- ▶ ☐ NA ☒ Y ☐ N Distal lower
- ▶ ☐ NA ☒ Y ☐ N Axial
- ▶ ☐ NA ☒ Y ☐ N Face
- ▶ ☐ NA ☒ Y ☐ N Neck
- ▶ ☐ NA ☒ Y ☐ N Voice
- ▶ ☐ NA ☒ Y ☐ N Fatigability

Other
(enter free text and choose among suggested ontology terms)

▼ MOTOR ABILITY

- ▶ ☐ NA ☒ Y ☐ N Difficulty walking
- ▶ ☐ NA ☒ Y ☐ N Progressive inability to walk
- ▶ ☐ NA ☒ Y ☐ N Loss of ability to walk
- ▶ ☐ NA ☒ Y ☐ N Inability to walk

Other
(enter free text and choose among suggested ontology terms)

▼ OTHER SIGNS

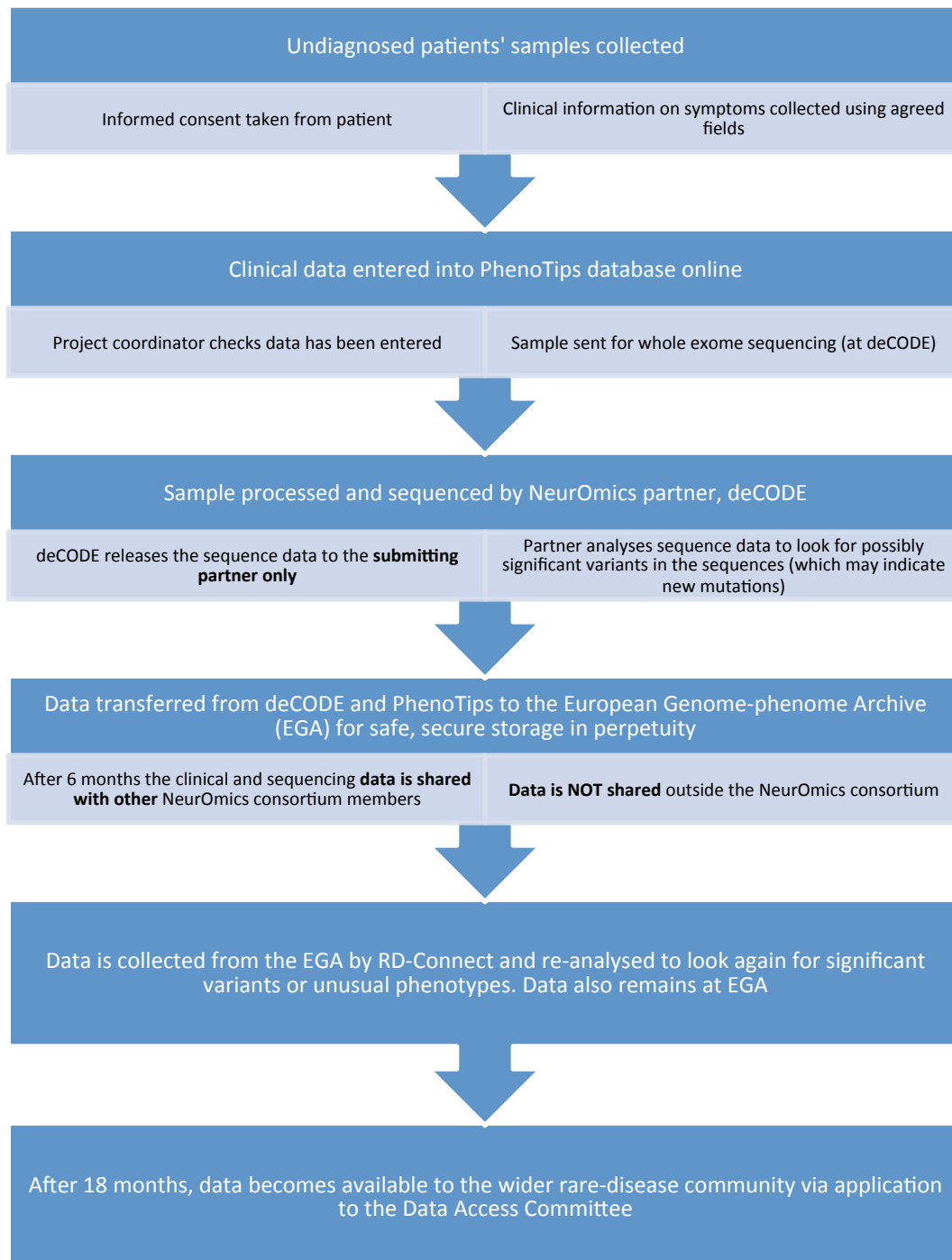
- ▶ ☐ NA ☒ Y ☐ N PEG (tube) feeding
- ▶ ☐ NA ☒ Y ☐ N Hearing loss
- ▶ ☐ NA ☒ Y ☐ N Seizures
- ▶ ☐ NA ☒ Y ☐ N Sensory impairment

Other
(enter free text and choose among suggested ontology terms)

An example of some of the clinical symptom information collected and stored

Data-sharing agreement between partners

Traditionally, researchers have been quite protective of data and sharing information before publication has been difficult. Within rare-disease research, it is important to try to overcome this and this is one of the aims of NeurOmics and RD-Connect. With this in mind, partners in NeurOmics have worked together in order to agree a ‘data sharing charter’. This has now been agreed and adopted by the project as an official policy. The charter requires that partners within NeurOmics share data from their research using patients’ samples within the consortium in the first instance and then afterwards with the wider rare-disease research field. Patients’ privacy will still be protected through the removal of identifying information (such as name and date of birth). Other researchers who wish to use the data generated in NeurOmics will also need to apply to a data access committee in order that access can be monitored and tracked and responsible use can be ensured.



A summary of the NeurOmics data-sharing charter showing how data will be shared

Sequencing of samples

1100 Samples from patients across the 10 disease groups but without a genetic diagnosis will be sent for whole exome sequencing during the first half of the NeurOmics project. So far, around 500 of these have been completed.

From the analysis of these samples, many potentially interesting variants have been identified which are now under further investigation. A number of new disease causing genes have also been confirmed and published in the literature:

| Number of novel genes | Disease group | Investigators in NeurOmics |
|------------------------------|---------------------------------|---|
| 18 | Hereditary spastic paraplegia | A. Brice, A. Durr, L. Schöls |
| 1 | Spinal muscular atrophy | B. Wirth |
| 1 | Facio-scapulo humeral dystrophy | S. van der Maarel |
| 2 | Limb girdle muscular dystrophy | G.J. van Ommen, A. Aartsma-Rus/ F. Muntoni |
| 1 | Bethlem myopathy | V. Straub |
| 3 | Myopathy | N. Laing |
| 2 | Ataxia | L. Schöls |
| 3 | Congenital muscular dystrophy | F. Muntoni |
| 2 | Hereditary motor neuropathy | V. Timmerman |

A summary of the published novel genes discovered as part of the NeurOmics research

What is whole exome sequencing?

The human body is made of cells and within the nuclei of these cells is genetic material in the form of DNA. The DNA is made from a long sequence of four different chemicals or bases: adenosine, thymine, cytosine and guanine (represented by A, T, C and G) and their arrangement is what is referred to as the genome. This is what contains the instructions to make the proteins needed to build a human body and allow it to function. When there are mistakes in this code because of mutations, either inherited from parents or which have occurred spontaneously, it may mean that a non-functioning protein is made. Depending on the normal role of this protein, this can cause problems such as genetic disease.

All the genetic information together makes up the genome but within this there are parts which give the instructions to make proteins (exons) and other parts which do not code for proteins (the introns). Introns have important roles but these do not involve coding for proteins. They are found in between the exons.

All the exons taken collectively in a genome are referred to as the exome. The exome only makes up around 1-2% of the total human genome but, because it codes for proteins, it is functionally very important. Whole exome sequencing (WES) identifies the sequence of the A,T,C and G bases in this part of the DNA in a patient's sample.

This is an important technique used in the NeurOmics project. WES allows researchers to compare the sequence of bases in the exomes from different people to identify similarities and differences between them.

Because there is so much variation between people, it is a huge challenge to find which differences in a sequence (known as variants) might be harmful and potentially disease-causing and which are simply part of other, harmless variation. To help with this, sophisticated software is used that is able to quickly compare a patient's sample with a set of reference samples. This software is able to make predictions about the likelihood of a variant being disease-causing based on its expected effect on a resulting protein, and it also provides information on previous research into the genes in which they occur. This kind of work would have taken months or years without such software but an analysis like this can now be done in a matter of days.

The variants identified in this way can then be further investigated by the researchers in NeurOmics. If the same variant is found to occur in 2 samples from the same family but only one person is affected with the disease, it is likely that that variant is NOT disease causing. If, however, the variant is found only in affected family members, it is likely that it IS a disease causing variant (then known as a mutation).

Once a suspected mutation is identified, the investigator in NeurOmics will ask their collaborators if they have found any variants in the same gene in any of their patients too. If they have, and those other patients have a similar condition, this is further evidence to suggest these variants and the identified gene are disease causing.

Alternatively, the investigator may ask for other patients with a very similar set of symptoms (or phenotype). If these patients can be found, samples can be taken from them and tested for the newly identified gene. If it is found in the new patients too, it is very likely that it is disease causing.

Biomarker studies

Additional patient samples from people at all the NeurOmics clinical centres who have already received a genetic diagnosis of hereditary spastic paraplegia, spinal cerebellar ataxia, Huntington's disease and neuromuscular disease are currently being analysed in Paris, Leiden and Bonn in order to find new biomarkers and to confirm (or validate) those we already know about. Discovery of biomarkers is very important to monitor treatment effect, disease progression, offer quicker diagnoses and prognoses and better classify patients.

What are biomarkers?

Biomarkers are substances in the body that offer a way to **measure** normal or abnormal body processes. Examples may include: a particular gene mutation; a protein found in the cerebral spinal fluid, blood or urine; even the results of a scan showing an increase in fatty tissue in muscle. This is important because a biomarker is always linked to a particular feature of a disease - for example, levels of a protein biomarker in the blood may increase as a disease progresses. This might allow disease progression to be accurately measured even if there has been no perceptible change in symptoms to the patient or clinician.

A major application of new biomarkers is in clinical trials. At the moment, when a new drug is being tested, researchers use a variety of ways to measure whether the drug has had a positive effect. One measurement often used in muscle disease is the 6 minute walk test. However, these measures are not always very good at showing small changes and improvements in a patient's symptoms, especially when the drugs are only being tested for a short time.

However, if we can find biomarkers in patients' blood or urine, samples of these can be taken throughout clinical trials. Measuring the levels of these biomarkers will show researchers clearly and accurately whether the drug being tested has had an effect or not.

There will be other benefits in discovering biomarkers for neuromuscular and neurodegenerative diseases:

- Blood and urine testing may be able to replace the use of painful and invasive muscle biopsies
- Diagnosis can happen earlier because testing for biomarkers is quicker and easier than genetic testing
- Disease progression can be accurately measured allowing better clinical management of symptoms
- Existing treatments (including drug dosage) can be adjusted to precisely meet the needs of individual patients to ensure they get the maximum benefit.

Next steps in NeurOmics

Over the coming months, samples will continue to be collected and sequenced in NeurOmics and the results of that sequencing will be analysed. This will result in the identification of new disease causing and disease modifying genes which, once confirmed will be fed back to those working in neurodegenerative and neuromuscular diseases in order that they can be considered in diagnostic testing.

The identification of new genes may also suggest possible new areas for therapy development, as through having a clearer idea of the genetic causes of a person's disease, drug development can be more targeted and therefore more likely to be successful.

Biomarker studies will continue and, as new disease-specific biomarkers are identified and validated, they can be used to help with monitoring disease, offering a more accurate prognosis and as ways to better measure effectiveness of new treatments in clinical trials.

As more data comes out of the NeurOmics research, ways of ensuring it can be securely but effectively shared with others working in rare disease will be established. This will ensure that people across the field are working together on the same resources, data and ideas in a collaborative manner. This will be done largely by working closely with RD-Connect to link our project with their platform.

This will begin to shift the way that researchers and clinicians access rare-disease data, and will also provide updates and feedback of new information to patients' records in registries and biobanks where their data and samples are held.

Whilst there is much to be done, a lot has already been achieved and ways of collaborative working and sharing resources have now been established both within NeurOmics and more widely, with RD-Connect. Plans are now in place to continue along this exciting path and we predict many more important developments during the coming 12 months,

For more information about NeurOmics and its progress towards improving diagnostics and therapy for rare neurodegenerative and neuromuscular disease, please visit: www.rd-neuromics.eu or email Cathy Turner, Communications Officer – catherine.turner@ncl.ac.uk