



EUCERD JOINT ACTION
WORKSHOP REPORT

**CROSS BORDER GENETIC TESTING OF RARE
DISEASES IN THE EUROPEAN UNION**

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Table of Contents

Acronym List.....	2
Introduction.....	2
Aims of the Workshop.....	2
Specific Questions addressed:.....	3
Executive Summary.....	3
Genetic Testing for RD within the context of policies and national plans for RD.....	3
Origins, Methodology and Results of the EJA Survey.....	5
Key problems associated with Cross-Border testing - Laboratory perspectives:.....	6
Academic/NHS laboratory.....	6
Private Laboratory.....	6
Key problems associated with Cross-Border testing? Clinician Perspective.....	7
Genetic testing: overview of the situation in the light of technology developments.....	7
Impact of NGS on cross-border needs: Country case-studies.....	8
The Netherlands.....	8
Slovenia.....	9
DECIPHER – Experiences of Cross-Border sample/data-sharing.....	9
Orphanet resources for laboratories and genetic tests.....	9
Patient Perspective of Cross Border Genetic Testing.....	10
Group Discussions.....	11
Group 1: Challenges of finding the right laboratory (Chaired by Ana Rath).....	11
Group 2: Challenges of ordering Tests (Chaired by Anelka Phillips).....	12
Group 3: Quality of the laboratories: (Chaired by Ros Hastings).....	12
Group 4: Affordability of cross-border genetic testing for RD, for healthcare systems and patients (Chaired by Ian Jacob).....	14
Group 5: Genetic testing, Europe and implementation of National Plans (Chaired by Steve Lynn).....	14
Final Discussion Session.....	15
Next Steps.....	16
ANNEX 1 – Workshop Agenda.....	17
ANNEX 2 - Participant List.....	19

Acronym List

ASHG	American Society of Human Genetics
CAVOMP	Clinical Added Value of Orphan Medicinal Products
CBGT	Cross Border Genetic Testing
CE(s)	Centre(s) of Expertise
CEGRD	Commission Expert Group on Rare Diseases
CNV	Copy Number Variation
EC	European Commission
EJA	EUCERD Joint Action for Rare Diseases
EQA	External Quality Assurance
ERN	European Reference Network
ESHG	European Society of Human Genetics
EuGT	EuroGentest
HTA	Health Technology Assessment
JA	Joint Action
MS	Member State (of the EU)
NGS	Next Generation Sequencing
NP/NS	National Plan or Strategy for Rare Diseases
QA	Quality Assurance
RD	Rare Disease
UKGTN	UK Genetic Testing Network
WP	Work Package

Introduction

The workshop was organised by the EUCERD Joint Action (EJA),¹ within the scope of Work Package 8 ('Integration'). It was held in the Institute of Genetic Medicine, Newcastle University, Newcastle upon Tyne on 15th-16th December 2014. The workshop was attended by over thirty experts in the field of rare diseases (RD) and genetic testing, amongst them representatives of laboratories (private and academic), genetics clinics, patient organisations, the European Commission (EC), national and international Learned Societies, key projects related to the sharing of genomics data, experts in health technology assessment, and legal experts.

Aims of the Workshop

The workshop addressed key issues identified through research conducted earlier in 2014 by Helena Kääriäinen and Pia Pohjola in the context of the EJA (WP8). This study targeted all 28 Member States (MS) and was designed to assess (via a Survey and Telephone interviews) the experiences of laboratories and genetics clinics regarding the volume of cross-border genetic testing (CBGT) for rare diseases (RD), the reasons for commissioning such tests abroad, eventual obstacles to purchasing tests abroad, and how testing laboratories and counselling clinics experienced the testing process in different Member States (MS). The results of this exercise demonstrate significant diversity across the EU, in terms of the nature and extent of difficulties faced by a) clinics requesting tests and b) laboratories performing the testing. These

¹ Co-funded by the EU : contract 20112201 (DG SANCO, EU Health Programme)

findings, by extension, suggest that substantial inequalities exist across the EU for patients seeking genetic diagnoses. For patients afflicted by a rare condition, obtaining an accurate and timely diagnosis is essential, as the diagnosis is the first step to accessing appropriate medical expertise and essential social support.

Specific Questions addressed:

- What are the key challenges/weaknesses around CBGT for RD and how these impact the RD field in particular?
- Should the ultimate goal be improving/facilitating CBGT or aiming for greater MS independence in terms of genetic testing capacities? How might next generation sequencing (NGS)-related diagnostic technologies affect these alternatives?
- Could there be practical solutions to
 - Improve access and funding to CBGT?
 - Facilitate the process of locating high quality laboratories involved in CBGT
 - Support standardised/similar consent requirements across the EU?
 - Simplify administration and logistics?

Executive Summary

The workshop brought together a diverse group of participants with expertise relevant to the topic of CBGT for RD. This is a complex issue, entailing an appreciation of the unique needs of people living with RD -and those who seek to diagnose, treat and care for them- whilst also understanding the legal and ethical implications of sending biospecimens and patient data across EU national jurisdictions. To create robust Recommendations capable of stimulating positive changes in practice, a health economist perspective on the principles of Health Technology Assessment (HTA) and healthcare affordability is important. Finally, given the unprecedented rate of progress in genetic testing capabilities and “omics” technologies, this topic also demands expertise from the broader field of NGS and genomics. Through presentations, group discussions and plenary debate, the preliminary draft Recommendations were analysed and refined, to reflect the consensus of the workshop.

Genetic Testing for RD within the context of policies and national plans for RD - Victoria Hedley

RD were declared a priority area for action in the 2nd EU Public Health programme 2008-2013 in view of the unique opportunities of this field to benefit from a collaborative approach. The number of patients with a particular RD in any given country will, by definition, be limited, making it very difficult for a single MS to build the requisite expertise to diagnose and care for these patients. To maximise EU added-value the European Commission (EC) published the Communication *Rare Diseases: Europe's Challenges* (2008) which was followed in by the Council Recommendation on an action in the field of RD (2009 C151/02). Whilst not legally binding, these policy documents are nonetheless very influential and form the basis of most countries' approaches to comprehensive RD diagnosis, treatment and care. The EUCERD (European Union Committee of Experts on Rare Diseases) was created to support the EC in formulating and implementing policies pertaining to RD, and was succeeded in this mandate on 31st July 2013 by the EC Expert Group on RD (henceforth referred to as CEGRD). A Joint Action was funded to help sustain this work: Task 3 of the *Integration of RD Initiatives* WP of the EJA is dedicated to the topic of genetic testing for RD. Recommendations have been adopted by EUCERD and the CEGRD on several key topics: Quality Criteria for Centres of Expertise (CEs) for RD; CAVOMP Information Flow; RD ERNs; RD Patient Registration and Data

Collection; Core indicators for RD National Plans; and Ways to Improve Codification for RD in Health Information Systems.² The anticipated outcome of this workshop is a set of Recommendations on CBGT.

The issue of genetic testing for RD is well-established in the key policy documents: the Commission Communication focuses on the importance of quality management in diagnostic laboratories, calling for “an efficient external quality assessment of the provided tests” and a “need to enable and facilitate the exchange of expertise through clearly stated, transparent, EU agreed standards and procedures.” The Council Recommendation advocates -in the context of gathering expertise at the EU level- the “development of European guidelines on diagnostic tests or population screening, whilst respecting national decisions and competences”.³

Centres of Expertise are a key concept in the RD field, as they are the institutions (virtual or physical) which provide expert specialist care for RD patients. EUCERD recommended that ‘CEs have links with specialised laboratories and other facilities’. CEs operating in similar disease areas will soon be linked by the first **European Reference Networks** (ERNs). ERNs are based in the Directive on the application of patients’ rights in cross-border healthcare (Directive 2011/24/EU) and accompanying legal acts (2014), and are the means by which cross-border healthcare will be facilitated. A key question for this workshop will be to consider how ERNs might interact with expert clinicians and laboratories and support genetic testing. The Recommendations for RD ERNs focus on quality assurance mechanisms for laboratory testing and state that it should be within the scope of RD ERNs to support the establishment of QA schemes applied in a relatively limited number of centres.

National approaches to genetic testing should be defined in National Plans/Strategies (NP/NS) for RD, which all EU MS were requested to adopt by the end of 2013, in order to demonstrate how RD activities will be/are being structured in the framework of the health care - and social systems across the EU. Many MS have now officially adopted a NP/NS.⁴ Unfortunately, few plans have appropriate budget attached, let alone budget dedicated to specific objectives. Furthermore, many stakeholders are unaware of the existence of these plans (as revealed in the EJA survey).

In addition to the NP/NS, information on national genetic testing activities (both in-country ‘offer’ and cross-border activities) can be accessed via the annual State of the Art Report published by the EJA. This Report demonstrates the variation in terms of in-country capacity to provide testing: offers range from 10 genes and the ability to diagnose 11 diseases, up to 1880 genes for 2074 diseases. Currently, no MS is able to provide tests for all RD (an estimated 6000-8000 clinical entities). This variation in terms of genetic testing availability leads to significant inequalities for RD patients across Europe. MS approach this topic very differently: some have created guidelines for testing whilst others have not; some publish clear lists of tests and reference laboratories available in-country, whilst others rely on more informal collaboration between labs. What may be taken as standard practice in one MS may not apply in another; for example, in Finland written consent is not required from patients, merely verbal. Smaller MS may have only a single genetics centre, whilst others have well-established genetic testing networks. Genetic counselling may be legally mandated, as in Spain. Some countries, such as Italy, operate their own national Quality Control

² Available http://www.eucerd.eu/?page_id=13 and http://ec.europa.eu/health/rare_diseases/docs/recommendation_coding_cegrd_en.pdf

³ Recommendation (2009) C151/02, 17

⁴ At the time of this workshop (December 2014) at least 18 MS had officially adopted a NP/NS

schemes for laboratories. Some MS acknowledge the difficulties of sending samples across borders to another MS and obtaining reimbursement, whilst others experience few difficulties here.

Nonetheless, in the near future substantial improvements in genomic diagnostics are expected.⁵ These novel technologies offer great potential but at the same time, in view of their cost, could arguably increase disparities in access to RD diagnostics. Finally, it should be noted that NP/NS ought not to recommend allocating reimbursement only for MS laboratories, as this may contradict EU competitive law and does not support the building of an EU-wide network that guarantees the most affordable testing strategies for RD.

Origins, Methodology and Results of the EJA Survey– Helena Kääriäinen

The possibilities for genetic testing are increasing due to the accumulation of knowledge on the genetic causes of RD, but as already stated currently no EU country is able to perform all gene-based tests. Initiatives such as EuroGenTest (EuGT; www.eurogentest.org) and the European Society of Human Genetics (ESHG; www.eshg.org) have been striving to improve quality and availability of genetic tests over the last decade.⁶ The fact that approximately 85% of RD are of genetic origin (usually monogenic) makes this a key issue for the RD field, which has been highlighted in European policy documents (as above). A workshop was held at EU JRC in Ispra, Italy in 2012, examining the genetic testing offer in Europe. The report of this workshop defined a number of action points.⁷ There was a focus on MS improving their systems, whilst also ensuring adequate provision of CBGT -where necessary- in respective NP/NS. The workshop also raised the prospect of ERNs supporting access to the laboratories offering NGS diagnostics. The Ispra workshop noted that the volume of (and obstacles to) CBGT in the EU had not been studied, and proposed that the “right level of organisation to maximise resources and expertise is the European, not the national one”. With this in mind, is CBGT still needed today? Given the variation in domestic genetic testing capacity, the answer is surely ‘yes’: in 2013, 871 RD were tested in only a single country in Europe (447 genes). 2285 RD were tested in 5 or fewer countries (1521 genes).

Few studies had been performed in this area and given the clear need for CBGT the EJA carried out a dedicated survey to assess the extent of challenges facing clinicians ordering genetic tests abroad and issues facing the laboratories providing them.

170 responses were received from laboratories and 105 responses from clinics, and almost all MS were represented. However, the response rate was relatively low, 11% and 17 %, respectively, of all those approached. The analysis of responses nonetheless enabled an estimation that 2.4 million RD patient DNA samples were tested in the EU in 2013, alone (excluding screening tests) and that approximately 90,000 samples were subjected to CBGT. Samples were typically sent abroad because the test was not offered in a patient’s home country. Most clinicians utilise Orphanet or GeneTest databases to locate a testing lab, although recommendations and reputation are also an important factor. It was clearly indicated that quality, reputation and price were the key decision-making criteria for the selection of a testing laboratory for CBGT. However, laboratories struggled to collect payments from some CBGT procedures, and different MS have different funding sources for CBGT which can, for some MS, make this a very difficult and protracted administrative process. In fact, some respondents confessed that the bureaucracy is so burdensome that it is “easier to send patients than to send samples”. The majority of clinics (80 %) claimed

⁵ It is already possible to utilise highly parallel ‘clinical exome’ NGS panels comprising over 4800 genes with known clinical phenotypes, the majority of which are RD.

⁶ See particularly Gert Matthijs et al: *Guidelines for diagnostic next generation sequencing* (forthcoming)

⁷ [Report](#) EUR 25684 EN.2013.

that less than 10 % of their overall testing volume was carried within CBGT. 7.2 % of clinics reported that 10-20 % of their tests were sent for CBGT, whereas 7.2 % claimed that over 30 % of their tests were sent abroad. This pilot survey became the basis for the EJA Newcastle workshop held in December 2014 which aimed to establish EU-level guidance to alleviate some of these challenges and simplify/streamline processes where possible.

Key problems associated with Cross-Border testing - Laboratory perspectives:

Academic/NHS laboratory - Maggie Williams, Bristol Genetics Laboratory (BGL) (UK)

Maggie presented the challenges associated with CBGT for RD, from the perspective of a major UK NHS/Academic laboratory. Between Dec '13 and Nov '14, 6.6% of the tests conducted by BGL were 'cross-border': 50% of these came from EU MS, equating to over 200 tests. The most frequently requested tests were for FSHD (Facioscapulohumeral Dystrophy) 1 and 2, and Nephrotic Syndrome (by NGS panel). Customers find these tests via UKGTN, Orphanet, GeneTests online database portals and the BGL's own website. There is a standard Genetics Request Form and a proforma for NGS Panel tests. The laboratory does experience delays when requesting clinical information, as well as delays in receiving samples from abroad. Sometimes the quality of samples is poor and the courier network has lost urgent samples in the past. Payment is received from various sources: healthcare systems, insurance schemes, and sometimes patients themselves. Occasionally users request less expensive tests and sometimes it is administratively difficult to obtain test reimbursement at all. After outlining several clinical cases, proposals were put forward to improve the situation for FSHD (but applicable to other diseases): elaboration of relevant best practice guidelines and EQA; a close laboratory/clinical network, involving workshops and training; a clinical proforma for detailed phenotyping; links with a registry for the disease; and access to some central funding for countries with challenging economic situations.

Private Laboratory - Carsten Bergmann, Bioscientia (Germany)

The Bioscientia Institute for Medical Diagnostics was founded in 1970 and is based in Ingelheim, Germany. Its Center for Human Genetics covers all areas of genetic testing and provides counselling. Bioscientia's experience with cross-border genetic testing has been reasonable. Turn-Around-Time for RD diagnostics tends not to be as critical as in other areas of in vitro diagnostic testing, and the material used (blood/DNA) is stable. Even if a test is available in-country, a laboratory abroad may be better-performing. The primary wet lab procedure is manageable – the crucial and more challenging part is the interpretation, which requires expert genomics knowledge. Some MS *do* prefer to keep the testing and analyses inside the country (even if more expensive). Helena's survey found that **50% of respondents were not permitted to order a test from abroad if it was also available in the home country.** And even if one *is* allowed to order from abroad, ordering domestically is easier. An option for cross-border genetic testing **within the EU is the S2 (E112) form via the European Social Insurance Regulation (providing permission is received from the insurer in advance).** It is important for tests to be truly comparable: price of test alone is not always a good indication of value. The scope can affect the value for money – e. g. is CNV detection included, segregational studies in the parents? It is also important to understand how different healthcare systems reimburse cross-border genetic testing.

Accreditation should be essential in all diagnostic labs. Bioscientia only collaborates with other accredited labs, except in the case of samples for *very* rare diseases when this is sometimes impossible. It is necessary

to harmonise external QA schemes and recognise national accreditation bodies. European Accreditation (EA) may aim at harmonizing National Accreditation Bodies across the EU, which would be a positive move. It must also be acknowledged that some countries have their own regulations e.g. Germany has the GenDG (the Genetic Diagnostics Act) which precludes predictive genetic testing in children or adolescents (if not of any direct medical interest or any therapeutic option is available) and imposes strict rules on prenatal testing. Nevertheless, it would be very helpful to standardise consent requirements across the EU, and to streamline EU and national regulations for sending biological samples.

Key problems associated with Cross-Border testing? Clinician Perspective - Helena

Kääriäinen

When attempting to diagnose people with RD, clinicians frequently need to make difficult decisions as to the appropriateness of genetic testing: should one always conduct a test if a suitable test exists, or only if there is potential for a confirmed diagnosis to have a 'meaningful' impact? If one accepts the likelihood that no single MS -let alone a single centre/laboratory- will be able to conduct genetic tests for all RD, how can priorities be set? How should priorities be set between testing when clinical symptoms are present and testing prenatally or at the pre-symptomatic phase? It is sometimes difficult to know what type of test to prioritise –known gene, panels, exome or whole genome? Despite the challenges involved in making such decisions, there is always the possibility that if expert geneticists do *not* make such choices, priorities will be set national by policy-makers who may lack this expertise. On a day-to-day basis, clinicians face challenges in terms of finding a laboratory to conduct the test they require, and furthermore in ensuring that the laboratory is quality-assured and offers the test at a reasonable price. Clinicians often rely quite heavily on recommendations from colleagues, as existing resources are not always as user-friendly as they could be. The EJA survey also demonstrated that clinicians would greatly value a means of sharing experiences on services received, both positive and negative.

Genetic testing: overview of the situation in the light of technology developments - Milan

Macek

There are increasing disparities in terms of the rapid production of biomedical data, by for example next generation sequencing technologies (NGS) in genetics/genomics, and lagging clinical validity and utility of such data within the domain of health care. The falling price of DNA sequencing which now exceeds Moore's law for semiconductors and the relative rapid increase in genetic testing outside of the traditional 'germ line' genome domain i.e. testing of somatic mutations in oncology, minimal residual disease in haematology, microbiology, creates strong pressures on finite resources in all solidarity principle based European health care systems. Moreover, some low-resourced countries are at risk of being completely left out of the 'omics' biomedical 'revolution' and are increasingly lagging behind with relevant health care applications.

In the absence of regulation every medical device (e.g. sequencer) will 'find its patient' and rapid commercialisation of diagnostic services compounds the situation by increasingly applied 'profit-oriented' testing and unwillingness to share e.g. variant data, even when financed from public health care funds. A recent study carried out in Germany found out that up to 70% of medical indications for genetic testing were not substantiated by evidence based approaches, while in most other countries the situation remains unmapped. Very often genetic testing is used as a last resort when standard differential diagnostic processes had been exhausted. This 'ex vacuo' approach in very rare diseases runs the risk that even at

high sensitivity and specificity of the test applied its outcomes could be biased by random mistakes appearing at a higher rate than the prevalence of the disorder under examination. Very good examples of incidental findings come from other fields, such as radiology (e.g. from MRI scans), where duties ‘to care and do no harm’ in medicine may lead to an increase in subsequent diagnostic procedures and thus also in costs.

Another important concern is the fact that European clinical genetic services are understaffed (clinicians, genetic counsellors, nurses), and there are marked disparities between various countries. The ESHG is monitoring genetic services provision in Europe on its website and liaises in this regard with the National Human Genetics Societies either directly or via annual meeting at European Human Genetics conferences.

The Czech Republic could be used as an example for the remainder of Central Europe. On the positive side, medical and laboratory genetics are well-recognised professional specialities, with board exams, medical societies and thriving state and private sectors, mostly operating according to European guidelines and recommendations. Law No. 96/2001Coll. codified the Oviedo convention within the Czech legal system. Law No. 373/2011Coll. is specific for genetic testing and has adopted most of the provisions of the Additional protocol on genetic testing for health care purposes of the Council of Europe, except for clinical utility clause, which was dropped at the last minute by the Parliament during examinations of the draft proposal prepared by the Czech Society of Medical Genetics (www.slg.cz). Examples of misuse of genetic testing and the lack of legal support for revision processes carried out in response by the Czech health insurance companies were given. The aforementioned professional association published in 2007 an open editorial in the most of country’s medical journals warning against the “misuse of genetic testing and potential for discrediting of the entire profession”. Based on well-publicised cases of misuse of genetic testing, where suspicions even ran very high within the political class (investigation is still ongoing), the Czech Ministry of Health started the work on necessary revisions of the Law No. 373/2011Coll. §28-29 in Spring 2014 in order to render legal safeguards for responsible and evidence-based provision of the modern genomic technologies within the national health care. Distinction has been made between trans-generational and intra-generational aspects of medical genetic services, their various roles, and associated necessity for specific legal provisions for patients and their families.

CBGT is available and fully reimbursed according to provisions of §16 of Act. 48 /1997Coll. which stipulates that when the test is not offered in the country (note: there is a dedicated database of available genetic tests curated by the Czech Medical Genetics Society- <http://www.slg.cz/pracoviste/vysetreni/>) and when it offers significant (i.e. diagnostic) benefit to the patient. Individual applications for CBGT are assessed by a “revisions genetics specialist endorsed by the Czech Medical Genetics Society. Czech insurance companies use standard procedures for reimbursement of CBGT with partner labs mostly located in Germany, Netherlands or the UK.

Impact of NGS on cross-border needs: Country case-studies

The Netherlands - Hans Scheffer

The Netherlands has 8 University Medical Centres (UMCs) which collaborate to perform a complimentary programme of genetic testing. For very rare diseases, tests are sent cross-border, usually by locating labs via Orphanet and GeneTests. Testing and counselling are reimbursed by basic health insurance. Introducing NGS into a country requires significant investments in sequencing and bioinformatics; in the Netherlands, NGS has resulted in overlaps of expertise between the national laboratories. Close contact with clinicians and researchers is essential to interpret results.

Techgene project examined the implementation of diagnostic exome sequencing. The risk of incidental findings is reduced by restricting the data analysis and interpretation to known pathogenic genes in a first filtering step. It is important to recognise that the line between research and diagnostics is very blurred in the case of RD. The UMCs have a standard informed consent form for exome sequencing, stating that all individuals must agree with the entire procedure and must agree to be informed about co-incidental findings. The results of sequencing have proven that the diagnostic yield for heterogeneous diseases is higher in exome sequencing, compared to Sanger. Several steps were proposed to improve sequencing for RD: European guidelines on NGS (EuGT); improved data-sharing to facilitate interpretation; closer communication between laboratories and clinics; closer communication between laboratories and research institutions (e.g. functional readout systems); and simpler regulations for cross-border sample transport.

Slovenia -Borut Peterlin

Smaller countries face particular challenges related to genetic testing; for example, there are a smaller number of genetic laboratories and tests available in-country and small numbers of patients. In addition, costs for consumables are often high. Slovenia spent €250,000 per year on cross-border genetic testing between 2009 -2012, alone. Each test averaged €1000, and 60 % were for heterogeneous disorders. It was decided that investing in greater expertise in Slovenia itself would be more cost-effective in the long run. In Slovenia, the Clinical Institute of Medical Genetics is composed of a centre for undiagnosed RD, a genetic counselling centre and a centre for Mendelian genomics. The team is focusing particularly on phenotype-based exome interpretation (associating phenotypic elements to genes) by utilising human phenotype ontology coding. Using exome sequencing has provided specific diagnoses for previously unclear diagnoses (e.g. 'accelerated ageing of unknown aetiology' can be confirmed as Hutchinson-Gilford progeria syndrome). Most of the diagnostic yield since introducing the technology has been in the area of neuromuscular and central nervous systems disorders

DECIPHER – Experiences of Cross-Border sample/data-sharing– Eleni Chatzimichali

Since 2004 the DECIPHER (Database of Genomic variants and Phenotype in Humans Using Ensembl Resources) project has promoted good practices in sharing data to facilitate the identification and interpretation of pathogenic variants. DECIPHER has over 1700 registered users across 250 projects and 43 countries. Anonymised data are shared publically, with additional records shared under managed access. The database has a powerful search interface and advanced search functionality. The database accepts clinical *and* research-generated data. Clinical data remains private and only accessible to the depositing project/team. Research data is managed, meaning visibility is restricted to users of named research consortia. If explicit consent is given, this managed (anonymised) data can become public. Therefore, users of the depositing project determine the appropriate level of access and always 'own' the data. DECIPHER is also very useful for sharing data (which can be customised, e.g. as photographs) across consortia. Since 2010, over 700 publications have emerged based upon publically-shared DECIPHER data.

Orphanet resources for laboratories and genetic tests – Ana Rath

The current representation of a genetic test in Orphanet is based on a targeted test model: a test is described by a label and linked to 1-n diseases and to 1-n genes proven to be involved in the diseases. Tests are further linked to EQA information if available, as well as the laboratories in which they are performed. Genetic tests can be searched by disease or by gene in the Orphanet website, and the results can be filtered by country and by the data on accreditation/EQA. In order to allow users to perform their queries

in a more efficient way, a new representation model will be developed: information on the purpose (i.e. pre-natal, pre-implantation, post-natal, pre-symptomatic diagnosis etc.), and on the technique used (i.e. mutation scanning, sequence analysis, whole exome sequencing, CGH-array, etc.) will be provided allowing for test or lab research by technique and/or by purpose. It will be also possible to link a test to a panel composed of as many genes and diseases/groups of diseases as necessary, regardless of the nature of gene-disease associations. This model will allow for NGS representation. This model can support the addition of new data (such as, for instance, the A-B-C NGS categories according to the EUGT guidelines). The way accreditation/EQA information is represented will be simplified to ease the quality control of these data by Orphanet teams. Despite these new facts, a number of challenges remain to be addressed such as keeping panels up-to-date in terms of new genes added and assessing the data on quality assurance for labs. A recommendation to laboratories to publish this information in Orphanet in a systematic way would help to have a reliable, centralised source of information on the genetic testing offer across Europe.

Patient Perspective of Cross Border Genetic Testing – Dorica Dan

There is no single response to the question ‘how do patients feel about testing and counselling?’ Patients need to consider what can be gained or lost by opting for testing. They must consider how much they really wish to know about themselves or their children, and often have concerns about who will know the results of the test and what the implications might be. For many patients, another important question is who will pay for it. As this is a very complex issue, with no right or wrong decisions, genetic counselling plays a crucial role. There are many benefits of genetic testing, including increased potential for future therapies and participation in research; however, these must be offset against the reality that even if a diagnosis is confirmed -not guaranteed- there may be no treatment or cure.

The underlying principle here is that RD patients and undiagnosed patients should be entitled to the same quality of treatment and care as other patients – they should not be penalized because of rarity, and if a test is not available in their home country they should be able to access it free of charge elsewhere. At present, patients can access healthcare treatment or services abroad if it is not available **within a reasonable timeframe** at home; however, this right only applies if the test in question is part of the national service offer (so-called ‘benefits basket’). If the test or service is *not* part of this list, patients may be able to access it abroad but without guaranteed reimbursement. There is a need for greater awareness-raising of the fact that predating the Cross-Border Healthcare Directive, Regulation (EC) 883/2004 (the Regulation on Coordination of Social Security Systems) actually provides options for RD patients to seek referrals to other MS even when those diagnostic procedures and treatments are not available at home. This 2004 Regulation states that, although authorisation is needed, based on S2 /E112 form it cannot be refused if ‘undue delay’ applies. Directive 2011/24/EU (the Cross-Border Healthcare Directive) states that where a process –e.g. genetic testing- *is* on the list of in-country benefits, reimbursement must be made on the basis of what this would cost at home.

The situation in Romania is that genetic testing is not included in the healthcare basket/list of benefits. It can be conducted for instance via the Mother and Child programme. Romania has 8 medical genetics centres, 6 of which are officially recognised. There is a good relationship between the Romanian Society of Medical Genetics (RSMG) and the National Alliance of RD patients. Genetic Testing is also promoted on the website of the RSMG. One key problem is that many tests are still performed in laboratories outside of Genetics Centres, which are not yet accredited. Furthermore, there are too few geneticists (50 for a population of 22 million) and the speciality of Laboratory Medical Genetics is not yet recognised. There are

also difficulties in sending samples abroad for testing and obtaining reimbursement for the process. A very positive step forwards for Romania would be to have genetic testing added to the 'benefits basket'.

Group Discussions

The participants were divided into five groups, and asked to debate a particular topic related to cross-border genetic testing (see Appendix 1). Key conclusions were shared and discussed in plenary, with the aim of agreeing points to incorporate in the draft Expert Group Recommendations.

Group 1: Challenges of finding the right laboratory (Chaired by Ana Rath)

- The survey found that, although alternatives exist, Orphanet remains an important resource for clinicians seeking laboratories providing genetic tests for RD. **The potential for ERNs to assume some of these roles in the future was raised.** It was agreed that there is scope to improve the services offered by Orphanet to be **more tailored to the needs of users seeking laboratories.**
- The Orphanet interface itself needs to be more user-friendly, as clinicians typically have a short time in which to locate a suitable laboratory, and often they make this decision in the clinical setting, in the presence of the patient.
- **Perhaps it is necessary to define the information that laboratories should provide to Orphanet, by establishing a template.**
- It is very important to be able to find accredited laboratories on Orphanet – to this end, Orphanet will continue to request certificates of accreditation from listed laboratories, and where these *have not* been provided, the entry will clearly be marked 'not assessed'.
- Laboratories could be asked to declare whether or not they wish to accept CGBT, and this willingness (or not) should be clearly marked on their Orphanet entry. Users should also be able to search for laboratories according to several criteria (e.g. by country, disease).
- It is essential that high quality, complete information is available - via Orphanet or an alternative resource. **It was suggested that MS themselves, or else the national Orphanet teams, could play more active roles in ensuring up-to-date lists of their laboratories and respective tests.** Two options were discussed: one is that MS should work closely with individual laboratories and genetics services to ensure they can display quality, complete information concerning their national 'offer' (e.g. UKGTN), which can then be conveyed to Orphanet. Where there is no such resource, the national Orphanet team could assume this responsibility. While having a complete picture is important, it is beneficial to also maintain direct links with the laboratories.
- **A mechanism to enable clinicians to provide feedback to laboratories would be very valuable.** A feedback system should be set-up (for instance by ERNs, ESHG or a similar initiative), either to pose specific questions to users or provide an open forum for comments. Orphanet could give access to such a resource, given the fact that for many clinicians the laboratory search engine is the most useful part of the Orphanet portal.

Group 2: Challenges of ordering Tests (Chaired by Anelka Phillips)

- Although certain MS (e.g. Finland) report few problems in obtaining permission to send samples across borders, for some others this is a complex, bureaucratic process. Could this be alleviated somehow?
- In terms of shared referral forms for use across the EU MS, **it would be good idea to develop a standard form with which to request tests, which labs can then adapt as needed.** Patient information could then be attached to this (electronic) form. It is difficult to reach a solution which will suit all, as needs vary from institution to the next, including legal regulation.
- The group was also asked to consider whether a shared consent form across the EU would be feasible. **Perhaps there are examples of this, with consensus on the minimum items to be included.**
- Acknowledging the problems in sending samples across borders, the group agreed **that improved tracking methods are required,** to enable the clinician to ascertain when a sample has arrived at a laboratory safely. Although the ISO accreditation does not require laboratories to issue receipts upon testing sample arrival, this would be a good practice to promote. This way, if a sample *has* been lost in transit the clinician would know sooner and eventually send a replacement. From the laboratory perspective, this process should be two-way: the lab should be alerted when the sample is on its way. This ability to track a sample is particularly important from a legal perspective.
- **Making these processes electronic, as opposed to using paper based forms,** would be a major improvement – if paper referral forms alone are used they can be misplaced. However, a signed hard-copy should rest with the indicating clinician for legal purposes.
- **The electronic tools described above could be part of the IT platform under development for ERNs.** These IT tools are being defined at present, and could perhaps be embedded as a best practice. (Naturally, the IT tools will officially be for ERN use only, which may be a reason to consider a genetics ERN).
- The data from genetic testing would be more useful if it were interoperable with the existing/emerging electronic healthcare systems across Europe. Several initiatives (e.g. E-Health Network and PARENT-JA) are working towards e-health interoperability, and aligning with these groups would be pragmatic. The Recommendations should acknowledge that, **given the likelihood that CBGT will remain essential for the RD field, the interoperability of healthcare systems should be ensured.** The group should prioritise a tool which ERNs or similar initiatives can use to facilitate this.

Group 3: Quality of the laboratories: (Chaired by Ros Hastings)

- To improve quality of laboratories, the group highlighted the need to **better promote existing and forthcoming policies** -for example the Recommendations on NGS⁸- which may not be widely known in the RD field. A comprehensive list of such guidelines should be promoted to MS to disseminate to their own genetic communities (perhaps via the CEGRD website, or in a Guide to RD Resources under the new JA.)
- **Perhaps the group should recommend a minimum of two labs in Europe for very rare diseases.** If only one centre offers a test it becomes very difficult to check each other's accuracy.

⁸ Gert Matthijs et al: *Guidelines for diagnostic next generation sequencing* (forthcoming)

- Laboratories should be **assessed through EQA on a regular basis**, ideally annually. EQA assesses the laboratories' analysis and interpretation of the genetic results as well as checking that equipment and/or quality systems involved are working accurately.
- Cross border reports should always be in English as a minimum (as should consent forms and information accompanying the referral form).
- **Laboratories should publish the following information on their websites, as a minimum:** accreditation status; testing methodology; turn-around-time (e.g. 90% in this timeframe etc.); EQA participation (can be European or national affiliation) etc. Pricing *parameters* should also be displayed – i.e. not actual price but what this is based on: does it cover one test, whole family etc. **It would also be useful to provide a proforma of the report so the buyer will know what it will look like. The group could recommend that ESHG or a similar body creates a proforma of what a laboratory is expected to display.**
- Perhaps the group should recommend that MS encourage laboratories to gain accreditation within a certain timeframe. The costs of accreditation could be added to the reimbursement fee.
- Interpretation is a key component of quality. **ISO 15189 is not specific about comprehensiveness of the interpretation and this is where EQA can assist.** But for this you need best practice guidelines; **therefore, the EU community or MS themselves need to publish these –following consensus- to ensure everyone is aware of the standard expected.**
- **There should be a cross-border genetic forum to relay concerns/feedback** – this could perhaps be facilitated by ESHG or one of the EuGT subcommittees. Either way, if a user has a complaint about a testing report they should submit a complaint to the laboratory, and -providing that laboratory is accredited- this will be detected in the accreditation review.
- If the plan is to ask Orphanet to clearly indicate which laboratories have accreditation certificates and which do not, the group could recommend laboratories also display this information clearly on their own websites. This would need to be promoted as a voluntary good practice, as unfortunately, displaying performance data is not mandated by the relevant ISO. Perhaps future ERNs could play a role here, as these networks will be evaluated in terms of how they perform – the group could recommend that **where genetic testing is part of the evaluation of an ERN it should include elements on QA and the public face of the lab.**
- Sharing data is a particular issue for RD, as having few patients makes it difficult to validate the pathogenicity of variants. ISO accreditation does not stipulate mandatory contributions to databases, although professionals are asked to *consult* them. The ESHG Guidelines similarly recommend *using* variant databases but say nothing about contributing. It was proposed that the workshop participants should write to ESHG and request this be included in the Guidelines. The Recommendations for the CEGRD **should also support the active contribution of genetic data to appropriate databases**, because although sharing clinical data is even more difficult than sharing research data, it is crucial for the RD field. Given the demands on clinicians' time, some participants questioned whether this would be feasible; however, time spent in this way would likely be recouped later, as the clinician would spend less time trying to confirm and match variant pathogenicity in future. The 'cost' of extra time spent on such activities should be incorporated to the price of the tests, as should accreditation costs.
- The group agreed that certain issues raised during this workshop would be useful for the genetics field more widely; therefore, it was suggested that the workshop report be disseminated to scientific societies and national genetics organisations.

Group 4: Affordability of cross-border genetic testing for RD, for healthcare systems and patients (Chaired by Ian Jacob)

- There is a difference between ‘affordability’ and the concept of ‘good value for money’ in health technology assessment (HTA). Although a procedure may represent good value for money, this does not necessarily mean a MS can afford it. It is fair to say that the affordability of RD genetic testing will vary between MS, as this is related to the relative strength of the economies. To promote solidarity at any level will ultimately mean a transfer of resources.
- There is a lack of clear, reliable information on the national ‘offer’ in some MS – **the group should recommend that MS publish a list of their laboratories** and tests, along with a statement on **how reimbursement systems work in different MS, including annual update of reimbursement policies (although they change frequently)**. This may make it easier to obtain cross-border access, when necessary (and reimbursement) as the process becomes more transparent. **Improved networking of national genetic centres could increase efficiency:** having laboratories within the same university, for instance, providing the same tests without collaboration keep costs high.
- The question of who should pay is complex, and the group proposed it was easier to say who should *not* pay (i.e. patients)
- Selecting which tests to offer and which not to offer is a priority-setting exercise: from an economist perspective this will always be necessary and the system will always vary from state to state. But as a minimum, baseline principle the group should recommend **that obtaining a diagnosis for all patients with RD is a priority, including access to genetic testing where possible.**
- The potential savings to healthcare systems by improving access to appropriate genetic testing for RD was emphasised strongly by the group. Diagnostic delay or incorrect diagnosis can result in additional unplanned hospital admissions and unnecessary, often invasive procedures e.g. biopsies. **Therefore, the Recommendations should highlight the possible economic advantages of genetic testing.** A challenge here is the lack of concrete data for RD.
- The possibilities of reciprocal cross-border agreements were discussed. The group also considered precedents for differential pricing for CBGT according to a country’s national GDP. However, it was acknowledged that issues of health system affordability are probably beyond the scope of this workshop. Nonetheless, genetic testing still comprises a very small fraction of the overall health care expenditure.

Group 5: Genetic testing, Europe and implementation of National Plans (Chaired by Steve Lynn)

- The group discussed how to **raise awareness of NP/NS) and strengthen their messages regarding genetic testing.** NP/NS obviously deal with national issues so where genetic testing IS mentioned it tends to be more about the national situation as opposed to cross-border sharing. The new JA on RD should support awareness-raising of NP/NS at the national level.
- **Possible roles for ERNs were considered; in particular, the IT platforms of ERNs could be used to support the process of reporting on laboratory quality and, especially, for the interpretation of the pathogenicity of findings.** In terms of affiliation with ERNs, most laboratories would probably be ineligible to join as members but under the Delegated and Implementing Acts they could probably be Associated National Centres or Collaborative National Centres.
- Data protection issues related to CBGT were considered, for instance how ERNs might share genetic data. Much of the current networking here takes place on the research level as opposed to

the public health level, **but the Recommendations should attempt to encourage a wider view on this.**

- The merits of having a transversal ERN specifically dedicated to genetics were discussed. Uniting genetic centres and laboratories in such a way could drive expertise forwards. Retaining the patient and healthcare-centric perspective would be important here.
- The approach here should be two-pronged: on the one hand, the field requires Recommendations at EU level, and on the other, genetic testing should be an important part of all NP/NS at MS level. **Therefore, accreditation schemes should be encouraged and the possibilities to consolidate genetics schemes explored.**

Final Discussion Session

The group worked through the preliminary draft Recommendation document and addressed any final points not already agreed during the Group feedback sessions.

Given the emphasis of some MS on enhancing national sequencing and testing capacities, the participants revisited the question of whether investment at the national or EU level (the latter having been recommended in the Ispra report) was preferable to improve access to genetic testing for RD. The group opted not to be too prescriptive on this point and agreed that the Recommendations should simply state that **access must be ensured one way or another**. There was agreement, however, that although the technical aspects of testing may be carried out locally or nationally, the **expertise must be shared at the EU level (and in fact beyond)**. The need for expert genetic interpretation of the pathogenicity of findings will remain.

MS have a duty to inform patients and clinicians of the testing resources available in-country, and of patients' rights to cross border healthcare including CBGT. This is a responsibility of the National contact points, as per Directive 2011/24/EU. Therefore, each MS displaying this information in a transparent, up-to-date manner is essential. Patient representatives view the transparency of the national 'offer' as very important – patients can advocate for improved services and less bureaucracy when information is available to demonstrate any inequalities in accessing genetic testing and by extension, diagnoses. The new State of the Art report should ensure that this sort of information is readily available.

The issue of consent was discussed in depth, and it was revealed that patients have many concerns about the consequences of undergoing tests, in terms of future implications as well as incidental findings. The ASHG and ESHG have published guidance on incidental findings, including decision trees, so perhaps these should be better promoted to the RD field. The need for counselling was also debated. Participants pointed out that the definition of 'appropriate' genetic counselling varies significantly from one case to the next; sometimes, a very short discussion is sufficient, but for other situations the process should be more comprehensive. Ideally a qualified genetic counsellor should perform this role; however, the group doubted that this could be mandated.

Finally, the arguments for and against a genomics/genetics ERN resumed. A transversal ERN on genomics *could* technically be proposed, providing it complies with the criteria in the Delegated and Implementing Acts. An alternative would be for each ERN to have a genetics 'forum' to share expertise. Although this topic is closely connected with research, **the line between research and healthcare is very blurred for RD,**

and the ERNs do have a responsibility to conduct research too, meaning this is not a barrier. A key question is whether an undiagnosed, dysmorphic patient can immediately be identified as having a 'rare skin disorder' or a 'rare heart disorder' which the clinicians in the group disputed. In such cases, a transversal ERN could care for undiagnosed patients, ensuring regular re-testing and re-interpretation of results, and consolidate genetic expertise across the EU.

Next Steps

A second draft of the 'Recommendations on Cross Border Genetic Testing of Rare Diseases' will be compiled, incorporating the discussions of this workshop. This will be circulated to participants for review, before a subsequent draft is disseminated to the EC Expert Group on RD, for initial consideration.

ANNEX 1 – Workshop Agenda



Day 1 Monday 15th December

- 13:00 **Welcome** – Kate Bushby
- 13:05 **Genetic Testing for Rare Diseases within the context of policies and national plans/ strategies for RD** - Victoria Hedley
- 13:25 **Origins, Methodology and Results of the EJA Survey**– Helena Kääriäinen
- 13:50 **What are the key problems associated with Cross-Border testing (1)? Country case-studies**
A Clinician perspective – Milan Macek (Czech Republic)*
A Patient perspective - Dorica Dan (Romania)
- 14.25 **What are the key problems associated with Cross-Border testing (2)? Laboratory perspectives:**
Academic laboratory - Maggie Williams, Bristol Genetics Laboratory (UK)
Private Laboratory - Carsten Bergmann, Bioscientia (Germany)
- 15:20 **Impact of NGS on cross-border needs: should the ultimate goal be facilitating-cross border testing or greater independence by increased MS capacity?** Hans Scheffer and Borut Peterlin
- 16:00 **DECIPHER – Experiences of Cross-Border sample/data-sharing**– Eleni Chatzimichali
- 16:15 **Orphanet resources for laboratories and genetic tests: what could be improved** – Ana Rath
- 16.35 **Presentation of identified problems, as basis for the Group Work and the Draft Recommendation** – Helena Kääriäinen

16:45-17:45 Group work: Discussions should address -whilst not limited to- the points suggested below

Group 1: Challenges of finding the right laboratory:

- What resources are available?
- Should Laboratories performing cross-border testing have websites offering data in a standardized format /in English language?
- How might Orphanet maintain up-to-date/ comparable data from laboratories?

Group 2: Challenges of ordering Tests:

- Should there be shared referral forms across EU Member States?
- Should the laboratory and clinician share the responsibility of pre-test information/counselling?
- Should there be shared consent forms (and processes) in all Europe?
- How can problems in sending samples be solved?

Group 3: Quality of the laboratories:

- How can we establish/ improve laboratory quality?
- How to improve accreditation, generate comprehensible reports etc.
- Could the customers share their experiences on the performance of the laboratory?

Group 4: Affordability of cross-border genetic testing for RD, for healthcare systems and patients?:

- Pricing, who pays, problems in billing, solidarity in pricing towards countries with economic problems in EU/outside EU, HTA in relation the genetic testing: when is it needed?

Group 5: Genetic testing, Europe and implementation of national plans

- According to the Survey, many clinicians/labs did not know if there was a national plan in the country or not? How could this be improved?
- What should be the role of ERNs in cross border testing?
- Data-sharing versus data protection in genetic testing?

Day 2 Tuesday 16th December

9:00 Group Work continued – consolidating the previous day’s discussions and agreeing possible recommendation points

09:45 Group Feedback in Plenary and Discussion

11:15 Group Feedback in Plenary and Discussion continued, moving into **Discussion and consensus on content to include in the draft Recommendations** - Chaired by Kate Bushby and Helena Kääriäinen.

13:00 Workshop Ends

ANNEX 2 - Participant List

Surname	First Name	Affiliation/Institution
Arles-Soler	Martin	Orphanet
Atalaia	Antonio	EUCERD Joint Action
Bergmann	Carsten	Bioscientia Laboratory, Germany
Boddy	Harry	Institute of Genetic Medicine, Newcastle University
Bushby	Kate	EUCERD Joint Action; CEGRD
Chatzimichali	Eleni	Cambridge University Hospital Trust and DECIPHER (DatabasE of Genomic variants and Phenotype in Humans Using Ensembl Resources)
Cornel	Martina	European Society of Human Genetics (ESHG) Public and Professional Policy Committee
Dan	Dorica	EURORDIS (European Organisation for Rare Diseases) and RONARD (Romanian National Alliance for Rare Diseases)
Ensini	Monica	MYO-SEQ –Sequencing Genetic Muscle Diseases
Evangelista	Teresinha	EUCERD Joint Action
Ferlini	Alessandra	Medical Genetics Section, University of Ferrara, Italy
Hastings	Rosalind	CEQAS Scheme, Oxford University Hospital Trust; ESHG
Hedley	Victoria	EUCERD Joint Action
Holm	Birthe	EURORDIS and Rare Disorders Denmark
Jacob	Ian	Institute of Population Health, University of Manchester
Johnston	Louise	RD-Connect (An integrated platform connecting databases, registries, biobanks and clinical bioinformatics for RD research)
Kääriäinen	Helena	EUCERD Joint Action, European Society of Human Genetics
Koskenvuo	Juha	Blueprint Genetics, Finland
Leeson-Beevers	Kerry	Alström UK and EURORDIS
Liehr	Thomas	European Board of Medical Genetics (EBMG)
Lynn	Stephen	EUCERD Joint Action
Macek	Milan	Department of Biology and Medical Genetics, Charles University, Prague, Czech Republic; ESHG; CEGRD
McCormack	Pauline	PEALS, Policy, Ethics and Life Sciences
Millan Salvador	Jose	CIBER (Centre for Biomedical Network Research on Rare Diseases) Biobank, Spain
Peterlin	Borut	University Medical Centre Ljubljana, Slovenia
Phillips	Andelka	HeLEX (Centre for Health, Law and Emerging Technologies) University of Oxford
Pohjola	Pia	Department of Medical Biochemistry and Genetics, University of Turku, Finland
Rath	Ana	Orphanet
Scheffer	Hans	Division of Genome Diagnostics, Radboud University Medical Center, Netherlands
Severin	Emilia	University of Medicine and Pharmacy, Romania
Turner	Cathy	NeurOmics: Integrated European Project on Omics Research of Rare Neuromuscular and Neurodegenerative Diseases
Waligora	Jaroslav	European Commission DG-SANTE
Williams	Maggie	Bristol Genetics Laboratory, UK
Witzl	Karin	University Medical Centre Ljubljana, Slovenia; ESHG

