Rare2030

Foresight in Rare Disease Policy

A knowledge-base summary:

RARE DISEASE DIAGNOSTICS

https://www.rare2030.eu/our-work

TABLE OF CONTENTS

1. INTRODUCTION TO THE TOPIC

This topic is complex and multifaceted. Diagnosing a rare disease entails a definition of what constitutes 'rare'. The 6-8000 diseases falling under this heading are extremely heterogeneous: the majority are genetic but perhaps ca.15% are acquired. For many reasons, the search for an accurate diagnosis is often a diagnostic 'odyssey'; for instance, the sheer number of conditions under the heading of 'rare diseases'; the scarcity (by definition) of patients with any single condition and the corresponding scarcity of experts *acquainted* with each condition; the tendency for rare diseases to manifest as complex, multisystemic conditions; these are but a few explanations. The lack of a diagnosis (or perhaps an accurate diagnosis) can have far-reaching consequences for patients. Heterogeneity of national capacities regarding genetic testing (and changing technologies for such tests) can impact on access to diagnosis. Newborn screening has the potential to detect diagnoses very early in life, for patients in whom very early interventions are essential; however, again there is significant variety from country to country (and even *within* countries). Primary prevention is an evolving but naturally very sensitive topic, and indeed ethical, legal and social issues are transversal across many of these subjects. This document touches upon (but avoids detailed coverage of) themes further addressed in other Rare2030 Knowledge Base Summaries, especially those on Research and on Data Collection & Utilisation.

Some of these topics were highlighted in the Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final]: After affirming that the EU will maintain the definition of a rare disease espoused in Regulation (EC) 141/2000, the Communication states *"**A more refined definition taking into account both prevalence and incidence will be developed using the Health Programme resources and taking into account the international dimension of the problem**."*

There is a dedicated section (5.8) on Neonatal Screening (see below), and a section on Quality management of diagnostic laboratories (see below). Section 5.10 is dedicated to Primary Prevention (see below). Some of these issues were directed as specific Recommendations to Member States (MS) the following year: the preface to the Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02 reads as follows:

"It is of utmost importance to ensure an active contribution of the Member States to the elaboration of some of the common instruments foreseen in the Commission communication on rare diseases: Europe's challenges of 11 November 2008, especially on diagnostics and medical care and European guidelines on population screening."

Section II, ADEQUATE DEFINITION, CODIFICATION AND INVENTORYING OF RARE DISEASES recommended that MS *"Use for the purposes of Community-level policy work a common definition of rare disease as a disease affecting no more than 5 per 10 000 persons."*

Section V. GATHERING THE EXPERTISE ON RARE DISEASES AT EUROPEAN LEVEL asked MS to

"Gather national expertise on rare diseases and support the pooling of that expertise with European counterparts in order to support:

(a) the sharing of best practices on diagnostic tools and medical care as well as education and social care in the field of rare diseases;

(c) the development of medical training in fields relevant to the diagnosis and management of rare diseases, such as genetics, immunology, neurology, oncology or paediatrics;

(d) the development of European guidelines on diagnostic tests or population screening, while respecting national decisions and competences;

Several sets of EU-level policies have a direct bearing on the topic of diagnostics for rare diseases; for example:

- **In June 2013, the EUCERD adopted** NEW BORN SCREENING IN EUROPE: OPINION OF THE EUCERD ON POTENTIAL AREAS FOR EUROPEAN COLLABORATION
- **In 2015, the EUCERD adopted Recommendations on Cross-Border Genetic Testing for Rare Diseases**

2. DEFINITION OF A RARE DISEASE

The EU Commission definition of a rare disease was confirmed via Regulation (EC) 141/2000 as a condition affecting no more than 5 in 10,000 people. The vast majority of rare diseases are in fact far rarer still, as illustrated by the Orphanet Report Series 'Prevalence and incidence of rare diseases' (January 2019 edition available here). Although most European countries have adopted the EU definition, a few have not (or else opt to apply that definition in varying ways).

3. THE DIAGNOSTIC 'ODYSSEY'

Reaching an accurate diagnosis for many rare diseases can be very challenging and time-consuming: it is unsurprising that this process is often termed the 'diagnostic odyssey'. In 2009, EURORDIS published 'Voice of 12,000 patients: Experiences and Expectations of Rare Disease Patients on Diagnosis and Care in Europe.' Approximately 12,000 patients with one of eighteen focal conditions (ranging from more common to very rare diseases) responded to two EurordisCare surveys across 17 countries (delivered in 12 languages), to share their experiences of seeking a diagnosis (amongst other topics).

The table below shows the median delays in diagnosis. To illustrate the variety in experiences even between patients with the same conditions, the survey results were presented to illustrate:

a) The median delay considering 50% of the respondents

b) The median delay considering 75% of respondents

For Duchenne Muscular Dystrophy (DMD), for instance, for 50% of the respondents the time from first symptoms to diagnosis averaged 12 months, but when including the 25% of respondents who waited the *longest* time, that median rose to 3 years.

Source of information	Delay in diagnosis for 50% of patients	Delay in diagnosis for 75% of patients
CF	1.5 months	15 months
TS	4 months	3 years
DMD	12 months	3 years
CD	12 months	5.8 years
PWS	18 months	6.1 years
MFS	18 months	11.1 years
FRX	2.8 years	5.3 years
EDS	14 years	28 years

Table 1 **Median time elapsed between the first symptoms and a correct diagnosis.**

Image is taken from EURORDIS (2009) Voice of 12,000 Patients

The survey also illustrated the likelihood of receiving an *incorrect* diagnosis (perhaps several): **41% of respondents reported at least one misdiagnosis before obtaining the correct one.** For conditions with an adult onset, these figures were particularly diverse. E.g. 56% of patients with Ehlers-Danlos Syndrome (EDS) reported at least one misdiagnosis.

The consequences of misdiagnosis were also highlighted: besides inappropriate psychological treatment and counselling, **significant proportions of patients also received inappropriate surgical procedures** (again, this was most likely in diseases manifesting in adulthood as opposed to childhood): 29% of MFS (Marfan Syndrome) respondents; 17% of EDS respondents and 17% of CD respondents, compared to 10% of DMD respondents, 8% of CF (Cystic Fibrosis) respondents, 7% of PWS (Prader-Willi Syndrome) respondents and 6% of TS (Tuberous Sclerosis) respondents. (See the survey results, especially p44-6).

The 6-8000 rare diseases differ significantly in origin, nature and time of onset, which naturally leads to a variety of routes to diagnosis. Diagnoses may be made entirely based on clinical observations, or may be based on/corroborated by genetic analysis. It is important to note that a significant number of conditions are *not* in fact genetically inherited.

A major contributing factor in the length of a patient's 'diagnostic odyssey' is often the speed and efficiency at which a patient can move from primary healthcare and general practitioners (GPs) into more specialised tertiary care centres: ideally, to a centre of expertise in rare diseases, assessed and designated as such by national or regional authorities, but either way a centre with expertise in recognising the patient's presentation, symptom and family history. The pyramid below illustrates the actors and routes to a diagnosis for rare disease patients.

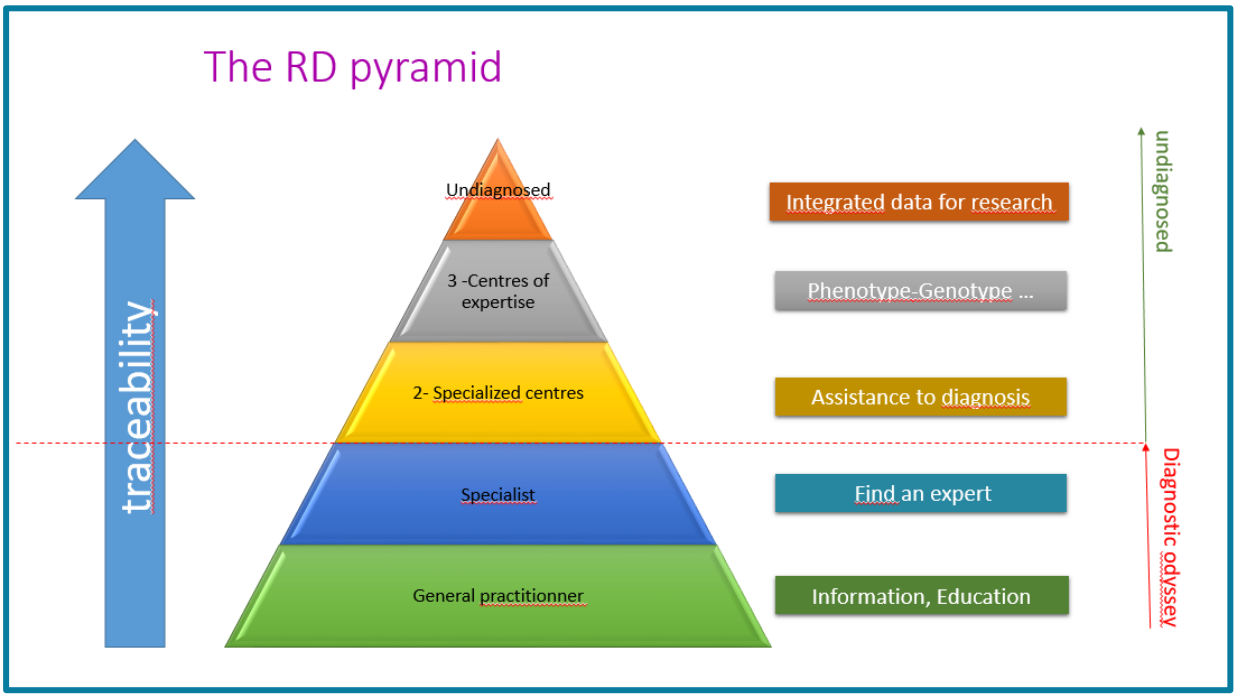


Image courtesy of Orphanet

4. ADVANCES IN DIAGNOSTICS THROUGH INTERNATIONAL COLLABORATION

Needless to say, professional guidance on strategies and approaches to utilising techniques such as Next Generation Sequencing have a huge impact on diagnostics for rare diseases: groups such as EuroGentest and European Society of Human Genomics, together with their global counterparts, are really driving forwards the application of NGS knowledge to translate into larger numbers of diagnosed patients (with more specific genetic diagnoses). Increasingly, rare disease diagnoses are enabled by the pooling/querying of data concerning a patient's genotype with 'deep phenotyping' data on the specific clinical presentation and symptoms displayed by that patient. The field of RD diagnostics has arguably benefited enormously from collaborations internationally, in the broader genomics arena, but also by incorporating the expertise of disciplines such as big-data management and analytics, bioinformatics, ethics, and more.

Numerous global databases now exist, in which genetic variants can be recorded and annotated, to support the identification of additional patients and families (necessary for clinicians/researchers to confirm that a variant found in their patient is pathogenic). Projects specifically dedicated to rare diseases have helped to advance these routes to diagnostics by cementing these sorts of collaborations and enabling the pooling or querying of the necessary data types (an example is the €12 million FP7–funded RD-Connect initiative, summarised in the table of resources below).

Increasing emphasis on standardising data through use of agreed and appropriate ontologies (for instance the Orphanet Rare Diseases Ontology and the Human Phenotype Ontology) will continue under, amongst other initiatives, the European Joint Programme for rare disease research.

5. GLOBAL GOALS REGARDING RARE DISEASES DIAGNOSTICS

Improved diagnostics for rare diseases (which demands both *better* science and greater *accessibility* of diagnostic solutions to patients who need them) is a key focus of the International Rare Disease Research Consortium, IRDiRC. A new overarching vision was adopted for the period 2017-2027: '**Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention'.**

To make this vision a reality, 3 new goals were agreed:

- **Goal 1**: **All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally-coordinated diagnostic and research pipeline**
- **Goal 2**: 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options
- **Goal 3**: Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients

6. UNDIAGNOSED RARE DISEASE PATIENTS

A major challenge in the field of rare diseases is 'diagnosing the undiagnosed'. Some patients are undiagnosed because although the condition they have *is* diagnosable, their clinical team has not yet 'solved' the case and determined the precise diagnosis. For other patients without a diagnosis, however, the field at present *has* no diagnosis to offer (i.e. the origins of the symptoms they are experiencing have not yet been identified or explained.) Dedicated groups and entities exist to attempt to address both types of issues.

Since approximately 2015, Europe has participated to the Undiagnosed Diseases Network International (UDNI). Based upon the United States' Undiagnosed Diseases Network, this is a platform to unite patients, researchers and clinicians. In 2018, a €15 million 4 year H2020 initiative 'Solve-RD: Solving the Unsolved Rare Diseases' commenced operations. These activities are summarised in further detail in the table starting on page 18.

Unsurprisingly, enabling a diagnosis for all rare disease patients is a key priority for rare disease advocacy groups world-wide. In 2016, a number of umbrella patient organisations (representing patients in Australia, Europe, Japan and North America) united to issue a set of *International Joint Recommendations to Address Specific Needs of Undiagnosed Rare Disease Patients*. The 5 high-level recommendations are as follows:

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

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

7. GENETIC TESTING FOR RARE DISEASES IN EUROPE

7.1. Translating Next Generation Sequencing (NGS) to the clinic

Traditionally, patients entering NGS pipelines have often done so via research-oriented projects/ courtesy of research funding. Confirmation of a diagnosis reached in this way would be followed-up with more traditional confirmation in the clinic, for instance through southern blotting. In recent years, however, initiatives have started to explore how NGS may be used as an increasingly routine part of a patient's diagnostic pathway in national health systems. A (non-RD-specific) example at European level was 3GbTest 'Introducing diagnostic applications of '3Gb-testing' in human genetics'. (See below, page 22).

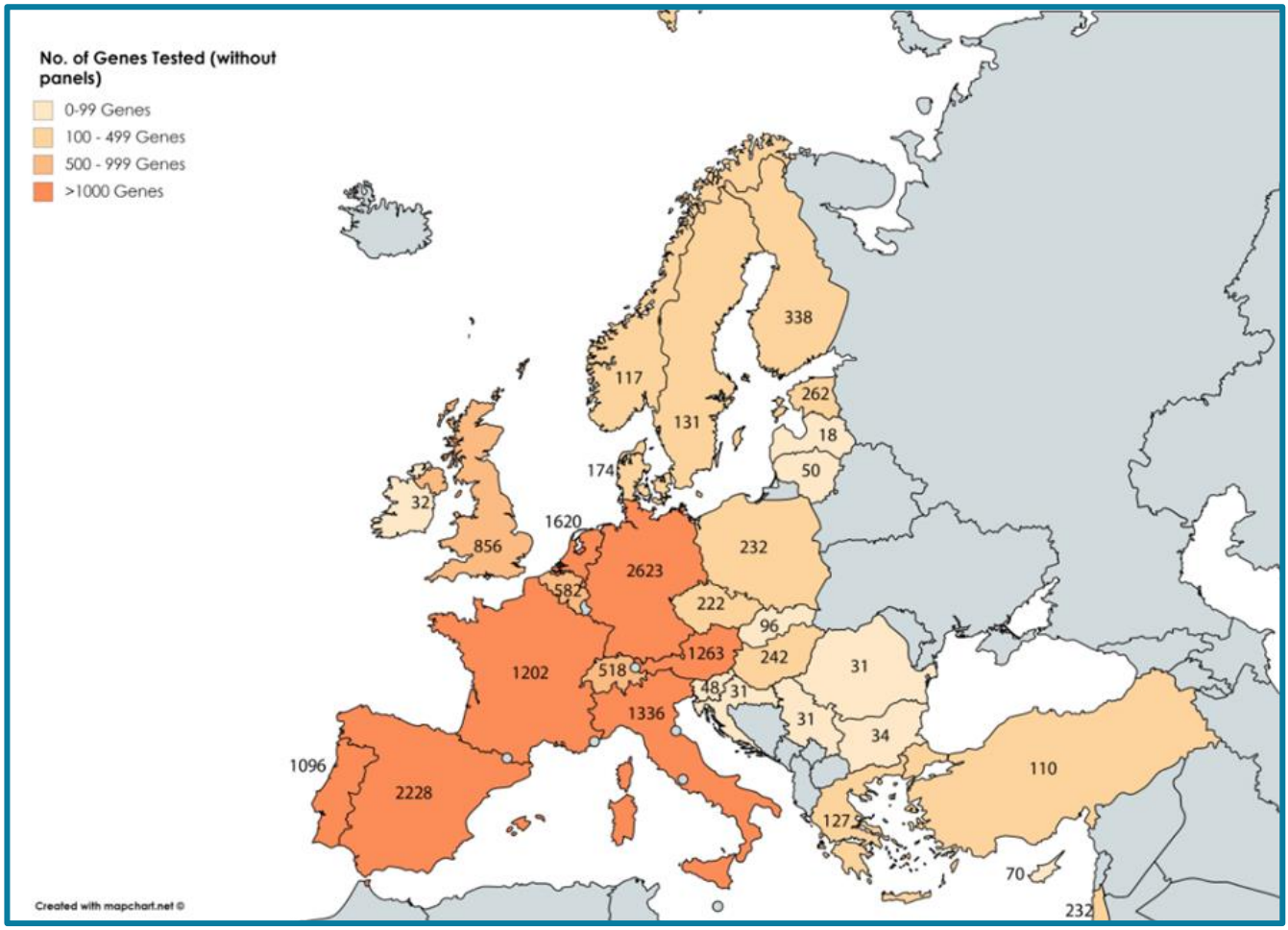
Early national efforts to incorporate NGS to the clinic include the UK's 100,000 genomes project, which to-date has sequenced 100,000 genomes from around 85,000 people, with the goal of creating a new genomic medicine service for the NHS. The initiative, announced in 2012, sought to bring concrete diagnoses to patients within the NHS with suspected rare diseases, whilst also facilitating new medical research by pooling omics data with medical records.

7.2. Genetic Testing Laboratories in Europe - the Status Quo

Expert clinical laboratories and diagnostic tests are an essential part of quality healthcare in the field of rare diseases. Major progress in gene identification has translated into diagnostic tests: these tests are now being offered internationally, through both public and private sector genetic testing services.

Orphanet set up a database of medical laboratories in the field of rare diseases in 1997 and over time, this resource has evolved to include information on quality management. Over time, the number of laboratories registering their activities with Orphanet has increased, to reach **1599 as of April 2019.** The Orphadata extractions enable a comparison of genetic testing capacity over time, both for single gene tests and also for panels (as panel testing becomes more commonplace in clinical settings).

	No. of Laboratories registered in Orphanet	No. of genes these laboratories test for (excluding panels)	No of diseases these laboratories test for (excluding panels)	No. of genes these laboratories test for (*with* panels)	No of diseases these laboratories test for (*with* panels)
June 2011	1049	1764	NA	NA	NA
Jan 2017	1301	2897	3658	4017	4421
Jan 2018	1388	3018	3737	4303	4421
April 2019	1599	3107	4105	5069	4399
June 2011	1049	1764	NA	NA	NA



Map created using OrphaData from April 2019

As the map above illustrates, the variation in genetic testing offer between medium and small sized countries in Europe is substantial, **and now ranges from 18 diseases and 18 genes (Latvia) to 2854 diseases and 2623 genes (Germany) without panels.**

The Orphanet data provides further evidence of the heterogeneity in genetic testing capacity across Europe:

SIGNIFICANT NUMBERS OF GENES ARE ONLY TESTED IN 10 OR FEWER COUNTRIES (EXCLUDING PANELS):

- 590 genes are tested in just 1 country;
- 1966 genes are tested only in 5 countries or fewer
- 2813 genes are tested in 10 countries or fewer

SIGNIFICANT NUMBERS OF GENETIC DISEASES ARE ONLY TESTED IN 10 OR FEWER COUNTRIES (EXCLUDING PANELS):

- 776 diseases are tested for in just one country;
- 2944 diseases are tested for in only in 5 countries or fewer
- 3823 diseases are tested for in 10 countries or fewer

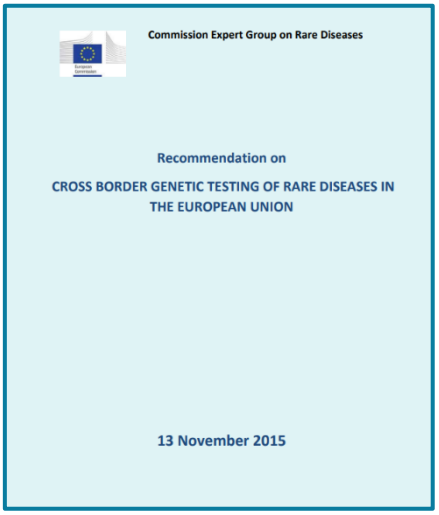
These figures alone demonstrate the need for a substantial cross-border exchange of specimens, as concluded by a 2015 study conducted as part of the EUCERD Joint Action. Quality Management of diagnostic laboratories is also a major factor, especially where countries are sending samples abroad for testing unavailable in-country. The topic was highlighted in the Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final] as follows:

5.9. Quality management of diagnostic laboratories

"Many rare diseases can now be diagnosed using a biological test which is often a genetic test. These tests are major elements of an appropriate patient's management as they allow an early diagnosis, sometimes a familial cascade screening or a prenatal test. Given the large number of tests and the need to design and validate a specific set of diagnostic assays for each, no single country can be self-sufficient in the provision of testing and in an efficient external quality assessment of the provided tests. There is a need to enable and facilitate the exchange of expertise through clearly stated, transparent, EU agreed standards and procedures. This could be achieved through the establishment of European reference networks of expert diagnostic laboratories (e.g. EuroGenTest). These laboratories will be encouraged to participate in proficiency testing with special attention to result in reporting and in the provision of pre- and post-test genetic counselling"

7.3. Recommendations on Cross-Border Genetic Testing of Rare Diseases

An appreciation of the status quo, particularly as highlighted via the aforementioned EUCERD Joint Action study, led to the preparation and eventual adoption in 2015 by the Commission Expert Group on Rare Diseases of a set of Recommendations on Cross-Border Genetic Testing of Rare Diseases.


Commission Expert Group on Rare Diseases

Recommendation on

CROSS BORDER GENETIC TESTING OF RARE DISEASES IN THE EUROPEAN UNION

13 November 2015

RECOMMENDATIONS TO THE EUROPEAN COMMISSION AND MEMBER STATES

1. Obtaining an accurate and timely diagnosis is a priority for all people with a potentially genetic RD; therefore, access to genetic testing -whether provided locally or on a cross-border basis - should be ensured, to facilitate such diagnoses, when there is a clear clinical indication.

1.1 The importance of adequate access to genetic testing for RD - including cross border genetic testing (CBGT) - when there is a clear clinical indication, should be stipulated in future National Plans and Strategies (NP/NS) for RD and should be incorporated when existing NP/NS are evaluated and revised.

1.2 MS should provide openly accessible information on genetic testing availability at the national level.

1.3 MS should have a transparent policy pertaining to CBGT: such policies should seek to streamline the process of CBGT, as far as possible.

1.4 The possibility of developing shared resources to facilitate CBGT of RD should be explored at the EU level.

2. The expert group underlines the importance of assessing genetic testing, on the basis that early diagnosis through clinically-guided genetic testing may avoid the need for further invasive and/or unnecessary exploratory and therapeutic procedures.

2.1 MS should consider, where possible, to share data on the assessment of genetic tests for RD - with full regard of the need to preserve patient anonymity - and further explore whether this exchange could be taken into consideration within the framework of the Joint Action 3 EUnetHTA on this basis.

2.2 Decisions on the purchasing/procurement of CBGT should be made on the same basis as any other medical investigations that are considered clinically indicated.

3. Whether genetic testing is provided on the national/regional level or on a cross-border basis, expertise should be shared at the EU (or global) level.

3.1 MS should promote the use of - and active contribution to - international variant databases when conducting genetic testing for RD, to improve the assessment of the pathogenic potential of genomic variants.

3.2. Cross border collaboration between laboratories, clinical genetics centres, and research initiatives dedicated to RD diagnostics should be supported, as this holds major potential for the RD field.

4. Appropriate information on genetic testing laboratories should be made available to facilitate cross-border genetic testing of rare diseases, particularly when pertaining to the quality of laboratories.

4.1 MS should support laboratories within the national territory in contributing - and updating - defined data elements to the Orphanet database (which at present is the main source of information on genetic testing laboratories for the RD field at European level).

4.2 To facilitate informed decision-making when selecting laboratories for CBGT, laboratory testing websites should display as a minimum their accreditation status, scope of the test offered, turn-around-time, and transparent pricing parameters.

4.3 Given the critical importance of quality for genetic testing of RD, MS should promote accreditation and the participation of laboratories in EQA.

8. PREVENTION

Prevention is traditionally categorised as primary, secondary or tertiary.

- Primary: aims to prevent the *onset* of the disease. This can range from greater education on medical risks to measures to decrease the risks of developing a disease, both at the personal and the community levels; for instance, preconception carrier screening, prenatal genetic and diagnostic testing, and preimplantation genetic diagnosis could fall under this heading

- Secondary: aims at an early detection of disease and actions taken to halt disease progression. A good example is newborn screening for inborn errors of metabolism (see below) and hearing defects

- Tertiary: activities to minimise further impact of conditions on functioning and disability by focusing on mental, physical, and social rehabilitation

This topic naturally carriers particular ethical sensitivities, particularly *primary* prevention. Patients and families sometimes fear an emphasis on primary prevention will only enhance the isolation which often accompanies life with a rare disease. In the wider fields of genetic testing and prevention, many policies, recommendations and reports exist: for the rare disease field, specifically, the topic was incorporated to the Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final] as follows:

5.10. Primary prevention: *"There are very few rare diseases for which a primary prevention is possible. Still, primary preventive measures for rare diseases will be taken when possible (e.g. prevention of neural tube defects by Folic Acid supplementation). Action in this field should be the topic for a debate at EU level led by the Commission aiming to determine for which rare diseases primary preventive".*

One notable example of subsequent EU-level activity was the **2012 collaboration between EUROPLAN** (European Project for Rare Diseases National Plans Development) **and EUROCAT** (European Surveillance of Congenital Anomalies) to generate guidance on primary prevention.

The final output was entitled 'Primary Prevention of Congenital Anomalies: Recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans and Strategies of Rare Diseases'

The recommendations are grouped into several areas, which -it is proposed- could benefit from policy actions to prevent congenital anomalies:

- **In the field of medicinal drugs** (recommendations here range from women taking medications to seek medical advice before trying to conceive, to providing a teratogen information service);

- **In the field of food/nutrition and lifestyle** (recommendations here range from the periconceptional supplementation of folic acid, to the promotion of effective information on diet and nutrition in women of childbearing age);
- **In the field of health services** (recommendations here range from making preconceptional care include genetic testing and counseling for families at risk, to ensuring evidence-based vaccination policies to protect women against infectious diseases associated with congenital anomalies);
- **In the field of environmental pollution** (recommendations here range from ensuring a sustainable surveillance system where environmental risks can be identified through the integration of congenital anomaly registers and biomonitoring, to minimizing the exposure of pregnant workers to workplace risks (chemical, physical and biological);
- **Types of primary preventive actions and their effectiveness** (recommendations here range from including health education campaigns targeted to potential future parents, to an integrated primary prevention plan involving all relevant health professionals)

9. NEWBORN SCREENING

Newborn screening (NBS) programmes for rare diseases emerged from the recognition that for some inherited diseases, the absence of a quick diagnosis would lead to irreparable damage for infants born with these conditions. Screening is still usually performed based upon a heel-prick blood test. NBS has been heavily influenced by the screening criteria published by Wilson and Jungner in 1968. The development of enzyme replacement therapies and advanced therapies makes early detection of patients particularly important. The Commission Communication on Rare Diseases: Europe's challenges (2008) [679 final] highlighted the issues as follows:

Section 5.8. *"Screening practices Neonatal screening for Phenylketonuria and congenital hypothyroidism is current practice in Europe and proved highly efficient in preventing disabilities in affected children. As technology evolves, many tests can now be performed, including those by robots, at low cost for a wide range of rare diseases, especially metabolic disorders and genetic conditions in general. It is recommended to encourage cooperation in this area to generate evidence on which decisions should be based at Member States level. An evaluation of current population screening (including neonatal screening) strategies for rare diseases and of potential new ones, will be conducted by the Commission at EU level to provide Member States with the evidence (including ethical aspects) on which to base their political decision. The Commission will consider such support as a priority for action."*

A European Tender was subsequently launched in 2009 ("Evaluation of population newborn screening practices for rare disorders in Member States of the European Union") through the EU Program of Community Action in Public Health. The Tender established a European Union Network of Experts on Newborn Screening (EUNENBS) to support activities and the creation of its outputs. The EUNENBS included experts from national competent institutions of all the EU MS and experts from European professional and scientific organizations involved in neonatal screening.

The main output of this tender was an Expert Opinion, the goals of which were as follows:

- "To provide as far as possible a shared view of the factors that should be considered in the whole process of implementation of a neonatal screening, from the evaluation of its opportunity and definition of its benefit, to its actual implementation and the assessment of its efficacy and quality.

- Moreover, this document identifies the activities for which the mechanisms of Community cooperation can be exploited profitably."

This document included a decision-making matrix, on the development of European policies in the field of NBS for rare diseases. The Tender also produced a report on the status quo in 2011, noting for instance that countries still usually refer to the Wilson & Jungner criteria. The number of diseases screened in EU countries at the time ranged from 2 to 29 and it was noted that number did not correlate to GDP.

Whilst respecting the principles of MS subsidiarity in healthcare, the EU Committee of Experts on Rare Diseases was asked to consider the results of this Tender. **In June 2013, the EUCERD adopted** *NEW BORN SCREENING IN EUROPE: OPINION OF THE EUCERD ON POTENTIAL AREAS FOR EUROPEAN COLLABORATION* **.** This document summarises the main outputs and findings of the Tender and proposed a list of topics for potential European collaboration in this field:

Topics for potential European collaboration

The topics which have been identified as areas for potential European collaboration are the following (in no particular order):

- Production of Standard Operating Procedures for the organisation and management of a Newborn Screening Process;
- Production of good practice guidelines for the management and follow-up of patients, for each screened disease;
- Adoption of Standard Operating Procedures for the communication with parents;
- Production of information material for prospective parents and the public, and for parents whose child was screened positive but whose diagnosis is not yet confirmed;
- Adoption of Standard Operating Procedures for the training of health professionals involved in the screening process;
- Organisation of European training schemes;
- Networking between laboratories to ease collaboration and resource sharing in order to improve the quality and cost-efficiency of national operations;
- Establishment of shared databases between NBS laboratories and centres of expertise in charge of the follow-up of patients to gain better knowledge of the screened diseases and to assess the benefit of the screening strategy;
- Discussion on the Wilson and Jungner criteria and other criteria to be used when considering any expansion of NBS, as views diverge in many countries on this issue;
- Common assessment of new proposals for NBS, between MS wishing to do so, when new technologies allow for such a consideration, via EUnetHTA;
- Establishment of public health key indicators for the continuous evaluation and monitoring of the screening programs.

9.1. Status Quo of Newborn Screening across Europe

There is significant heterogeneity between European Member States in terms of NBS programmes. The table and map below show the status quo as of May 2019. The *national* programme for screening ranges from 1-26, with certain regions of Italy offering screening for at least 58 diseases.

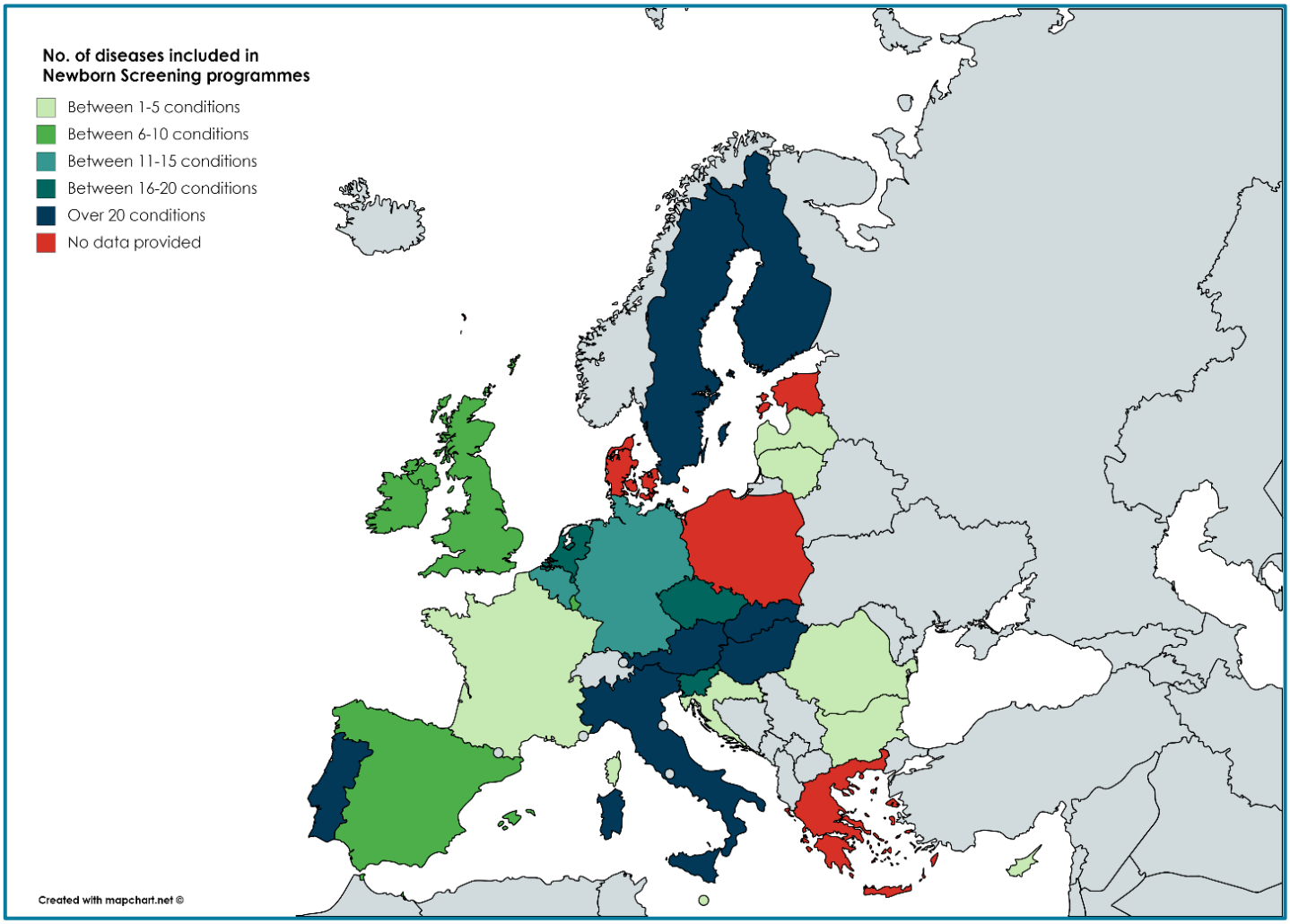
The data comes from the *Resource on the State of the Art of Rare Disease Activities in Europe (SotAR)*. Countries are asked to provide information on their national activities pertaining to rare diseases by responding to a structured survey. The questions in this survey are designed to enable countries to provide the data they pledged to submit when adopting the *EUCERD Recommendations on Core Indicators for Rare Disease National Plans and Strategies* in 2013. Here, countries were asked "*How many rare diseases are covered in the neonatal screening programme in your country?*"

NB:

- Please note that data for a number of countries is still awaiting update; **therefore, these figures may change slightly in the coming months**
- Hearing tests and vision tests have *not* been included in the calculations below
- Note that Spain and Italy report significant variety between the national and regional level practices: Italy has been included in the higher category on the map, as specifics were provided

EU MS	No. Of Diseases in NBS Programme	Comments Provided in the SotAR submissions
Austria	25	
Belgium	11-13	11 in Flanders; 13 in French Community
Bulgaria	3	
Croatia	2	Potentially several more metabolic but no details provided
Cyprus	2	Plus congenital hearing defect screening
Czech Republic	19	
Denmark	??	No data provided
Estonia	??	No data provided
Finland	21	

France	4	Also sickle cell anaemia but only for those at particular risk
Germany	15	
Greece	??	No data provided
Hungary	26	
Ireland	8	
Italy	3 - 58	3 diseases in the national programme 14 regions guarantee screening for between 25-58 metabolic diseases Consensus has been reached between the Ministry of Health and Regions on a technical proposal for a panel of 38 inherited metabolic diseases to be screened (not yet implemented it seems)
Latvia	2	Plus congenital hearing defect screening. The NBS programme is due to expand in July
Lithuania	4	Congenital hearing, vision, and heart defect screening also in place
Luxembourg	5	
Malta	2	Clarification needed
Netherlands	19	
Poland	??	No data provided
Portugal	26	
Romania	2	Plus congenital hearing screening
Slovak Republic	23	
Slovenia	18	
Spain	7	7 diseases in the national programme. Most regions cover more, but no specific figures provided
Sweden	24	
UK	9	Also screening for congenital cataracts, hearing, heart disease, developmental dislocation of the hip and cryptorchidism



10. TABLE OF RELEVANT RESOURCES, INITIATIVES AND OUTPUTS

Given the various disciplines involved in the broad issue of 'diagnostics', it is unsurprising that many initiatives and resources are focused on enhancing diagnostic capacity and availability for people living with rare diseases. Given the challenges in diagnosing complex rare diseases, it is also unsurprising that several of these initiatives span the healthcare and research domains. The table below seeks to summarise –***far from exhaustively***, particularly with regards to the scientific outputs behind this topic- a number of key initiatives of particular relevance to this topic. Initiatives and outputs more relevant to Newborn Screening and primary Prevention are at present included in the dedicated sections above

Initiative/ Collaboration/ Resource	What is it?	Why it is relevant to this debate?
Solve-RD: 'Solving the Unsolved rare diseases'	Solve-RD is a ca. €15million project, funded under the H2020 call 'Disease characterisation of rare disease (SC1-PM-03-2017)	The project will run from 2018-2022. Solve-RD contributes towards the IRDiRC goal of delivering diagnostic tests for most rare diseases by 2020. The partners seek to solve undiagnosed cases with unknown molecular causes, via sophisticated combined 'omics' approaches (incorporating not only genomics but proteomics, cell activity, and more). The second major goal is to improve diagnostics of RD patients through contribution to, participation in and implementation of a "genetic knowledge web" which is based on shared knowledge about genes, genomic variants and phenotypes Particular emphasis is placed on integrating with European Reference Networks (both in terms of partners ERN-RND; ERN-ITHACA; ERN-EURO-NMD, and ERN GENTURIS plus an additional 6 ERNs.) This reflects the acknowledgment that ERNs will increasingly become hubs for complex, unsolved cases, and hold major potential to capture omics and deep phenotypic data from Europe's RD population. Outputs will be available here:
RD-Connect	RD-Connect was established as an FP7 Initiative 2012-2018, establishing a platform to support RD research by linking data from biobanks, registries, databases and bioinformatics. Funding period expired, but the core output is sustained	The RD-Connect platform consists of three systems: Genome-Phenome Analysis Platform; Registry & Biobank Finder; and Sample Catalogue, which are open to any rare disease. The Genome-Phenome Analysis Platform (GPAP), which is the main outputs of the funded period, is not only a data repository but also a full-featured genomic analysis interface *with a particular focus on diagnosis and gene discovery*. It enables researchers and clinicians (even without bioinformatics training) to easily identify disease-causing genes and find matching cases across databases. RD-Connect also conducted a considerable body of ELSI research on issues related with capturing and ;sharing' data in the RD field, which has some relevance to the question of diagnosis

		The GPAP will be further developed under the European Joint Programme Co-Fund for Rare Disease Research (see below)
IRDiRC (the International Rare Disease Research Consortium)	IRDiRC was established in 2011 to unite researchers with research funders, to advance RD research globally. It currently has over 56 member organisations.	A new overarching vision was agreed, for the period 2017-2027: '**Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention'.** To make this vision a reality, 3 new goals were agreed. The first in particular is very relevant to this topic: Goal 1: All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally-coordinated diagnostic and research pipeline IRDiRC operates through three Scientific Committees, one of which is dedicated to Diagnostics. Within each Committee, there are a number of dedicated Task-Forces, uniting experts worldwide. The following are particularly relevant to the topic of Diagnostics (however the boundary between diagnostics and 'research' for RD is often quite indistinct, and the work of other TFs will have a bearing here too): Indigenous Populations Solving the Unsolved Matchmaker Exchange – a joint TaskForce with the Global Alliance 4 Genomics and Health Reports generated by each TF are available here:
EJP for Rare Disease Research	The European Joint Programme Co-Fund (EJP) will run from 2019-2023, funded under H2020 to a maximum EC contribution of €55 million (likely exceeding €110 million in total budget)	The activities of EJP Pillar 2, in particular, should have an impact on diagnostics for rare diseases (Pillar 2 will create a sustainable and interoperable ecosystem of resources -the 'EJP RD virtual platform'- coupled to robust standards, tools and procedures that will infuse 'FAIR' principles into advanced and secure forms of data discovery, linkage and sharing)
Undiagnosed Diseases Network International	UDNI was inspired by the 2013 U.S Network funded under the NIH. https://undiagnosed.hms.harvard.edu/	Undiagnosed Diseases Network International seeks to improve the level of diagnosis and care for patients with undiagnosed diseases through the development of common protocols designed by a large community of investigators.

		The UDNI operates on a number of set principles, including the following (abbreviated): Patients enrolled in the UDNI should be selected for the unique characteristics of their disorder and for its potential to inform new aspects of cell biology, pathogenetic mechanism(s) and therapy. Candidate patients should have been extensively examined already, so that obvious diagnoses have been eliminated. Accepted patients should be thoroughly evaluated by the UDNI, preferably at no cost to the patient. Patients should consent to share their data with other investigators within the group. NGS and other -omics analyses should be performed on enrolled families/patients(trios or quartets when possible), and analysed with some uniformity and according to state-of-the-art protocols. The -omics and phenotypic data should be shared among members of the UDNI. Functional studies should be performed to substantiate causal relationships between a candidate gene and the phenotype and address novel therapies.
SWAN (Syndromes Without A Name) Europe	SWAN UK has been supporting UK patients without a diagnosis since 2011, as part of the UK's Genetic Alliance UK. A European branch was launched in 2017.	SWAN Europe is a coalition of groups, organisations and support networks working with families and/or patients affected by syndromes without a name and/or undiagnosed genetic conditions. The aims of SWAN Europe are as follows (from launch announcement)
Global Commission to end the diagnostic odyssey for children with a rare disease	The Global Commission is a multi-disciplinary enterprise established in 2018, combining knowledge and technological expertise	Established in 2018, the Commission is co-chaired by Takeda, EURORDIS and Microsoft Health Services. In February 2019 it launched a series of actionable recommendations around 3 'tracks': Empowering patients Equipping frontline providers with tools for diagnosis and referral Reimagining the genetic consultation

		These tracks are accompanies by 3 pilot proof-of-concept projects: Multifactorial machine learning to recognize symptom patterns; Enable Collaboration Tools for "Intelligent Triage" and Clinical Geneticist Virtual Panel Consultation; Explore a Blockchain-based Patient Registry and Rare Disease Passport
International Joint Recommendations to Address Specific Needs of Undiagnosed Rare Disease Patients	A set of 2016 Recommendations issued by global advocacy groups (on behalf of patients living with undiagnosed and rare diseases across Europe, North America, Australia and Japan).	This resource consists of a series of 5 high level recommendations to address the specific needs of undiagnosed rare disease patients. Each of those 5 recommendations is accompanied by an explanation of the needs and several proposals to improve the situation. The document was co-created by SWAN UK (the support group run by Genetic Alliance UK), the Wilhelm Foundation, EURORDIS, Rare Voices Australia (RVA), the Canadian Organization for Rare Disorders (CORD), the Advocacy Service for Rare and Intractable Diseases' stakeholders in Japan (ASrid) and the National Organization for Rare Disorders (NORD).
Orphanet	The portal for rare diseases and orphan drugs	Orphanet provides information on clinical laboratories and diagnostic tests for rare diseases, searchable geographically or by specificity. Details on Accreditation and EQA (External Quality Assessment) are also provided, where possible.
European Society of Human Genetics	The European Society for Human Genetics (ESHG) was established in 1967 and is a founding member of the International Federation of Human Genetics Societies	A long list of Recommendations and policies relating to diagnostic issues (not specifically for rare diseases) is available here:
EuroGenTest	EuroGentest was funded as a Network of Excellence by the European Commission back in 2005. A joint committee was established with the ESHG, in 2013.	The goal of EuroGentest was to develop tools and guidance to harmonise and improve the quality of genetic services (not purely for rare disease, but with a natural relevance to this community). Amongst the most important outputs of the joint committee were the 2016 EuroGentest and ESHG Guidelines for Diagnostic Next Generation Sequencing Additional activities of EuroGentest include: Supporting the evolution of Orphanet's directory of genetic testing services (which now includes quality management information).

		Creation of clinical utility gene cards (CUGCs) intended for multistakeholder audiences and regarding the clinical utility of genetic testing.
Global Alliance 4 Genomics and Health	GA4GH is a research-oriented, international, non-for-profit initiative uniting over 500 leading healthcare, research, patient advocacy, life science, and information technology organisations.	GA4GH seeks to 'create frameworks and standards to enable the responsible, voluntary, and secure sharing of genomic and health-related data.' Though not directly focused on diagnostics, the activities of GA4GH hold significant potential to advance RD diagnostics. GA4GH supports 'driver projects' to develop and pilot the tools and resources created. They have dedicated workstreams which should advance RD diagnostics, such as those dedicated to Clinical & Phenotypic Data Capture and to Genomics Knowledge. Many of the current driver projects also have a relevance to RD diagnostics, and should help guide development efforts and pilot GA4GH tools
3GbTest	FP7-funded project 'Introducing diagnostic applications of '3Gb-testing' in human genetics'	3GbTest was funded under FP7 until 2015. This project sought to increase Europe's level of preparedness for innovations in molecular testing, factoring i the need for quality assessment schemes, HTA support, change management amongst health systems and healthcare professionals). Deliverables of the 3GbTest project are available here

11. RESULTS OF THE LITERATURE REVIEW*

**The earlier sections of this document were elaborated via research, partner expertise, and data stemming from the Resource on the State of the Art of Rare Disease activities in Europe. This final section is a summary of the results of a literature review performed by INSERM Orphanet, and is designed to highlight peer-reviewed publications which may suggest trends in this broad topic.*

Obtaining a diagnosis is a crucial step in the patient's odyssey towards adapted care and treatment. Hence, ensuring that the patient receives a correct and timely diagnosis is of prime importance. The diagnostic process has witnessed many changes in past years, notably linked to technological advancements. They enable more precise, non-invasive tests and limit the uncertainty associated with the detection of rare diseases. Indeed, one of the most impactful changes is the **possibility to sequence the genome** with next-generation sequencing technologies (Behjati and Tarpey 2013). **Whole-exome sequencing and whole-genome sequencing as well as newborn screening have revolutionised the practice of diagnosis** and one can easily distinguish a tendency to rely more and more on these tools for rare genetic diseases (Boycott 2019; Fernandez-Marmiese et al. 2018; Johnston et al. 2018). The adoption of these new technologies goes hand in hand with the emergence and development o**f precision medicine** focusing on the patient's personal characteristics (Baynam et al. 2016; Gainotti et al. 2018).

Our literature review also detected **voices calling for a more cautious use of these techniques** and a need for restraint. For instance, some researchers emphasise the fact that if used indiscriminately, they might have a negative impact, notably leading to the disruption of family dynamics, a waste of medical resources and may affect public trust (Johnston et al. 2018). The review also raised fundamental issues in terms of **ethical considerations** such as the intrusion in the genetic characteristics of an individual, the issue of informed consent, and the possibility of discrimination and stigmatisation. There is a current call for norms and standards regarding the implementation of genetic testing (Dhondt 2010; Johnston et al. 2018; Lohmann and Klein 2014). Furthermore, the **limitations of next-generation sequencing methods** are also pointed out - problems of limited coverage, lack of accuracy, the generation of false positive results - which prompt a current effort to improve precision, adapt and facilitate the interpretation of the results of these diagnostic tools (Lohmann and Klein 2014).

Another trend regarding diagnostic approaches is the **integration and combination of various approaches in order to produce a more detailed and valid diagnosis.** One can observe a tendency to include more **phenotypic analyses** and combine them with genotypic information in order to link all types of data and create a disease-phenotype-genetic association network (Gainotti et al. 2018; Shen et al. 2018). Regarding this use of phenotypic information and of a multidisciplinary approach, some scientists even suggest to include anthropological methods and knowledge in the diagnosis processes most notably to help detect phenotypic variations for diseases with a common cause (Anthropology). The development of **deep-phenotyping methods** are also used for the design of imaging techniques and tools for diagnosis such as facial recognition via an artificial intelligence programme (Baynam et al. 2017, Gainotti et al. 2018).

As regards the trend pushing for the establishment of more precise and stringent rules and standards, it is specifically noticeable in the EU. Indeed, the drive and particular need for **harmonisation** for the advancement of rare diseases research and treatment requires common practices among the Member States. However, this is not currently the case and the variations in reimbursement, authorisation policies and required documentation act as a hurdle for cross-border testing and create an unequal access to genetic testing in the European Union (Pohjola et al. 2016). A distinguishable tendency is the organisation of

networks for collaboration on diagnostic research, for instance the Rare and Undiagnosed Network as well as European initiatives within the ERNs or the Solve-RD programme (Baynam 2016, Ren and Wang 2019). Furthermore, some supra networks such as EuroGentest, a network of networks, are established in order to gather all expertise and critics on diagnosis procedures as well as genetic testing and counselling so as to set up standards and improve the overall quality of the services across European borders (Cassiman 2005). There is also a drive towards the **development of inclusive approaches**, for example taking into account the specific case of isolated and genetically less referenced populations such as indigenous communities (Baynam et al. 2017).

Another theme derived from our academic scanning is the delicate process of **diagnosis delivery.** More attention is paid to the various negative or positive psychosocial impacts which the announcement of test findings might have on a patient and their surroundings, such as acceptance of the situation, better coping with feelings of guilt, loss of hope, loss of social network of peers, anxiety, creation of tension and conflict in the family (Dhondt 2010; Krabbenborg et al. 2016). Overall, there is a recognition that parents experience ambivalent feelings from the findings, partly due to their high expectations regarding the test, and finally find themselves in a complex context of uncertainty (Chassagne et al. 2019). All of these considerations lead to an appraisal of genetic counselling and to demands for more psychosocial support for the patient, the caregiver and the family (Chassagne et al. 2019; Mendes et al. 2019). It is notable that, in spite of the ability to deliver a genetic diagnosis, a trend has emerged whereby some families and patients choose not to know the results of tests (Mendes et al. 2019).

REFERENCES FROM THE RARE DISEASE FIELD LITERATURE REVIEW

FULL LIST OF ARTICLES / PUBLICATIONS FOUND IN THE LITERATURE REVIEW:

https://docs.google.com/spreadsheets/d/1SRXASsFiD9sdQz286SVo860XdTpGaOIncyjlhGphULI/edit#gid=364400914

SELECTED BIBLIOGRAPHY OR KEY PUBLICATIONS

- Baynam, G., Bauskis, A., Pachter, N., Schofield, L., Verhoef, H., Palmer, R.L., Kung, S., Helmholz, P., Ridout, M., Walker, C.E., Hawkins, A., Goldblatt, J., Weeramanthri, T.S., Dawkins, H.J.S., Molster, C.M., 2017. 3-Dimensional Facial Analysis—Facing Precision Public Health. Front. Public Health 5. https://doi.org/10.3389/fpubh.2017.00031

- Baynam, G., Pachter, N., McKenzie, F., Townshend, S., Slee, J., Kiraly-Borri, C., Vasudevan, A., Hawkins, A., Broley, S., Schofield, L., Verhoef, H., Walker, C.E., Molster, C., Blackwell, J.M., Jamieson, S., Tang, D., Lassmann, T., Mina, K., Beilby, J., Davis, M., Laing, N., Murphy, L., Weeramanthri, T., Dawkins, H., Goldblatt, J., 2016. The rare and undiagnosed diseases diagnostic service – application of massively parallel sequencing in a state-wide clinical service. Orphanet J Rare Dis 11, 77. https://doi.org/10.1186/s13023-016-0462-7

- Behjati, S., Tarpey, P.S., 2013. What is next generation sequencing? Arch Dis Child Educ Pract Ed 98, 236–238. https://doi.org/10.1136/archdischild-2013-304340

- Boycott, K.M., Hartley, T., Biesecker, L.G., Gibbs, R.A., Innes, A.M., Riess, O., Belmont, J., Dunwoodie, S.L., Jojic, N., Lassmann, T., Mackay, D., Temple, I.K., Visel, A., Baynam, G., 2019. A Diagnosis for All Rare Genetic Diseases: The Horizon and the Next Frontiers. Cell 177, 32–37. https://doi.org/10.1016/j.cell.2019.02.040

- Cassiman, J.-J., n.d. EuroGentest – a European Network of Excellence aimed at harmonizing genetic testing services. European Journal of Human Genetics 3.

- Chassagne, A., Pélissier, A., Houdayer, F., Cretin, E., Gautier, E., Salvi, D., Kidri, S., Godard, A., Thauvin-Robinet, C., Masurel, A., Lehalle, D., Jean-Marçais, N., Thevenon, J., Lesca, G., Putoux, A., Cordier, M.-P., Dupuis-Girod, S., Till, M., Duffourd, Y., Rivière, J.-B., Joly, L., Juif, C., Putois, O., Ancet, P., Lapointe, A.-S., Morin, P., Edery, P., Rossi, M., Sanlaville, D., Béjean, S., Peyron, C., Faivre, L., 2019. Exome sequencing in clinical settings: preferences and experiences of

parents of children with rare diseases (SEQUAPRE study). Eur J Hum Genet 27, 701–710. https://doi.org/10.1038/s41431-018-0332-y

- Dhondt, J.-L., 2010. Expanded newborn screening: social and ethical issues. J Inherit Metab Dis 33, 211–217. https://doi.org/10.1007/s10545-010-9138-y
- Fernandez-Marmiesse, A., Gouveia, S., Couce, M.L., 2018. NGS Technologies as a Turning Point in Rare Disease Research , Diagnosis and Treatment. CMC 25. https://doi.org/10.2174/0929867324666170718101946
- Gainotti, S., Mascalzoni, D., Bros-Facer, V., Petrini, C., Floridia, G., Roos, M., Salvatore, M., Taruscio, D., 2018. Meeting Patients' Right to the Correct Diagnosis: Ongoing International Initiatives on Undiagnosed Rare Diseases and Ethical and Social Issues. IJERPH 15, 2072. https://doi.org/10.3390/ijerph15102072
- Groft, and Posada de la Paz. 2017. Preparing for the Future of Rare Diseases, in Posada de la Paz (eds), Rare Diseases Epidemiology: Update and Overview. Advances in Experimental Medicine and Biology. https://doi.org/10.1007/978-3-319-67144-4_34
- Lohmann, K., Klein, C., 2014. Next Generation Sequencing and the Future of Genetic Diagnosis. Neurotherapeutics 11, 699–707. https://doi.org/10.1007/s13311-014-0288-8
- Mendes, Á., Paneque, M., Clarke, A., Sequeiros, J., 2019. Choosing not to know: accounts of non-engagement with pre-symptomatic testing for Machado-Joseph disease. Eur J Hum Genet 27, 353–359. https://doi.org/10.1038/s41431-018-0308-y
- Pohjola, P., Hedley, V., Bushby, K., Kääriäinen, H., 2016. Challenges raised by cross-border testing of rare diseases in the European union. Eur J Hum Genet 24, 1547–1552. https://doi.org/10.1038/ejhg.2016.70
- Ren, Q., Wang, J., n.d. Network established to collaborate on diagnosis and treatment of rare diseases in China: A strategic alliance backed by tiered healthcare is the key to the future.
- Różdżyńska-Świątkowska, A., & Tylki-Szymańska, A., 2019. The importance of anthropological methods.Journal of Pediatric Endocrinology Metabolism. https://doi.org/10.1515/jpem-2018-0433
- Johnston, J., , Lantos, J. D., Goldenberg, A., Chen, F., Parens, E., Koenig, B. A., and members of the NSIGHT Ethics and Policy Advisory Board, 2018. Sequencing Newborns: A Call for Nuanced Use of Genomic Technologies, The Ethics of Sequencing Newborns: Recommendations and Reflections, special report, Hastings Center Report 48, https://doi.org/10.1002/hast.874

Rare2030

Foresight in Rare Disease Policy

The health of 30 million people living with a rare disease in Europe should not be left to luck or chance. The Rare 2030 foresight study prepares a better future for people living with a rare disease in Europe by gathering the input of a large group of patients, practitioners and key opinion leaders to propose policy recommendations.

Since the adoption of the Council Recommendation on European Action in the field of Rare Diseases in 2009, the European Union has fostered tremendous progress to improve the lives of people living with rare diseases. Rare2030 will guide a reflection on rare disease policy in Europe through the next ten years and beyond.

PARTNERS

EURORDIS RARE DISEASES EUROPE

orphanet Inserm

Newcastle University

FONDAZIONE Telethon

Innovation for sustainability isinnova

PRESIDIO OSPEDALIERO UNIVERSITARIO Santa Maria della Misericordia di Udine

European Reference Network | MetabERN European Reference Network for Hereditary Metabolic Disorders

SERVIZIO SANITARIO REGIONALE EMILIA - ROMAGNA

European Reference Network | Bone disorders (ERN BOND)

Imperial College London

The Rare2030 project is co-funded by the European Union Pilot Projects and Preparatory Actions Programme (2014-2020). This leaflet is part of the pilot project PP-1-2-2018-Rare 2030. The content represents the views of the author only and is his/her sole responsibility; it cannot be considered to reflect the views of the European Commission or any other body of the European Union.

This document was elaborated by Rare 2030 WP4, under the leadership of Newcastle University and with input from all partners. The document should be referenced as follows: Hedley, V., Rodwell, C., and Simon, F. (2019) ***Rare 2030 Knowledge Base Summary on Rare Disease Diagnostics*** **https://www.rare2030.eu/our-work/**