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Proceedings From The 11th International Conference On Rare Diseases And Orphan Drugs (ICORD). Cape Town, South Africa, 20-22 October, 2016

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PROCEEDINGS FROM THE 11th INTERNATIONAL CONFERENCE ON RARE DISEASES AND ORPHAN DRUGS (ICORD).

Cape Town, South Africa, 20-22 October, 2016

Introduction from the President

The 11th annual ICORD meeting was a successful event taking place as part of RareX in Cape Town, South Africa, 20-22 October 2016. Around 200 participants, from 27 countries and all continents and representing many different stakeholders such as patients, patient support groups, health care professionals, researchers, industry, policy makers, regulator and health authorities, came to take part of an inspiring programme, to network and to share their experiences in the field of rare diseases and orphan drugs.

On behalf of ICORD I wish to express my sincere gratitude to our local partner, Rare Diseases South Africa (RDSA, www.rarediseases.co.za), in contributing to the success of the meeting and for RDSA's great work and commitment. I also wish to acknowledge Rare Diseases International for its support in the programme planning and enhancing the attendance of patient groups. In addition, ICORD is very grateful to the sponsors and the extraordinary contribution of the speakers and session chairs!

The ICORD conference in Cape Town offered a wide range of sessions with exceptional speakers on diagnostics, congenital malformations, access to treatment, global RD policies and programmes, research, quality of life and empowerment of patient support groups. Furthermore, the participants got the opportunity to network in smaller discussion groups and in a poster session with the aim to stimulate discussion, initiate collaborations as well as sharing models of best practice and specialist knowledge around rare diseases. The presentations from a majority of the speakers are available at the ICORD website, www.icord.se.

ICORD is delighted by the significant statement on rare diseases by UNDP Administrator Helen Clark (available at www.icord.se), which provided a great opening of the ICORD meeting. ICORD also expresses its gratitude to South African Director General of Health, Ms MP Matsoso, for her opening address stating the need for a collaborative approach to treating neglected diseases, including rare diseases, and the closing words of Benjamin Djoudalbaye, African Union Commission, Ethiopia. Furthermore, during the conference the African Alliance for Rare Diseases was launched. The Alliance, which is a Rare Disease South Africa initiative, aims to bring all umbrella rare disease patient organisations in Africa into one community. ICORD looks forward to future development and commitment for rare diseases in South Africa and Africa.

While reflecting on the success of this meeting in South Africa, we now look forward to the year ahead and the next meeting. The 12th annual ICORD meeting will be held in Beijing, 8-10 September 2017 and organised together with the Chinese Organization for Rare Disorders and the Peking Union Medical College Hospital (PUMCH). ICORD looks forward to a fruitful meeting, with the aim to contribute to increased awareness of rare diseases in China and an improved situation for rare diseases patients in China and world-wide. ICORD warmly welcomes you to interesting days in Beijing!

Manuel Posada,
ICORD President

11th Annual ICORD Meeting – Organisation Committee

ICORD

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Abstract Review

Each submitted abstract was blinded and scored by a minimum of two reviewers according to the scientific or institutional merit of the abstract, originality and adherence to instructions. Abstracts of oral presentations have not been reviewed by the publisher or by ICORD. These abstracts are published as received from the authors, plus some editorial adoptions on its structure. The opinions and views expressed are those from the authors who accept the responsibility for the statements made or the accuracy of the data presented.

Abstract Review Panel

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Kelly Du Plessis (Rare Diseases South Africa, South Africa)
Stephen Groft (National Institutes of Health, USA)
Ann Nordgren (Karolinska University Hospital, Sweden)
Annika Larsson (ICORD Secretariat, Karolinska University Hospital, Sweden)
Emilio Roldan (GADOR SA, Argentina)
Maja Stojiljkovic (University of Belgrade, Serbia)

About ICORD and the 2017 Annual Meeting in China

ICORD (International Conference on Rare Diseases and Orphan Drugs) is an International Society for all individuals active in rare diseases and/or orphan drugs, including health care, research, academic, industry, patient organizations, regulatory authorities, health authorities, and public policy professionals. The mission of ICORD is to improve the welfare of patients with rare diseases and their families world-wide through better knowledge, research, care, information, education and awareness (for more information or becoming a member see www.icord.se or email the ICORD secretariat, icord.karolinska@sll.se).

The next annual ICORD meeting will take place in Beijing, China, 8-10 September 2017 and will be organised together with the Chinese Organization for Rare Disorders, the Peking Union Medical College Hospital (PUMCH) and Rare Disease International (RDI). The conference will be the twelfth since the first ICORD took place in Stockholm, Sweden, 2005. The meetings are usually attended by 200-300 participants representing all stakeholders in the rare disease field from all continents. In addition to an excellent scientific program, the annual ICORD meetings are very collegial and provide a great opportunity for interaction, networking and sharing of best practices. Many of the attendees are international and regional key leaders.

Board of ICORD (2016-2018)

ICORD welcomes its new Board which was elected during the ICORD General Assembly 20 October in Cape Town. ICORD also expresses its gratitude to the departing Board members for their great contribution and commitment the last two years.

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Conclusions of the discussion groups

The ICORD discussion or working groups offer an opportunity for the conference participants to meet and discuss matters of importance with other delegates with similar interests. The discussion group session provides a forum where conference attendees can network, learn from each other and bring new ideas back home. The groups are open to everyone and their contents are decided by the participating delegates. Each discussion group has a coordinator who functions as facilitator to drive the discussion.

ICORD and the group coordinators acknowledge the great contribution by all participants of the discussion groups and for providing input to the written summaries.

Discussion Group A: Obtaining a diagnosis through available diagnostic procedures

Group coordinators: Ann Nordgren, Centre for Rare Diseases, Karolinska University Hospital, Sweden and James Chipeta, University of Zambia School of Medicine, Zambia

Report compiled by: Annika Larsson, Centre for Rare Diseases, Karolinska University Hospital, Sweden

This Discussion Group focused on the topic "Obtaining a Diagnosis Through Available Diagnostic Procedures". The current status, difficulties and future priorities and possible collaborations were discussed.

Today in Africa diagnostics are not accessible to everyone, especially for individuals with rare diseases. There are many reasons for this. One major obstacle is a lack of awareness, both among healthcare professionals and the general public. In many cases the parents do not understand that the symptoms they see in their child might be the cause of a disease so they do not even go for a check-up. Knowledge links to diagnostics and the pathway to diagnostics needs to be developed. This pathway may look different in different countries depending on how the healthcare system is developed but also how the information channels to the general population can be utilized for information purposes. Despite poverty being wide spread in Africa, including South Africa, an estimated 85% of the South African population has smart phones. Internet access is still low in these poor communities but it is possible to reach out through social networks such as 'WhatsApp', 'Facebook' and even through conventional media like television and radio. Another obstacle mentioned during the group discussions was the stigmatization of individuals with rare diseases. This is still a major problem in many parts of Africa and prevents patients from diagnostics, care and quality of life.

In addition, the knowledge level of rare diseases among healthcare professionals needs to be raised significantly in order for the diagnostics of rare diseases to be improved. Rare diseases specialists are either scanty or not available at all in the majority of African countries, especially Sub-Saharan Africa. For instance in South Africa there are only 11 clinical geneticists. There was also a discussion on affordability and whether Whole Genome Sequencing (WGS) or panels should be used for diagnostics. The problem of WGS in the future will not only be the cost but the amount of information that will come out of each analysis, and ethical aspects. By WGS there will be incidental findings and the non-causative mutations might be difficult to discern from the disease-causing mutations. The lack of bioinformaticians in Africa makes diagnostics through WGS challenging. The increased access to genetic data requires procedures to be developed on data protection and how data is made anonymous. There is need for measures to be put in place concerning consent, something which has been a major issue in South Africa and the rest of Africa.

General practitioners and clinicians need more training in diagnostics and phenotypes of different rare diseases so that only genetic testing of the most likely possible diseases are requested. Currently clinicians ask the genetic departments to check for many diseases, many of which are not connected to the symptoms of the patients. If testing would be used wisely a lot of money could be saved. There are tools available, e.g. FACE2GENE, that are freely accessible and facilitate diagnostics. Another bottleneck in the diagnostic pathway is the lack of time available for each patient and that many healthcare professionals are overworked. Geneticists have to trust clinicians that they provide the patients and families with the correct information about the diagnosis. This is unfortunately not always the case. To ensure that the information reaches the patient and family it was suggested that geneticists provide two different reports, one for the clinician and one for the patient/family.

In many African countries, newborn screening is not offered to the general population. In South Africa it is only privately available. There was an agreement in the group to include a general newborn screening for diseases for which treatments exist and that are seriously debilitating if left untreated. Screening of other diseases was also proposed, but the timing and ethics were mentioned as important factors to be taken into consideration when setting up screening programmes. For example, it might not be ethical to inform parents that their child will get a serious disease in the future, especially if there is no treatment for the disease. It was stressed that the prevalence of rare diseases varies throughout the globe and different countries in Africa might need to set up their own panel of diseases included in a national newborn screening programme. Because of genetic variation between regions, African genetic databases should be developed in order to facilitate diagnostics in Africa. Today there is limited information about genetic variants in the South African and African population.

Accessibility to diagnostics in South Africa varies depending on what income group you belong to. If you are in the lowest income group, health care is freely provided by the state. The middle- and high income population have to pay for their healthcare. Unfortunately, this system creates a big gap in accessibility as the middle-income population does not afford diagnostic

testing. Another disadvantage of the South African diagnostic system is that obtaining a diagnosis sometimes can exclude individuals from society. One example given and discussed was the state education system for children with autism in South Africa. If a child is diagnosed with autism in South Africa that child might no longer be permitted to continue its education in the same school but might be forced to change school and be placed in a special school. Autism and other behavioral phenotypes are common among rare diseases and disserve a special focus during awareness campaigns and training of healthcare professionals.

Another example of inaccessibility of diagnostics and lack of know-how was given from Zambia. They previously successfully piloted newborn screening for congenital hypothyroidism using the conventional method based on radio-immunoassay. With the development of mass spectroscopy (MS) for newborn screening world-wide, companies supplying radio-immunoassay reagents run out of business and after a few years radio-immunoassay reagents were not commercially available. This caused a problem for Zambia with regard to scaling up the newborn screening for congenital hypothyroidism in the country as MS was unaffordable. It was further mentioned that mass spectrometers have been donated to Africa but they have not been effectively utilised due to lack of human resource with appropriate technical know-how.

In conclusion, there was a consensus in the group that the awareness of rare diseases needs to be raised in order for improved diagnostics. Many countries share similar challenges, such as lack of education among health care professionals and the general public. It was made evident that the advancement in the rare disease field varies between countries and exchange of best-practices is recommended to facilitate the development. There is much too learn from each other and ICORD is one vehicle to promote knowledge, collaboration, networking and raise awareness. However, there have to be adaptations to different countries and regions dependant on existing incentives, healthcare and social-cultural systems as well as the available infrastructures. During the session it was stressed that successful diagnostic work is based on multidisciplinary teamwork, consisting of clinical geneticists, different medical specialists along with genetic counselors and bioinformaticians. In order to progress, rare disease policies are needed in Africa. Until now African governments have been very silent and prioritizations in support of rare disease patients and their families have been insufficient.

Discussion Group B: Congenital malformations

Group coordinators: Michael Urban, Stellenbosch University, South Africa and Manuel Posada de la Paz, Instituto de Salud Carlos III, Spain

Report compiled by: Michael Urban

Background

The discussion focused on congenital malformations and chromosome abnormalities in South Africa, since most participants in the group were based locally. It was recognised that the problems in South Africa may not be the same as those found elsewhere, including in other African countries.

Aims

The aims were to identify gaps in the current approach to congenital malformations in South Africa, and priorities for the future.

Topics

Congenital malformations (CMs) remain under-recognised contributors to the burden of disease in South Africa, in part because of the impact of the HIV pandemic in recent decades. However, HIV care has improved, resulting in improved life-expectancy and infant mortality rates. For this reason, the group highlighted the need to advocate for care and prevention of CMs.

Studies of individual conditions, as well as the March of Dimes Global Report on Birth Defects (Christianson et al, 2006), show that CMs are relatively common in South Africa, and that foetal alcohol spectrum disorder (FASD) is a particularly important problem. However, the national surveillance system for CMs is under-resourced, resulting in severe under-reporting (Lebese et al, 2016). This contributes to the low priority given to CMs and hampers appropriate allocation of resources. It is essential that surveillance for CMs aim for much higher reporting rates and the group recommended that new approaches be explored, such as the use of sentinel sites. There is also a need to include indicators for genetic health services in the National Health Indicator system.

Successful prevention of CMs depend on many factors, including: (1) provision of relevant health services e.g. for contraception and prenatal diagnosis, (2) health promotion e.g. regarding teratogens such as alcohol consumption (3) education of a wide range of healthcare providers.

Several gaps were identified in provision of preventive services. For example, the emphasis on HIV prevention resulted in the National Department of Health (NDOH) prioritising provision of condoms over other aspects of family planning. The NDOH has recently prioritised general contraception services, and it is hoped this will reduce unplanned and unwanted pregnancies with CMs. Fetal medicine and prenatal diagnosis services remain limited to a few metropolitan areas, or to private health sector. Fetal medicine centres need to be strengthened and referral pathways from primary health care improved.

The need for more systematic measures to prevent FASD was highlighted. This would address an important cause of childhood disability and also help South Africa meet its UN Sustainable Development Goals. Currently only a few broad measures are in place to reduce alcohol use e.g. a tax on alcohol, warning labels on drinks, and some advertising regarding the risks of drinking in pregnancy. The group recommended that more targeted approaches to reducing risky drinking among pregnant

and reproductive age women be assessed. Options include (1) training of community care workers, who are quite widely employed to undertake some community-based care and health promotion activities, in order to allow them to provide health promotion regarding risky drinking (2) introduction of brief interventions for risky alcohol-use, for example in the context of antenatal care.

Education emerged as an important theme, as the group felt that knowledge about CMs is limited. This is true for women, mothers and communities, but also for health providers such as nurses and doctors. While education needs to be addressed at multiple levels, we discussed particularly the use of social media in health promotion for mothers, and in continuing professional development for health professionals. The NDOH provides a program called 'NurseConnect' which gives continuing professional development in the form of regular cell-phone messages. In addition, it provides a program called 'MomConnect' which gives regular health promotion cell-phone messages to women who are pregnant or mothers of young children. The latter program reaches hundreds of thousands of women, and represents an opportunity to disseminate evidence-based messages relevant to the prevention, identification and care of birth defects.

Medical care for CMs is largely based at tertiary centres, and availability is limited by resources. We discussed the example of cardiac surgery for children with Down syndrome. While tertiary cardiac surgery facilities no longer discriminate against children with Down syndrome, not all facilities are able to offer more complex procedures such as repair of atrioventricular septal defects. In addition, although surgery may be available at a tertiary centres, it is likely that many children lack meaningful access to services, for reasons including lack of or late diagnosis, or delays in the referral system. The extent of this problem should be assessed.

There are several patient support groups with a long-standing national footprint, including those for Down syndrome, haemophilia and muscular dystrophies. Two important developments in recent times have been (1) the increase in number of support groups for rare conditions, though these are often dependent on single individuals and therefore unstable (2) the establishment of Genetic Alliance South Africa as an umbrella body with international links – this replaced a previous body which faltered in recent years. A need was identified to improve links between patient support groups and professionals treating CMs.

A number of gaps in policy were identified. An important one is the lack of national legislation or policy regarding rare diseases. There is a need to advocate for such a policy, and likewise to increase the profile of the International Rare Diseases Day, perhaps by finding a well-known champion. Current NDOH guidelines for management and prevention of genetic and congenital disorders are in want of an update. This is important to address changes in a very dynamic field, and also to reflect the increasing priority that CMs and other congenital disorders should receive.

Main conclusions and lessons learned

- There is an increasing need to prioritise care for, and prevention of, CMs in South Africa
- Inadequate surveillance for CMs has hampered appropriate allocation of resources, and surveillance must aim to achieve much higher reporting rates
- The HIV pandemic has negatively impacted on services for prevention and care of CMs, although this has improved in recent years. The relative prioritisation of condom-provision versus broader contraceptive services was discussed as an example
- Specific measures are required to target prevention of FASD, since it is a common problem in parts of South Africa
- Education regarding CMs is required both for health professionals and communities. The NDOH uses social media on a large scale for both purposes. This creates an opportunity to include evidence-based messaging about prevention, identification and care of CMs
- Both foetal medicine services and services for surgical management of CMs are patchy and are largely based in tertiary care. There is a need both to strengthen services and to improve referral pathways from primary care
- Patient support groups are growing in number, and the recent establishment of Genetic Alliance South Africa is an important development. Stronger collaboration between health providers and support groups is required
- There is a need to advocate for a national rare disease policy, and to increase the profile of International Rare Diseases Day

Acknowledgement

The coordinators of this group, Micheal Urban and Manuel Posada de la Paz, express their gratitude to the participants of the group: Ntombenhle-Louisa Bhengu, National Health Laboratory Service, South Africa; Merlyn Glass, National Health Laboratory Service, South Africa; Engela Magdalena Honey, University of Pretoria, South Africa; Helen Malherbe, Genetic Alliance South Africa, South Africa; Thirona Naicker, Inkosi Albert Luthuli Hospital, KZN, South Africa; Yugashnee Naidoo, KZN Department of Health, South Africa; Tarryn Shaw, University of Cape Town, South Africa; Tina-Marie Wessels, University of Cape Town, South Africa and David Woods, Perinatal Education Trust, South Africa.

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Discussion Group C: Global RD policies and programmes

Group coordinators: Saffiya Dharssi, Pfizer, USA and Stephen Groft, NIH, USA

Report compiled by: Saffiya Dharssi

The session on Global Rare Disease Policies and Programs was a small group discussion with cross-stakeholder participants (including government, patients, health care professionals, researchers and industry). The discussion centered on some of the ongoing challenges that participants currently see in the global policy environment for rare diseases. Challenges discussed included the need for Health Care Provider specialists, clinical guidelines, lack of tertiary centers or centers of expertise, limited capacity and health system resources and number of researchers working in isolation. There was also a discussion from the patient representatives that they had significant difficulty garnering political support and finding a champion for rare diseases within their countries. They often felt that it was difficult to embed polices within country due to political factors (political will), lack of awareness, competition with other diseases, funding and competing burdens. They also felt that there was a lack of data or difficulty in obtaining data for supportive evidence that legislative decision makers in individual countries require to understand the issue at large.

Following a discussion on current challenges, the group embarked on a discussion regarding potential solutions to help overcome these issues. One thought was to look to current policies in place and amend these policies to include provisions for rare diseases and utilize cross-disease stakeholders to help support political will. For example, leverage models/expertise in the Cancer Control Space, policies/programs regarding disabilities for newborn screening/diagnosis programs and the Sustainable Development Goals (SDGs) for Maternal Health Policies to embed programs for rare diseases. There were also discussions that countries should promote consortia and specialist communication from a national/regional perspective, utilize regional networks and share best practices from other disease areas or countries. On the issue of lack of data, there were discussions to leverage International data and extrapolate for the specific country. On funding issues, we discussed innovative and practical financing and funding solutions (i.e., recent Rare Disease Law in the Philippines funded by a sin tax on cigarettes). Lastly, there was a robust discussion on utilizing the genomic revolution to support data needs for the diagnosis, treatment and care of patients and families with rare diseases and promote collaboration and support for electronic health records.

Discussion Group D: Access to treatment

Group coordinators: Emilio Roldan, SLADIMER, Argentina and Vinciane Pirard, Genzyme, Belgium

Report compiled by: Vinciane Pirard

A two hour break out session on access to therapy was organized during the XI th ICORD meeting to collect views on the current challenges faced by rare disease patients to access treatment in Africa and in South Africa in particular. Patients, care givers, patient's representatives, health care professionals and some international guests attended the break out. We provide here a summary of the discussion.

The group started by discussing that access is a chain of events that need to be engrained in the routine of the healthcare system to be effective and systematic. The critical building blocks that were identified during the discussion were training for health care professionals, supply chain, facilities and data.

Awareness for rare diseases amongst healthcare professionals and their ability to diagnose and monitor the diseases are a well-known challenge for rare disease patients all over the world. The limited numbers of geneticists and genetic counsellors in South Africa make the situation even more challenging. Small populations are not a priority for national health programs.

The existing infrastructures face logistical challenges to make certain technology/products available to the patients. Multiple causes concur to irregular supply of medicine (e.g. storage conditions, short shelf life, limited size of orders and the cost of international transport). The cost to bring a drug to market is high and small markets are not a priority for companies. Pragmatic and innovative approaches are required to bridge gaps in the systems.

The role of data and registries in accessing therapies was discussed in some details. Recording the number of affected patients, the severity of the symptoms and the natural history of the disease helps patients to give visibility to their problems and to advocate for their needs based on concrete facts. It can both stimulate the development of effective treatments and make the case for health system to grant access to existing treatment options and monitor their use. Bureaucracy can be an ordeal for patient seeking reimbursement for a rare disease. They will have to identify the "right person" in the administration that can help navigate the system. Administration and patients will have a different sense of urgency and might have different expectations of the treatment. Patients face an uncertain future and clear, transparency treatment guidelines and predictable reimbursement policies will help reduce patient anxiety. The administration will have competing priorities and it is critical for patient advocates to know the "numbers" (number of affected patients in need of treatment, cost of treatment, the administration priorities, spending and inefficiencies within the system). In some instances court cases and enacting right to health is the last resort to gain access to treatment. For patients and parents this quest for treatment access is very demanding and comes in addition to the daily chores and the emotional burden to care of a sick relative. A broader support both emotional and material from local and international organization helps not to face these obstacles alone.

How to provide funding for medications and the role of costs in access to therapy was eventually also discussed. When it comes to rare diseases a bit of context is needed. Even if rare diseases are numerous not all diseases will ultimately require treatment or will be amenable to treatment and not all drugs for rare diseases are expensive. On the other hand when it comes

to small patient population the price is what is creating the size of the market and as such it has an influence on the availability of a treatment. If there is no market there won't be development and limited chances to get cheaper drugs in the long term. In the overall healthcare budget the budget impact for rare disease remains limited and good negotiations with providers should deliver creative solutions to enable access in good conditions. The role of patient organizations was emphasized and how they could contribute to influence rare disease policy.

An orphan drug act can provide a framework but is not an immediate solution to accelerate access. It is something to talk about and refer to, it acknowledge the need of the rare disease patients and show some political willingness to tackle the challenge. South Africa has good scientific resources which could be translated to industry and produce options for the region, or contribute to international developments but the region should also be more encouraged to participate in collaborative research plans. Such a framework should integrate cultural perspectives and not all country or institutions need the exact same definition for rare diseases. They should adopt what works for them.

In conclusion the task ahead is enormous but small concrete steps were identified to favor better access. Patients can collaborate and create strong organizations to support each other and share facts and numbers to support their cause. The administration can designate a dedicated contact person for rare diseases that could champion the needs of this specific patient population within the system. Training more healthcare professionals to recognize and diagnose rare diseases is another important step to create the condition and equity for access to therapy. The use of new technology and especially telemedicine that helps people to connect with expert center across the world can be considered in that context. Eventually it was suggested that ICORD could act as an international repository for legal text on rare disease frameworks.

Discussion Group E: Research and research funding- African Challenges and Opportunities for Rare Diseases Research

Group coordinators: Petra Kaufmann, NCATS/NIH, USA and Gareth Baynam, Western Australian Department of Health, Australia

Report compiled by: Gareth Baynam

Introduction

Rare diseases research requires international collaboration to address this important global burden, with an estimated 6-8% of the global population living with a rare disorder (1). It also requires solutions that are tailored to individual jurisdictions and regions. To make a difference for the over 6,000 rare diseases, a group of national, African continental and international stakeholders met in Cape Town, South Africa, at the Rare Diseases Conference 2016 featuring the 11th International Conference on Rare Diseases and Orphan Drugs (ICORD) meeting, and the official launch of the African Alliance for rare diseases. ICORD is an international society for all individuals actively involved in rare diseases and/or orphan drugs, including health care, research, academic, industry, patient organisations, regulatory authorities, health authorities, and public policy professionals. The mission of ICORD is to improve the welfare of patients with rare diseases and their families world-wide through better knowledge, research, care, information, education and awareness. The African Alliance seeks to unite countries across Africa in their efforts to improve awareness, accessibility to treatment and supportive care as well as development of comprehensive, shared policies amongst member nations.

Aims

During this meeting a deliberative style discussion (2) on research for rare diseases in Africa, featuring a diverse group of stakeholders including funders; clinicians; fundamental, clinical, translational and health communication researchers; patients with rare diseases and others, was performed to identify a number of current challenges and opportunities under three themes; data sharing; patient engagement; and sustainable research models. These are described below.

Topics discussed

Data sharing is an important tool to accelerating research progress for rare diseases, and a necessity in rare diseases because of the limited number of patients and researchers. The identified challenges included: (i) A lack of overarching policy. (ii) A lack of common data elements and standardization to enable interoperability of existing or new projects. (iii) Limitations in consent forms, specifically a lack of uniform approaches to data sharing for retrospectively or prospectively ascertained data. (iii) Real or perceived academic disincentives to sharing, including a fear of reduced competitiveness with breakdown of data siloes, and relatedly a lack of guidelines and best practices (e.g. publication policies) to frame data sharing. (iv) Researchers wishing to share data in multi-site studies also face the resource impediment inherent in multiple ethics review. (v) Public perception, including privacy fears and fears of commercial misuse of data. Opportunities included: (i) The potential partnership with existing local infrastructure and process (e.g., H3Africa(3)) and other international partnerships (e.g., ICORD). (ii) That there is patient support for data sharing; a "push" for data sharing. (iii) The interest by multiple stakeholders in sufficiently large datasets (e.g. industry, government); a "pull" for data sharing. (v) The opportunity to bring together multiple stakeholders for a data-driven discussion and deliberation to support the informing and generation of enabling policy.

Patient Engagement is a catalyst to research progress because working hand-in-hand with researchers, government and private sector funders, and industry, patients can promote education, awareness, research participation, and implementation of results. Identified challenges included: (i) A lack of information on the pathways or opportunities for patient engagement, and relatedly the uncertainty on how to find accurate and reliable information online. (ii) A fear of stigmatization if an in-

dividual discloses her or his diagnosis. (iii) Linguistic, cultural and religious differences in a diverse continent. (iv) The fragmentation of the patient community, and geographic dispersion of patients and researchers. Opportunities included: (i) The formation of an umbrella organization i.e. African Alliance, that can provide a unified voice, "lumping rather than splitting". (ii) The use of social media or mobile technology such as smart phones; building on existing initiatives to support new ones. (iii) The ability to build on, or create, active partnership throughout the research process (e.g. protocol development groups and institutional review boards).

We need sustainable models to translate the advances in genomics, information and communications technology and imaging to better understand disease mechanisms, and to deliver better diagnostics and treatments for patients with rare diseases. With upwards of 6,000 rare diseases, there are challenges to rare diseases diagnosis reflected in the diagnostic odyssey of rare diseases patients (4), and with disease specific treatment, with for instance only a few hundred specific treatments for these diseases. We need deliver innovative research that is more sustainable and scalable. Identified challenges to sustainable rare diseases research included: (i) A misalignment of stakeholder pathways and incentives between patients and researchers in academia or industry. (ii) A lack of national and international coordination of rare diseases research priorities. (iii) A lack of harmonized policies, with and between jurisdictions on the continent. (iv) A duplication of efforts and re-inventing the wheel. (v) The rare diseases "myth", that rare diseases are not a significant burden worthy of prioritization and coordination in developing countries; that they are not a significant African public health concern. Opportunities included: (i) Sharing of existing resources and approaches. (ii) The benefit of studying indigenous populations, for continental solutions, equitable innovation and also recognizing this as a way to contribute internationally to an increased understanding of the relationship between genetic variations and disease. (ii) Harnessing the power of patients as disease experts, advocates and research partners. This includes adapting techniques that have been successfully employed in African health activism; engaging with extant health activist organizations and networks and leveraging their expertise, experience, influence, and connections to promote awareness of rare diseases, overcome stigma, lobby authorities, and otherwise advance the rare disease agenda. (iii) The use of social media and mobile technologies e.g. noting the ubiquity of smart phones. (iv) The continuing emergence of bioinformatics and technological solutions for data management. (v) Re-phrasing the goal; that rare disease research has progressed, and will further progress, understanding and solutions for common diseases (5) and rephrasing the patient's goal for the outcome of good management: rare diseases as a model for patients in the lead to define individual and personalized measures of outcome instead of parameters of outcome that are defined by medical standards only.

Conclusion

This first African deliberative style multi-stakeholder engagement on rare diseases research created through ICORD identified a number of challenges and opportunities for rare diseases research to inform and stimulate the ongoing discussion and actions to accelerate and harmonize rare diseases research for this public health priority. At the same time, it has been recognized that the existing knowledge and experience of international organizations such as ICORD should be used to accelerate research endeavors in developing countries, as well as to effectively disseminate harmonized guidelines worldwide.

Acknowledgement

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Discussion Group F: Improved quality of life

Group coordinators: Monica Esser, Stellenbosch University, South Africa and Kelly du Plessis, RDSA, South Africa

Report compiled by: Kelly du Plessis

This was a comprehensive group consisting of parents, patients, social workers, doctors, carers, and academia, most of whom have been impacted by a rare disease in some way.

3 critical questions were asked:

1. What does Quality of life mean to us?
2. What are the GAPS to achieve good quality of life?
3. What are the goals to achieve Quality of life for rare disease patients?

1. What does Quality of Life mean to us?

It is clear that quality of life has different meaning and context to different individuals and is flexible based on personal circumstance. There is often a mismatch in perceptions between healthcare professionals and patients. Quality of life is also not only limited to the patient but that impacted family and immediate community.

The discussion group found the following critical aspects when discussing quality of life:

- Being "mindful" – Live your life as best as you can.
- Don't let your condition define you as an individual. You may be affected by a disease, but you are not the disease.
- You need to be comfortable with yourself and find acceptance within your situation.
- Having access to appropriate resources is critical to cope.
- Being pain free or having a balance between pain and quality of life is the goal.
- Having autonomy, and being able to be independent, including and advanced care plan, is necessary, particularly for adult patients.
- One's happiness is defined by their own ability to smile.
- Ensuring the affected individual is able to reach their maximum potential always needs to be the focus.
- Having the energy to maintain their daily functions needs to be a priority.
- Ensure that you capture the memories – it is often all the families will be left with.
- Society needs to be aware of the changing perceptions on quality of life, specifically in terms of the youth and their needs and desires.

2. What are the GAPS to achieve Q.O.L?

- Multidisciplinary teams who collaborate, and communicate with one another are essential. The patient is the centre of this team and requires consultation in terms of treatment plans and decisions.
- Rare Diseases need specialised clinics at dedicated centres of excellence.
- Our community needs passion to have integrated systems – as patients we are time consuming and lots of extra work, the team needs to have enough passion to overcome this.
- Lack of choice and availability needs to be addressed and discussed with the patient.
- Empowerment of both healthcare professionals, and patients & caregivers is needed. An empowered patient generally has an improved quality of life over a dependant patient.
- Parents generally become experts in a disease – their opinion matters and needs to be heard, however, they should not feel responsible for managing the entire team as they are still the primary nurturer and caregiver to the patient.
- Patients need to be included in meetings, congresses and discussions regarding policies and treatment plans etc, as they represent a very different, but equally valuable perspective

3. Goals to achieve Q.O.L

- THRIVE, NOT SURVIVE!
- Improve access to meetings and discussions for focused topics (ie: disease specific, palliative care, end of life plans etc).
- Ensure the patient and family are not stigmatized, provide necessary education and information to surrounding community.
- Build rare disease networks, and clinics: A team approach ensures shared responsibility which limits malpractice and dissatisfaction.
- Get involved with Ethics, and promote Ethics review boards at various clinics.

Discussion Group G: Patient organisations

Group coordinator: Durhane Wong-Rieger, Canadian Organization for Rare Disorders, Canada

Report compiled by: Durhane Wong-Rieger

Participant organizations

The patient organizations who took part in the discussion group included organizations supporting a single rare condition (Prader-Willi Syndrome Association of South Africa, Moebius Syndrome Foundation Africa, Pierre Robin Sequence Foundation, Pulmonary Hypertension Association of South Africa) local chapters or members of an international rare disease

organization (South African Haemophilia Foundation, Gaucher & LSD Society), rare disease alliances (Genetic Alliance South Africa, Primary Immunodeficiency Network of South Africa), national networks based in Africa (Botswana Organisation for Rare Disease, Rare Diseases South Africa), service/support organizations in South Africa (Stepping Stones, The Children's Therapy Centre), service and support organizations (Stepping Stones, Reach for a Dream, The Children's Therapy Centre, World Courier South Africa, Umduduzi – Hospice Care for Children), and foreign-based networks (Indian Organization for Rare Diseases, Canadian Organization for Rare Disorders, Wilhelm Foundation).

Similarities in purpose

There were strong commonalities expressed by all participants regardless of the purpose of the organization and their primary mandate. Almost all patient organizations were volunteer-based. Many participants were the founders of the rare disease organization represented, especially those of extremely rare conditions. They had been started the groups based on their own experience of "feeling all alone" when they (their child) had been diagnosed and they could not find adequate information, support, or other resources. Even local chapters or members of international disease networks were often initiated or "resurrected" by an affected individual or family member and expressed feelings of isolation. Key concerns were visibility (awareness, advocacy, and affiliation) as well as sustainability (fundraising, volunteer recruitment, and succession planning). Most relied heavily on social media for outreach, education, and support.

Accomplishments and challenges

When asked to share accomplishments (things they were "proud" of) there were many similar and some unique items. Most were proud that they were able to stabilize the organization, increase membership of usage, and provide valuable service or support, often beyond their local community, despite being a small organization, with little or no paid staff. They shared information and support (through Internet on Facebook, social media groups, twitter chats, and websites); some offered face-to-face support to local members, through meetings, hospital visits, or social activities. Most indicated they had increased awareness (of their condition), effectively advocated for needs, and in some cases have been able to move policy makers and affect change.

When asked to identify their challenges (things they were "sorry" had happened or were unresolved), there were again many common themes. Most were sorry about their lack of successful outreach: to other areas in the country, to all persons in need, to rural or low-income patients, to healthcare professionals and the medical community, especially into the public sector (and not just private healthcare). They also raised concerns about funding, better use of social media, and networking with other patient organizations. Finally, many expressed the need to engage more volunteers, to learn how to delegate, and to develop new leaders.

Most felt that the newly formed network, Rare Disease International, would be most helpful to them locally in three areas: providing tools and awareness for raising funds; providing data, support (and credibility) for government relations; and providing tools and serving as a contact for activities like Rare Disease Day.

Finally, they identified three key barriers to better collaboration. In terms of other patient organizations, a key barrier is the perception of a "zero-sum game" with limited resources to share and investment of time and effort without a perceived benefit. Second, collaboration with health professionals was difficult because of their "ego", lack of a perceived benefit to partner with patients, and reluctance to be identified as an advocate. Finally, participants identified the need for professionalization of the patient associations, with training, tools, and templates and support for national organizations to develop local groups.

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Oral Presentations

Session 3. Obtaining a diagnosis through available diagnostic procedures

THE NIH UNDIAGNOSED DISEASES NETWORK: HOPE FOR MORE FAMILIES AND LINKS TO THE INTERNATIONAL RARE DISEASES COMMUNITY

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The NIH Undiagnosed Diseases Program (UDP) evaluated over 850 desperate patients between 2008 and 2015. Overwhelming enthusiasm for the successful program spawned the NIH Undiagnosed Diseases Network in 2015. A consortium of 7 clinical sites plus core facilities including a coordinating centre, two next generation sequencing laboratories, a biorepository, two model organisms facilities, and a metabolomics laboratory operate under a single IRB protocol and freely share data among investigators. With the goal of helping families secure a diagnosis and advancing biomedical research, in its first 10 months of operation the UDN received 864 applications (https://undiagnosed.hms.harvard.edu/apply/) and evaluated 86 patients. Exome or genome sequencing of 456 probands and family members helped to provide 11 diagnoses. Many strong candidate genes not previously associated with human disease have been identified for further study in vitro and in model organisms.

To facilitate data sharing more broadly, the UDN has sponsored 3 international workshops culminating in the Undiagnosed Diseases Network International (UDNI) (http://www.udninternational.org/), a consortium of 17 countries driven to provide answers to patients globally, and to further the work of the rare diseases community. The UDN and the UDNI are eager to identify physicians and researchers, particularly in Africa, as collaborators in the undiagnosed diseases effort, to share information on rare and undiagnosed diseases for the benefit of patients and their families.

Every rare disease was once an undiagnosed disease!

BEHAVIOUR AND DIAGNOSTICS IN RARE DISEASES

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Rare diseases are individually rare, but collectively quite common. Most present with physical manifestations but many people with rare diseases also have neurodevelopmental, mental health, intellectual, scholastic, neuropsychiatric or psychosocial problems. Living with a rare disease places a very high burden of disease, treatment, and care on families.

Globally, clinical services have improved their ability to identify and treat the physical manifestations of rare diseases. However, we are still very poor at screening for, diagnosing, and treating the neuropsychiatric disorders associated with rare diseases. Here we will use tuberous sclerosis complex (TSC) as example to illustrate some of the challenges of rare diseases, before proposing some solutions to this global challenge.

TSC is a multi-system genetic disorder with a birth incidence around 1:6,000. It is caused by mutations in the TSC1 or TSC2 gene, and is associated with non-cancerous tumour formation in almost all organ systems, including the brain, heart, kidney, and skin. Almost 90% of people with TSC will have some neurodevelopmental, mental health, intellectual, academic, neuropsychological, or psychosocial difficulties at some point in their lives. However, a recent UK survey suggested that only 18% of children and adults with TSC ever received assessment and treatment for these problems. Some of the reasons for poor evaluation included lack of expertise and access to mental health and neurodevelopmental services, confusion about mental health and neurodevelopmental terminology, and being overwhelmed by the apparent 'uniqueness' of each individual's profile of needs.

In an attempt to create a common language and to encourage regular screening for these difficulties, we introduced the term TSC-Associated Neuropsychiatric Disorders (TAND), and recommended that all individuals with TSC should be screened at least annually for TAND. We created a short TAND Checklist to aid this process.

In TOSCA, an international, natural history study of TSC, which includes >2000 participants from 31 countries, the rates of TAND were very high. Interestingly, autism spectrum disorders (seen in about 50% of individuals with TSC) had

a mean age of diagnosis at 7.6 years, suggesting very late diagnosis of ASD. Academic difficulties were identified in 57.8% of participants, but only 48.6% of those identified with academic difficulties received further assessment for them. Physical manifestations were carefully documented in the TOSCA study in almost 100% of participants, but 25-44% of TAND data were missing. Overall, these results from a large rare disease study suggest that, even in expert centres around the world, neuropsychiatric problems are likely to be under-diagnosed and under-treated.

We strongly recommend that routine screening for neuropsychiatric disorders associated with rare diseases should be introduced globally, that access to diagnostic services should be established, and that appropriate resources to train non-mental health professionals on neuropsychiatric aspects of rare diseases should be developed. We applaud the efforts of parent organizations to educate health and other professionals and urge that these partnerships be strengthened around the world, but particularly in low- and middle-income countries, where access to screening, diagnosis and treatment of neuropsychiatric disorders is extremely limited.

DIAGNOSIS FOR PRIMARY IMMUNODEFICIENCY (PID) BY ACCESSING AVAILABLE RESOURCES IN SOUTH AFRICA

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Background: A correct diagnosis is critical for disease management and is needed even more so for rare diseases such as PID. Obtaining a diagnosis is listed among the top priorities by the International Patient Organization for Primary Immunodeficiencies (IPOPI).

At the same time there is a desperate need to expand treatment modalities for major global infectious diseases with persistently high mortality. New therapeutic approaches focus on "host directed" therapies which rely on improved understanding of the host immune response.

Sharing capacity and knowledge for these two needs, can address the lack of diagnostic capacity for primary/genetic immune deficits with accessing existing laboratory infrastructure for major diseases to yield better understanding of immune pathways of novel PID for potential host directed therapies.

Discussion: There are many obstacles to PID diagnosis in Africa generally and South Africa specifically, including prioritization of health resources to diseases of major global concern (e.g. TB), lack of registries on the prevalence of PID, lack of regional warning signs, lack of clinical immunology training and lack of laboratory infrastructure or access to such. The findings of the South African Registry for Primary Immunodeficiency reflect serious underreporting of PID. Established in 2009, only 320 patients are recorded of an estimated minimum of 5500 PID in the population. Black patients at 80% of the population make up only 14% and reporting is lacking from several of the 9 different provinces. A positive family history is noted in almost half the patients as one of the most important alerts for PID.

A collaborative project PIDDGEN (Primary Immunodeficiency Diseases Genetic Network) was started in 2013 to link PID investigation with molecular including exome sequencing infrastructure for TB genetic research at the University of Stellenbosch. PIDDGEN illustrates the potential of networking and the value of molecular diagnosis. 80% of South African patients rely on Public Health Funding with limited access to advanced immune investigations. However with clinical recognition and basic immune diagnostic available for HIV and TB care a provisional diagnosis can be formulated and submitted for molecular diagnosis. This applies especially to severe forms of combined immunodeficiency (SCID/CID), Hyper IgE syndromes and Chronic Granulomatous Disease.

Conclusion: Molecular genetic diagnosis is envisaged to play a major diagnostic part in Africa for PID and other rare diseases. As the cost for gene sequencing continues to decrease rapidly and with the relative ease of sample transport requirements of whole blood or extracted DNA, it will become available to an increasing number of patients. Novel mutations or findings of unknown significance are to be expected and expert data analysis and genetic counselling are essential components of molecular genetic investigations. For all families but especially for families with high rates of consanguinity the genetic confirmation of a PID diagnosis will have important implications for earliest diagnosis and family planning and it holds promise for future application of corrective gene manipulation.

COMMON INHERITED METABOLIC CONDITIONS IN SOUTH AFRICA: DIAGNOSING "RARE" DISEASES IN GENETICALLY UNIQUE AND UNDERSTUDIED POPULATION GROUPS

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Objectives: To present combined rare disease data from the National Health Laboratory Services (NHLS) Inherited Metabolic Diseases (IMD) Laboratories at the Red Cross War Memorial Children's Hospital (RXH) and Groote Schuur Hospital (GSH) from the past 10 years (2006 -- 2016).

Methods: Data from inherited metabolic disease cases with confirmed diagnoses were retrieved from existing databases at these two referral centres. All identifiable patient information has been removed.

Results: Of 255 inherited metabolic disease diagnoses made at the RXH IMD laboratory over the past 10 years, glutaric aciduria (14.5%), cystinosis (13.7%), galactosaemia (7%), X-linked adrenoleukodystrophy (XALD) (5.5%), propionic acidaemia (5.1%), mitochonrial cytopathies other than neurohepatopathies (as a group: 5%), and urea cycle defects (3.9%) are among the most diagnosed disorders in South Africa, with mitochondrial neurohepatopathy diagnoses rising rapidly. The remaining 45% is made up of a combination of more than 40 other rare disorders.

With the more than 30 different genetic tests offered at the GSH IMD molecular laboratory, a similar picture has emerged. With glutaric aciduria, galactosaemia, mitochondrial neurohepatopathy and cystic fibrosis among the most diagnosed currently. Other diagnoses confirmed in this setting include among others primary hyperoxaluria, XALD and congenital adrenal hyperplasia.

Conclusions: To date, the five most common inherited metabolic disorders that we know of in South Africa, other than congenital hypothyroidism and cystic fibrosis, consist of Glutaric aciduria, Cystenosis, Galactosaemia, Propionic acidaemia and XALD. However, the more recent identification of a novel MPV17 mutation is leading to rapidly increasing numbers of mitochondrial neurohepatopathy positive diagnoses in SA. The majority of these disorders affect mostly the poorer resourced black South African population. Four of these disorders are significantly amenable to low cost treatment or intervention if diagnosed early.

Mitochondrial cytopathies other than neurohepatopathies as a group comprise a significant number of cases, however individually they are rare.

Most of these disorders are considered extremely rare in other population groups, with only XALD and X-linked urea cycle disorders following similar prevalence as overseas.

At least four (glutaric aciduria, galactosaemia, cystenosis and mitochondrial neurohepatopathy) owe their high prevalence to what appears to be widespread founder mutations in Black South African patients. A further common mutation in the AGXT gene accounts for the primary hyperoxaluria numbers seen at the GSH molecular lab. However, as the vast majority of these patients are from Gauteng region, it could indicate a more recent genetic founder event.

It is clear from this data that rare disease prevalence data from elsewhere in the world cannot and should not be extrapolated to South African population groups.

Session 4. Congenital malformations

THE WESTERN AUSTRALIAN REGISTER OF DEVELOPMENTAL ANOMALIES AND ABORIGINAL GENOMICS AND PHENOMICS

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Western Australia (WA) has a small population of 2.5 million people distributed over 2.5 million square kilometres, making it perhaps the largest single public health jurisdiction in the world. In 2011, there were just under 70,000 Aboriginal Western Australians, a number that is similar to the estimated number of children living with rare diseases in WA. WA is the first jurisdiction in the Southern Hemisphere to adopt a state rare diseases strategic framework, the WA Rare

Diseases Strategic Framework 2015-2018. The Framework reaffirms a commitment to improve the lives of individuals living with rare diseases through contributing to and promoting local, national and international initiatives. Because of need, its isolation and centralized services, a number of long-standing population based clinical services and registers have developed, these include Genetic Services of Western Australia and the Western Australian Register of Developmental Anomalies, both of which receive key health system manager support from the Office of Population Health Genomics. Partnerships between these services have delivered clinical service, policy and population health innovations and implementations as well as a commitment to improved Aboriginal Health, including for those with genetics and rare diseases and developmental anomalies. Aspects of these services will be presented as a basis for exploring synergies and new partnerships with Africa.

CONGENITAL DISORDERS AND MEDICAL GENETIC SERVICES IN SOUTH AFRICA

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Congenital disorders (CDs) are abnormalities of structure or function present from birth, including all disorders caused by environmental, genetic and unknown factors, whether evident at birth or manifesting later in life. CDs, including rare diseases, are the first non-communicable diseases experienced by people and affect 6.8% or 1 in 15 live births in South Africa (SA). As in many middle low income countries, their contribution to the disease burden is not recognised. National surveillance in SA currently under-reports CDs by 98% due to inadequate facilities and a lack of skilled clinicians to diagnose and treat CDs. Many CDs remain undiagnosed, or are misdiagnosed and the cause of death incorrectly assigned. This inaccurate data results in an underestimate of the true disease burden of CDs in SA, which impacts the political commitment and funding to the medical genetics sector.

Following the HIV/AIDS epidemic, SA is now back in positive epidemiological transition, but genetic services for the care and prevention of CDs have been severely compromised as a result of these competing health priorities. Child mortality was significantly reduced between 2005 and 2011, reaching lower levels than prior to the HIV/AIDS epidemic. However, since 2012, reductions in child mortality rates stagnated, indicating health issues other than those currently being addressed require prioritisation -- including CDs.

As SA transitions epidemiologically and mortality from communicable diseases drops - the proportion of deaths caused by CDs is increasing, revealing the previously hidden disease burden of CDs. This follows the trend in industrialised countries where CDs emerged and remain as the leading cause of death and disability in children -- contributing up to 28% of under-5 child deaths. Mortality data is starting to reveal this trend in SA, with congenital anomalies (a sub-set of CDs) overtaking infection as the 3rd leading cause of neonatal deaths in 2013.

Since up to 70% of CDs can be prevented or ameliorated, it is essential that CDs are prioritised and relevant, accessible services for their care and prevention are implemented. A good legislative and regulatory framework exists in SA for the provision of services, but implementation has been poor and fragmented. With an IMR of 28/1000 live births, SA is well below the point when genetic services should be implemented to further reduce child mortality and to care for those who are disabled as a result of CDs. Comprehensive genetic services are available in only three of the nine provinces, provided by 11 medical geneticists and fewer than 8 genetic counsellors. This excludes more than 60% of the population from accessing the services required.

It is imperative that CDs are comprehensively prioritised as a health care issue, in accordance with World Health Assembly Resolution WHA63.175 to achieve the human dignity and constitutionally and legally enshrined rights of affected South Africans. To meet Sustainable Development Goal 3 targets to reduce preventable deaths of new-borns and children under 5, genetic services must be developed, expanded and accessible so no child is left behind.

Session 5. Global RD Policies and Programmes

THE INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM (IRDIRC)

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The International Rare Diseases Consortium (IRDiRC) is a consortium of research funding agencies and interested parties acting to accelerate research through international collaborations to stimulate, better coordinate, and maximize output of rare disease research efforts around the world. Begun in 2010, IRDiRC now leverages efforts of funding agencies, scientists, companies, and patient organizations to increase the pace of understanding, diagnosing, and treating rare diseases. This presentation will summarize the history, goals, activities, and future plans of the IRDiRC collaborative.

ANALYSIS OF RARE DISEASE GLOBAL POLICIES & PROGRAMS TO ADVANCE ACCESS TO CARE AND TREATMENT

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Background and context: The rare disease policy landscape is rapidly evolving, evidenced by the increased international awareness and development of Rare Disease National Plans (NRDPs) in many countries at both high and middle income levels with developed and newly developed health systems. However, they vary considerably in terms of their content and focus with differences in even "core" areas such as diagnosis, care and treatment, access to medicines, community support, and research. However, across all nations, disparities in quality and access to care and treatment for rare disease patients persist relative to access for more common conditions. For example, evidence suggests that fewer than one in ten rare disease patients receive disease-specific treatment regimens. NRDPs vary in their scope, rigor, and level of implementation, reflecting not only differences in national healthcare systems and infrastructure supporting disease education and treatment but also serendipitous factors, including influence by specific patient groups and clinical specialists. Globally, a comparison of NRDPs provides insight into their development and implementation as well as advancement of rare disease research and services.

Objective: To increase the understanding of the global rare disease policy landscape and identify factors contributing to their development as well as the opportunities arising to improve patient access to care and treatment through further policy development.

Methods: To evaluate the current policy environment across the rare disease care continuum, a comprehensive analysis of existing NRDPs and public health policies and programs was conducted in 12 countries: Brazil, Mexico, Argentina, Taiwan, Hong Kong, Philippines, China, Turkey, Bulgaria, France, Germany and UK. The analysis focuses on five dimensions of national rare disease plans: patient awareness/support, diagnosis, coordination of care, access to treatments, registries. The analysis sorted countries along a spectrum of NRDP development with the intention to identify key NRDP elements that can help countries worldwide improve their standard of care for patients with rare diseases. These findings were further informed by regional stakeholder insights and measured against current government policies and non-governmental organization programs. Importantly, this characterization of countries strives to improve the implementation of rare disease policy through the functional application of the findings to countries not included in the original analysis, as well as through the international sharing of best practices.

Results: Final analyses will be available in late 2016 or early 2017. Initial findings reveal wide range of development and implementation of NRDPs across the sampled countries and that many countries can benefit from improving critical elements of their specific plans. Current data suggests that national policies which include well-developed patient engagement and support programs, excellent ongoing education, and continued research, improve ongoing patient access to therapies and care.

Conclusions: This study provides a unique opportunity to share knowledge and experiences; all with the aim of advancing the global rare disease policy conversation. It is hoped that this survey analysis will present impactful recommendations for rare disease specific program development in an effort to improve patient care, access to treatment, and quality of life.

Session 6. Access to treatment

CLOSING THE GAP: THE WORLD FEDERATION OF HAEMOPHILIA'S EXPERIENCE IN RESPONDING TO THE CHALLENGES OF A GLOBAL RARE DISEASE

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On World Haemophilia Day, April 17, 2003, the World Federation of Haemophilia (WFH) launched a very ambitious program aimed at improving national programs for patients with bleeding disorders in developing countries. The Global Alliance for Progress (GAP) Program is the WFH flagship development program aimed at closing the gap in treatment between developed and developing countries in three key areas: the number of people born with haemophilia and those who reach adulthood; the estimated and actual number of people known with bleeding disorders; and the need versus the availability of treatment products.

While the majority of people with bleeding disorders in developed countries have been diagnosed and receive treatment, in developing countries most remain undiagnosed, receive little or no care and are less likely to survive into adulthood. The primary goal of GAP was to target 20 countries and increase the number of patients identified with haemophilia worldwide by 50,000 within a ten year period (2003-2012).

Through many years of healthcare program experience, the WFH created a comprehensive development model aimed at introducing sustainable care and treatment for all: the WFH Development Model. Over the years, this model continued to develop to address the needs within GAP and has been used within all of WFH country programs, helping many countries set priorities and strategies, execute national programs, and improve treatment and care.

After more than 14 years and 31 participating countries, the GAP Program continues to bring demonstrable change and significant measurable improvements worldwide:

- Increased number of people identified with a bleeding disorders (over 28,700 in GAP countries)
- Increased level of government support for bleeding disorders care
- Improved knowledge and expertise of healthcare professionals working in bleeding disorders (over 20,200 trained)
- Improved diagnosis capacity through in-country training and participation in the WFH Internal External Quality Assessment Scheme (IEQAS) Program
- Increased access and availability of treatment products (over 3.940 billion IUs purchased in GAP countries)
- Stronger and more resourceful patient organizations
- New educational tools which benefited the entire community

In South Africa, GAP achievements include: the launch of a national bleeding disorders care program; substantial increase of the government's bleeding disorders budget; the increase of CFC purchase by 3.4 million IUs in 2015; the training and establishment of full comprehensive care teams in 11 major treatment centres; the capacity-building training provided to the patient organization; and the strong collaboration fostered with the South Africa Department of Health.

Despite the GAP Program's track record and achievements, much work remains to be done. There is still an enormous gap in care. To continue to address this challenge, the WFH initiated a new Decade of Global Development with the launch of the second decade of GAP (2013-2022) and the Cornerstone Initiative. The new overarching goal is to increase the worldwide number of people identified with all bleeding disorders by 50,000 and ensure that 50% of those newly diagnosed are from the world's most impoverished countries.

With these two programs, the WFH is moving one step closer to its vision of *Treatment for All*.

LOGISTICAL ASPECTS OF ACCESS TO TREATMENT

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Africa Healthcare sector review: There are key healthcare trends which can have a significant impact on the access to treatment, for example: the evolution of regulation (e.g. evolution of mandatory information on labels), institutional vision (e.g. new models of healthcare to treat people in remote areas), population and consumers (e.g. 60 percent of Africa's population will be urbanized by 2050), and the advancement of operating models (e.g. access to healthcare will spread to

rural areas and drive the need for cold chain supply networks) and the various needs and players (e.g. public health: streamline supply chain to prevent shortages and strengthen healthcare infrastructure and skilled workforce).

Logistics challenges: Despite recent growth and surging foreign investment, Sub-Saharan Africa remains a challenging frontier for many. Only 21.2 percent of the logistics industry executives surveyed said their companies have operations there. Another 12.7 percent said they are in the planning stages to enter African markets. More than 43 percent said they have no plans to set up in Africa.

Challenges operating in Africa

High costs: High operating cost due to lower volumes in single domestic markets, high cost of assets, high or non-harmonized tax regimes especially when operating cross-border, lack of trust in financial soundness of partners, lack of transparency across supply chain (no end-to-end and inventory cost) and uneven service levels by logistics providers.

Capacity and infrastructure: There is a low capacity of logistics hubs, relatively poor connectivity between countries – impacting transit times, scarce physical capital (e.g. vehicles, warehouse space), lack of validated and calibrated cold chain infrastructure, poor road conditions and poorly managed airports, and a lack of qualified human resources resulting in poor operational performance and critical skills shortages.

Business Environment: There can be diverse, complex and fast-changing government regulations across countries, for example the change of customs requirement "overnight", non-harmonized tax regimes, inefficient customs processing, opaque regulations, inconsistent customs information provided, corruption and compliance, versatile security and political environments.

Customs challenges in Africa: Africa has the highest customs delay in the world (12 to 37 days on average), the inability for local customs authorities to adhere to all rules (corruption), an ever changing regulatory environment, lack of enforcement and different treatment for different importers, tariff protection and high import duty costs can be expected in some African countries, regulatory interpretation and complex day-to-day customs management (multiple working locations, working hours, different time zones, etc.).

Creating a successful logistics outcome involves a solid business plan with a clear approach including all regulatory requirements, innovation, adaptability and flexibility, strong distribution and supply chain, a partner with strong agents that acts locally and has a solid infrastructure, a reduction in the infrastructure deficit, shipment visibility and security through technology, technical and regulatory expertise, and cold chain expertise and sustainability.

Marken is simple, efficient and compliant. It offers full control of the supply chain and regulatory compliance and guidance as well as the continuous investment infrastructure and network.

THE NEED FOR INNOVATIVE THINKING TO TREAT RARE DISEASES IN AFRICA

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Due to the lifelong nature of rare diseases, combined with the lack of curative treatments, there is a definite need for innovative thinking on how to holistically manage these conditions taking into account social, economic, education as well as health needs. Limited financial support and lack of policy in Africa creates further difficulty for patients to access the much needed support and treatment.

Long term disease management in Rare conditions needs to take recurrent hospitalizations, doctors' appointments, continued treatment, investigations as well as general health needs into consideration. Collaboration and a creative approach in terms treating patients is needed to ensure all the above is addressed whilst impacting the patient's 'day to day' routine and budget as little as possible. Allowing the patients some control and encouraging their engagement in the decision making process is needed. Consideration towards other members of the family (siblings, grandparents etc), as well as the economic impact on the family as a whole needs to factored in to decision making processes.

Treatment of rare diseases is not a one size fits all approach, and innovative thinking that improves overall care and quality of life is needed to ensure maximum economic value.

GSK'S GRADUATED APPROACH TO PATENTS AND INTELLECTUAL PROPERTY TO WIDEN ACCESS TO MEDICINES IN THE WORLD'S POOREST COUNTRIES

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In March 2016 GSK announced that it would adopt a graduated approach to intellectual property (IP) reflecting a country's economic maturity. The company stated that it would not file for patent protection in Least Developed and Low Income Countries, and would seek to grant licenses to generic manufacturers to supply versions of GSK medicines in Lower Middle Income Countries. Furthermore the company announced it intends to commit future oncology products to patent pooling and would explore this approach with the Medicines Patent Pool in response to the increasing burden of cancer in developing countries. The company also committed to make information about its patent portfolio freely available.

Improving access around the world requires a flexible and multi-faceted approach to IP protection. While IP stimulates and underpins continued investment in research and development, companies that are more flexible with their IP can help address pressing health challenges in developing countries.

GSK's IP approach is part of a broader strategy designed to address healthcare challenges in the developing world. For example, the company has implemented not-for-profit and tiered pricing, and an open innovation strategy for diseases that disproportionately affect the developing world, including malaria and Ebola, community investments and innovative collaborations to improve access to medicines.

On pricing of medicines, the needs of multiple stakeholders must be balanced. A fair and appropriate balance between the need to reward innovation with the broader cost expectations of payers and other stakeholders must be struck. Prices should enable optimal use of resources for healthcare systems, recognising the potential for medicines to slow the progression of illness and prevent costlier medical care; improve access to value-adding medicines for patients; and reward added-value to encourage further research and scientific breakthrough. Innovative pricing strategies should be considered. GSK for example has implemented a tiered pricing approach on vaccines which has resulted in ~75% of the company's vaccine supply going to developing countries through the GAVI Alliance and other mechanisms. Medicine prices to the world's Least Developed Countries are capped at 25% or less of European prices.

Open innovation is made possible by being more open with IP e.g. royalty-free voluntary licenses, participation in patent pools, being more open with institutional resources e.g. 'open labs', and being more open with data and compounds e.g. screening compound libraries for activity in neglected diseases. The intent is to create an enabling environment for research and development, particularly for neglected or rare diseases.

In summary, widening access to medicines for populations and patients who need it is not only the right thing to do, it also makes good business sense. Sustaining corporate growth is more likely when symbiotically aligned to a population's economic and social progress.

Session 7. Research and research funding

GAINING ACCESS TO AVAILABLE NCATS RARE - DISEASES AND TRANSLATIONAL-RESEARCH RESOURCES

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The mission of the National Center for Advancing Translational Sciences (NCATS) is to catalyse the development of new science, technologies, and operational processes that will make translation of fundamental discoveries into health interventions more efficient and effective, and thereby get more treatments to more patients more quickly. Started in 2011, NCATS has a special focus on rare diseases across its preclinical and clinical programs, all of which operate via collaborative models that involve partners from academic, non-profit, patient advocacy, and biopharmaceutical organizations worldwide. NCATS' integrative approach aims to dramatically increase the pace of understanding of rare diseases and their treatment. These programs and how partners can work with them will be described.

CATALYSING PROGRESS FROM DISCOVERY TO HEALTH BENEFIT: PROGRAMS IN THE OFFICE OF RARE DISEASES RESEARCH

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There are more than 6000 rare diseases, but treatments for a few hundred only. To accelerate addressing this great need for progress, we must leverage partnerships and harmonize efforts.

The Office of Rare Diseases Research (ORDR) at the National Center for Advancing Translational Sciences (NCATS) promotes such partnerships and harmonization in its programs including the following.

The Rare Diseases Clinical Research Network (RDCRN) program consists of 22 consortia, each focusing on a group of diseases (grouped by clinical or etiological communalities). Collectively, the RDCRN is studying over 200 rare diseases in natural history and pilot interventional trials at 266 sites located in the US and 17 countries. Currently, there are more than 90 active protocols, with over 40,000 patients enrolled. The consortium has more than 3,000 collaborative members, and has trained over 250 early stage investigators. The RDCRN program promotes participation of patient advocacy groups (PAGs), and in fact each consortium must include at least one PAG as research partner, starting at the time of application. There are over 140 PAGs who together form a coalition, the RDCRN-CPAG. The RDCRN program promotes harmonization, having all protocols and data collections developed and implemented by one data management and coordinating centre (DMCC) thus promoting common standards, quality, sharing of data and best practices across consortia and disease areas.

The Global Rare Diseases Registry (GRDR) program has developed common data elements (CDEs) for registries, and is conducting pilot studies in collaboration with investigators at Harvard University. In these pilot studies, registry datasets from PAGs are mapped into an ontology-based infrastructure that provides PAGs and authorized users access to their data to facilitate research and data sharing. Building on the experience of the GRDR program, NCATS now plans to partner with stakeholders to further promote standards and harmonization so that tools and data can more easily be shared, with the goal to generate high quality data sets that are fit for the purpose of supporting the therapeutics development and approval process.

To contribute to a more sustainable enterprise, the ORDR aims to promote synergy so that different data collections are harmonized and can be leveraged. This would allow for more streamlined integration of data collected by different stakeholders (such as patients, clinicians, or industry), data collected from different sources (such as mobile devices, or electronic health records), and data collected across different diseases. The ORDR/NCATS aims to partner with stakeholders in the patient, industry and academic research communities to promote standards and data quality and thus promote datasets that can materialize their full value in support of the therapeutics development process.

CHARACTERIZATION OF NOVEL RARE GENETIC VARIANTS IDENTIFIED BY NEXT GENERATION SEQUENCING

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Majority of rare diseases (~80%) are genetic diseases and therefore identification of specific gene defect in each patient is important. Using next generation sequencing (NGS) for simultaneous analysis of all genes related to symptoms perceived in a patient, all clinically relevant genes or the whole genome has increasingly become method of choice for molecular genetic diagnostics of rare diseases. Thus, identification of a new rare genetic variant possibly associated with rare disease has become a frequent event. As the number of new genetic variants is blooming, the evidence on their functional effect and firm association with the phenotype is lacking behind.

Scientific and medical literature as well as different kinds of databases (population-specific and disease-specific) is useful to find previously reported information on a particular variant. However, databases that automatically add new data without detail reviewing them should be used with caution as they could contain incorrectly classified variants. Computational programs are also useful as the first line in the assessment of the variant effect, but they should never be used as the only evidence of variant pathogenicity. As variants of uncertain significance should not be used in clinical decision making, their functional characterisation should be a priority.

Although determination of enzymatic function directly from biopsied tissue from the patient or an animal model provide strong and reliable evidence on the genetic variant's effect, such assays are not always possible. Therefore, expressing the protein in various in vitro assays to determine its characteristics is indispensable. Well-established, validated and reproducible function-

al assays in cell culture should be designed to assess mRNA stability, mRNA processing, translation process, protein structure analysis, protein localisation, protein residual activity and other characteristics in an attempt to portray full biological function. Functional in vitro assays should be designed to be the closest approximation of the biological environment. If possible, the response of an aberrant protein to a certain drug should be assessed in vitro before administration of the drug to patients.

When associating new genetic variant to a phenotype extreme caution is necessary. A genetic variant could be shown in vitro to be damaging to the protein for which it codes, but not necessarily implicated in the pathogenesis of the particular rare disease. Therefore, data from in vitro functional assays should always be combined with the clinical and biochemical data presented in a patient or more preferably in the group of patients with specific rare disease.

Session 10. Improved quality of life

OVERCOMING UNMET SOCIAL AND DAILY LIFE NEEDS OF PEOPLE LIVING WITH A RARE DISEASE

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The rarity, complexity and lack of treatment of rare diseases, accompanied by their strong relation to disability, lead to significant health and social needs, which are experienced by people living with a rare disease and their families across countries and continents. These must not be underestimated and require urgent attention from all stakeholders, from health to social care, to community services and to the community at large.

Social Services and integrated care provision are instrumental to the improvement of the health, well-being, autonomy and social integration of people living with a rare disease and their families, supporting them in the full realisation of their fundamental human rights.

However, social services are still scarce in certain regions of the world and, even when they are not, they are often not adapted to the needs of people living with a rare disease. Integrating rare diseases into social services and policies remains a challenge in most countries, as does the need to adapt health and welfare systems to rare disease patients' unprecedented needs, and the necessity to bridge the existing gaps between health, social and local care for people with rare complex diseases.

This presentation will bring to light the relation between rare diseases and disability as well as various significant social and daily life needs from people living with a rare disease.

The actions being undertaken to overcome these needs in the European context will also be briefly presented, with a particular focus on: the European Commission Expert Group on Rare Diseases Recommendations to Support the Incorporation of Rare Diseases into Social Policies and Services; good practices for social services elaborated by the European Joint-Action on Rare Diseases (EUCERD Joint Action, 2012-2015); and the new EU-funded INNOVCare, focused on developing a care pathway that to bridges the gaps between health, social and local care for people living with a rare disease.

A PROGRAM OF THE NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES: THE GENETIC AND RARE DISEASES INFORMATION CENTER (GARD): 13 YEARS OF PROVIDING ACCESS TO GENETIC AND RARE DISEASES INFORMATION

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Limited access to current, reliable, and easily understandable information about the more than 6,500 rare and/or genetic diseases can be very frustrating for patients, their families, and health care providers, thereby adding to the stress of the diagnosis and informed decision-making. For more than 13 years, the Genetic and Rare Diseases Information Center

(GARD), funded by two components of the National Institutes of Health (NIH)--the National Center for Advancing Translational Sciences' Office of Rare Diseases Research (NCATS-ORDR) and the National Human Genome Research Institute (NHGRI)--has provided free access to experienced and highly trained information specialists who respond to questions in English or Spanish.

GARD has responded to more than 56,000 requests for rare or genetic disease information and currently responds to approximately 500 inquiries per month from across the globe. GARD Information Specialists, who include genetic counsellors and a medical geneticist, are mindful not to provide genetic counselling, but instead provide personalized responses to questions via a toll-free hotline or emails or letters that may include plain-language disease summaries, answers to complex questions, referrals to genetic services, testing information, clinical trials, links to NIH or other federal resources, high-quality, vetted Web resources, advocacy organizations, and more.

Each month, more than 200,000 people visit the GARD Information Center's website, which provides access to a database of information and resources at http://rarediseases.info.nih.gov. More than 6,600 diseases have an individual Web page where GARD Information Specialists post answers to de-identified questions and provide information about many resources, including disease management guidelines, CLIA-certified genetic testing laboratories, FDA-approved orphan products, Human Phenotype Ontology signs and symptoms, patient advocacy groups, and more.

A new interactive GARD Information Navigator tool is also available for diseases about which GARD has often received questions. The Navigator is an educational tool to help people navigate the site and, by using audio descriptions, facilitate a better understanding of the resources available. The Navigator tool is added to more diseases every month. Additionally, GARD have developed videos to answer frequently asked questions such as "How to Find a Disease Expert", "Tips for the Undiagnosed", and "Financial Aid". Coming soon are a plain-language glossary for difficult concepts and access to GARD's information in electronic health records (a collaborative effort with the NIH's ClinGen Electronic Health Records Working Group).

The GARD Information Center's Information Specialists and expanding online collection of resources are of great benefit for patients, health care providers, and others as demonstrated by the increasing usage. Benefits include quickly finding quality information, resources and services to support individuals living with a rare or genetic condition.

Session 11. Patient organisations: a panel discussion

STEPPING STONES KENYA: WHAT WE DO

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Motto: Step by step, Stone after stone, Together we shall overcome

Stepping Stones is a patient organization support group for parents of children with rare diseases and/or special needs. It is a forum whereby parents can share, vent, ask, and most importantly feel like they are not alone. It is not geared to any specific disability, neither is it prohibitive to parents only. It is a place where anyone afflicted by a child with special needs (or even individuals themselves) can feel welcome and at home.

As the name suggests, Stepping Stones is meant to help fellow special needs parents grow in the journey that they have been called to make. It is for each individual to be a stepping stone to the other, to assist one another go a mile further.

It was founded in August 2013 out of a need of parents coming together to support one another. It consists of not only parents but also experts ranging from doctors, physiotherapists, psychologists among others. It is currently in the process of being registered as a society.

BOTSWANA ORGANISATION FOR RARE DISEASES (BORDIS): WHAT IT'S ALL ABOUT

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BORDIS was founded by a family whose two of their children have rare conditions. The journey towards diagnosis and management of the conditions inspired the establishment of BORDIS. The sole purpose of BORDIS is to raise a voice of Rare disease patients and their families in Botswana ensuring they are heard and their needs met. BORDIS is a

non-profit, patient advocacy and Non-Government Organisation (NGO) which is registered with the Registrar of Societies in Botswana. BORDIS membership is open to patients and their relatives, individuals and organisations supporting BORDIS' work as well as other patient advocacy groups.

BORDIS works to create an environment that enables Rare disease patients to thrive. This will be achieved through building strong collaborations and networks in Botswana and globally to harness resources and any necessary inputs to ensure access to diagnosis, and that the right treatments and management are available to Rare disease patients in Botswana. BORDIS is characterised by its pursuit of good HEALTH, INTEGRITY, LIFE and LOVE.

In Botswana there are few registered cases of different rare diseases and there is potential for more with awareness and diagnosis. Currently more work is going into creating awareness of rare diseases and BORDIS' existence, building relationships with relevant stakeholders and getting support and right treatments to patients. Though BORDIS is fairly new, there is positive response from the health practitioners in Botswana towards awareness efforts that BORDIS is driving.

GENETIC ALLIANCE SOUTH AFRICA

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Genetic Alliance South Africa (GA-SA) is a non-profit, membership organisation uniting patient support groups, healthcare professionals and other stakeholders relevant to the care and prevention of congenital disorders (CDs). The vision of GA-SA is to improve the lives of those affected by CDs by providing support through advocacy, support, education/awareness, and research.

The aims and objectives of GA-SA are to:

- Undertake advocacy activities to promote accessible, effective and relevant genetic services for the care, prevention and treatment of CDs for all South Africans.
- Provide a network of support and fellowship for individuals, families and groups affected by CDs, and those concerned with their health and welfare, including support groups.
- Promote the education of relevant medical health professionals on CDs through specific training interventions.
- Educate and raise awareness of the general public on CDs.
- Promote, facilitate and support research related to the cause, prevention, treatment, and monitoring of CDs in South Africa.

GA-SA bridges the gap between the patient support community and government, ensuring the rights of those affected by CDs are upheld by calling for accessible, effective and relevant genetic services for the care, prevention and treatment of CDs for all South Africans.

GA-SA was formerly known as the Southern African Inherited Disorders Association (SAIDA), initiated in 1973 at the request of a family affected by Tay Sachs disease who needed support. SAIDA soon became an umbrella organisation for 20+ support groups for other conditions, and activities over the past 40 years have also included training of medical professionals, basic counselling skills for support groups, public awareness events, and facilitating research.

With the competing health priorities of HIV/AIDS and TB diverting funds and political commitment, SAIDA was forced to cease all activities in 2013 due to financial challenges. After two years of inactivity, SAIDA underwent a process of evaluation, review and re-branding and was re-launched as GA-SA in August 2015, aligning with like-minded organisations globally. While continuing to focus on the three core aims of support, education/awareness and research, GA-SA incorporated the new focus area of advocacy to leverage support for improved genetic services for the care and prevention of CDs in SA.

While basic activities are underway, including a new website launched in October 2015 and ongoing advocacy activities, the key focus has been on incorporating good governance and developing a five-year strategic plan to ensure future sustainability. Developing the membership base and building strong, unified networks with the community of patient support groups and key stakeholders are crucial if we are, together, to improve the lives of those affected by CDs in South Africa.

OVERVIEW OF RARE DISEASES SOUTH AFRICA

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Rare Diseases South Africa is a registered Non-Profit Organization assisting all patients affected by rare diseases to access life-saving treatment and supportive care for improved quality of life.

Founded in 2013 by Kelly du Plessis after her son was diagnosed with a rare condition, Rare Diseases SA was initially established as a support group to fill the void of dedicated support for patients and their families confronted by the diagnoses of a rare condition.

However, due to the rapid growth and increase in members in the first 2 years, RDSA quickly evolved into a fully registered NPC focusing on all aspects of advocacy and support for rare disease patients.

Our Mission is to facilitate advocacy and engagement between those with ability to prevent, intervene, treat and provide supportive care for patients and families affected by rare diseases living in South Africa.

Our Objectives include

- Providing support and practical aid to individuals and families impacted by rare diseases
- Creating awareness about rare diseases by providing information too individual, families, healthcare professionals, and the general public
- Establishing a network to connect all stakeholders who have the ability to improve the quality of life of our patients

Individually rare but collectively common, rare diseases are life-threatening and chronically debilitating conditions which are so uncommon that special combined efforts are needed to address them.

Abstracts- poster presentations

CONGENITAL ANOMALIES IN SPAIN: A POPULATION-BASED MORTALITY STUDY

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Congenital anomalies (CA) are an important cause of childhood death, chronic illness, and disability in many countries. Most of CA are low prevalence conditions, therefore considered as rare diseases (RD).

Objective: The aim of this study is to analyse the mortality of those CA identified as RD and to assess time trends and geographical differences in Spain.

Methods: CA were identified as those included in the 17th chapter of the International Classification of Diseases ICD 10th revision "Congenital Malformations, Deformations, and Chromosomal Abnormalities". Deaths due to CA were extracted from annual official mortality databases of the National Statistics Institute of Spain (1999-2013). Only those ICD-10 codes considered as RD by experts were included in this study. Annual sex- and age-specific adjusted mortality rates per 100,000 inhabitants were calculated and time trends were performed by joinpoint regression analysis. Geographical differences were assessed by Smoothed Standardized Mortality Ratio at district level for the complete period.

Results: 13,501 deaths (53.3% males, 46.7% females) were associated to CA identified as RD during the period 1999-2013 in Spain. Annual age-specific adjusted mortality rates went from 4.111 (CI95%: 3.857 - 4.377) per 100,000 inhabitants in 1999 to 1.766 (CI95%: 1.631 - 1.909) per 100,000 inhabitants in 2013. This decline is statistically significant ($p<0.001$) with an Average Annual Percent Change (AAPC) of -5.2%. Both sexes showed a decline in the mortality trend as well: males rates vary from 4.389 (CI95%: 4.026 - 4.778) in 1999 to 1.785 (CI95%: 1.598 - 1.988) in 2013 (AAPC: -5.5, $p<0.001$), and females rates from 3.839 (CI95%: 3.490 - 4.215) in 1999 to 1.762 (CI95%: 1.570 - 1.972) in 2013 (AAPC: -4.8, $p<0.001$). Geographical analysis evidences higher risk of mortality due to CA in some regions located in the South of Spain.

Conclusion: This study has allowed assessing CA mortality in Spain, expected to decline in the last 15 years. In addition, a possible spatial pattern has been identified. The reasons which explain the higher risk of mortality due to CA in the South of Spain might be studied more in depth in posterior analyses.

DESIGN AND IMPLEMENTATION OF AN INTERACTIVE MAPPING TOOL TO REPRESENT THE DISTRIBUTION OF RARE DISEASES - RELATED IN SPAIN

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The cartographic representation of the spatial distribution of mortality caused by rare diseases (RD) offers clues to the analysis of environmental factors that influence prevalence of these diseases. Access to visualization tools supporting the exploration and analysis of the spatial dimension of these phenomena is still scarce.

Objective: To design and implement an interactive cartographic information system allowing for visualization and querying of data on mortality caused by RD in Spain.

Methods: The geographic extent of both data and maps is the Spanish territory. It comprises about half a million square kilometres and is home of 46 million inhabitants. Mortality estimates between 1999 and 2013 due to RD were provided by the Institute of Rare Diseases Research, Instituto de Salud Carlos III. Number of cases and rates per 100.000 inhabitants are aggregated at provincial level, while the Smoothed Standardized Mortality Ratio (Smoothed-SMR) data are aggregated at district level. In all instances, mortality estimations are grouped according to the chapters division proposed by the 10th International Classification of Diseases. The geographic information base representing the required two sets of administrative boundaries was obtained from the Spanish National Geographic Institute in shape format in order to be displayed in Geographic Information System software. Kompozer, a web authoring software, and CartoDB, an online platform for online mapping production, were adopted for their publication and diffusion on the internet.

Results: 60 maps represent the distribution of the Spanish 326 districts and 52 provinces with different variables: sex,

chapter of disease and Smoothed-SMR. The interactive platform is organized by tabs where spatial aggregation level, sex, the group of RD or the variable to query can be selected, subsequently a choropleth map will be displayed. By hovering over one of the spatial areas, a new pop-up window containing statistic variables appears. This system permits the comparison between geographic areas quickly and easily. This project is ongoing so results are still preliminary. This is a joint effort between the Instituto de Salud Carlos III and the University of Alcala, and final online platform will be available to the community on the websites of both institutions in 2017.

Conclusion: The availability of this online cartographic tool facilitates new approaches to RD distribution analysis. It brings to light patterns hidden under figures and tables and, as an online document, it would be accessible to all. To what extent this tool is going to impact on RD Spanish studies is still soon to know. Monitoring of use and assessment of validity as a research supporting tool is still to be undertaken.

HOPE FOR A RARE CONDITION

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An 11 year old female presented with hypertrophic nail dystrophy and subungual hyperkeratosis of her hands and feet. She also had evidence of palmar-plantar keratoderma bilaterally plus follicular keratosis of her lower limbs, all of which had been present since birth. The history and clinical presentation were in keeping with Pachyonychia Congenita, which is a very rare group of autosomal dominantly inherited genodermatoses, with approximately 1000 known cases worldwide. It is categorized under the group of ectodermal dysplasia's and is caused by mis-sense or small in-frame insertion or deletion mutations in keratins 6a, 6b, 16 and 17 which are expressed in the differentiated epithelial tissues. To date, the classification of this condition has been based on clinical features alone. However, a new classification has recently been suggested, which is based on gene mutation. This has resulted in a diagnostic dilemma, as many centres do not have access to genetic testing, leaving patients as 'unclassified'. But, there is hope for this rare condition. Pachyonychia Congenita is one of the very few rare skin diseases for which a consortium has been developed, which encourages and funds research into the condition by paying for genetic testing to be carried out worldwide. This International Pachyonychia Research Registry is currently at the forefront of genetic therapy development in the field of dermatology and, thanks to their efforts, an orphan drug has been developed. This may possibly correct the genetic defect and thus change the face of Pachyonychia Congenita forever. In doing so, this represents a paradigm of hope for other rare skin diseases.

MORTALITY DUE TO HEREDITARY ATAXIA: TIME TRENDS AND SPATIAL DIFFERENCES IN EUROPE

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Background/Objective: The aim of this study was to determine time trends and geographical distribution of mortality due to Hereditary Ataxia (HA) in Europe.
Method: Deaths due to HA were identified from WHO/Europe information system about mortality by G11 code, according to the International Classification of Diseases 10th revision. Age adjusted mortality rate was performed from 1999 to 2012. Time trends were assessed by Joinpoint regression analysis. ArcGIS was used in cartographic representation.

Results: 2644 deaths due to HA (48% women, 52% men) were identified from 1999 to 2012. Countries with more registered deaths were Germany, Spain and the Netherlands, together accounting for 60% of cases in the studied period. The overall HA mortality rate was 0.056 x 100 000 population (0.063 men vs 0.049 women x 100 000 population). Finland, Denmark, the Netherlands presented higher mortality rates than the global European mortality rate. On the other hand, countries with the lowest mortality rates are Moldova, Czech Republic, Latvia and Poland. Mortality due to HA remains stable from 1999 to 2012 in most European countries. Lithuania and Germany are exceptions since mortality have increased annually by 8.7% and 2.5%, respectively. In addition, temporal increase of HA mortality rate in women has been shown in the Netherlands (4.2%) and Spain (2.5%). Regarding geographical analysis of HA mortality, countries of the North, West and South of Europe showed higher rates than Central and South-East European countries. The countries of Western Europe have more risk than Eastern Europe.

Conclusions: Geographical differences in mortality due to HA are evident in Europe. Heterogeneity in the prevalence of different types of HA, in reporting deaths among countries, or other causes, may justify this variability. More extensive studies are needed in order to identify regional risk factors related to HA mortality in Europe.

THE INTERNATIONAL FUTURE FOR EHLERS-DANLOS SYNDROME: THE EHLERS-DANLOS SOCIETY

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The Ehlers-Danlos Society launched in May 2016 as a non-profit organization serving the global community to effect positive change and progression in the Ehlers-Danlos syndromes.

The society anticipates a time when all those with Ehlers-Danlos Syndrome can achieve an early diagnosis and appropriate management for their condition. With this goal, geography should not determine a patient's access to information and all medical professionals should be familiar with EDS, knowing how to achieve accurate diagnosis and correct management.

The rare types of Ehlers-Danlos Syndrome (EDS) are a group of heritable connective tissue disorders with multiple manifestations. The skin, joints, blood vessels and hollow organs are variably affected. Each is a separate and specific condition, distinct in features and genetic basis. In some types the effects are life threatening and many can manifest from childhood. The genetic basis of most rare types of EDS has now been elucidated.

The 1997 Villefranche Classification of EDS requires updating as new genes for further types of EDS have since been discovered. Working towards an agreed new classification to aid diagnosis is a prominent driving force for the Ehlers-Danlos Society.

The Society's mission is to promote collaborative and cooperative working by bringing together medical professionals from all over the world to work on this group of rare conditions. Medical professional symposiums are planned every two years towards update of the diagnostic criteria and management guidelines. The first symposium was held in New York in May 2016. This meeting of minds facilitates the generation of reliable up to date medical literature, approved though our medical and scientific board of international experts.

The Society has a pivotal role in signposting both patients and medical professionals to information, resources, support and education.

Our plans involve bringing together and uniting our patient community by providing annual conferences to distribute information and creating opportunities for interaction and mutual support. This will be aided by our aim of uniting EDS support groups and charities from around the world, providing resources and information where needed. Consolidation will enable us to establish and support new chapters internationally so that The Ehlers-Danlos Society becomes globally recognized, allowing benefit for all EDS patients.

We believe this will give hope to people whose lives are affected by Ehlers-Danlos syndrome.

The Ehlers-Danlos Society endeavours to steadily advance universal understanding of EDS. Our hope starts with our commitment to know more and to do more. This will build the frameworks necessary to advance medical knowledge, create a supportive community, and achieve the awareness necessary to further the next generation in discovery which can translate into enhanced patient experience.

AWARENESS OF FABRY DISEASE AMONG CLINICIANS IN TURKEY

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Objectives: Fabry disease is an orphan inherited disorder caused by deficient activity of the lysosomal enzyme α-galactosidase A. Burning peripheral pain with triggered crises of excruciating pain and gastrointestinal dysmotility, angiokeratoma, corneal deposits, and hypohidrosis are common early manifestations. Progressive dysfunction of the kidneys, heart, and/or brain develops in adulthood. Therapeutic outcomes with enzyme replacement therapy are generally more favourable in early stages of the disease. However usually it is not well recognized by the physicians and diagnosis is often delayed.

Methods: A questionnaire concerning about a 15 year old male fabry patient was prepared and was asked to physicians via e-mail. Among 98 physicians 62 (%60) answered the given questions.

Results: The patient's history revealed recurrent episodes of peripheral pain in his hands, becoming worse during fever and responding poorly to analgesics. Based on this initial information, only 30% considered Fabry disease in the differential diagnosis. A slightly higher level of suspicion (41%) was detected after providing additional signs and symptoms typically seen in young Fabry patients. A further increase of the percentages (68%) was found after providing information suggesting a positive family history.

Conclusion: Our study demonstrated that Fabry manifestations are generally poorly recognized and that awareness of appropriate diagnostic tests is low.

DEVELOPMENT OF A SCORING SYSTEM IN THE DIAGNOSIS OF MUCOPOLYSACCHARIDOSES

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Objective: Mucopolysaccharidoses (MPS) are disorders characterized by a wide variation in symptoms and progression rates. Usually patients with nonspecific symptoms are not recognized by the physicians and diagnosis is often delayed. In severe forms, the disease progresses very quickly and goes to death before 10 years of age. Therefore, early diagnosis and starting enzyme replacement therapy before the irreversible defects are crucial. Enzyme analysis of every suspected case is very expensive. For this purpose, selective clinical diagnostic methods (scoring system) are needed to ensure the recognition of paediatric patients with MPS. This paper discusses a scoring system based on the clinicopathologic features and their potential usefulness in case finding studies.

Methods: 107 Patients attended to 3 metabolic clinics from different regions of Turkey were enrolled in this retrospective study. The MPS Physical Symptom Scoring System (PSSS) based on the general clinical features of the disease was applied to all patients. This scoring system was based on literature review and clinician feedback. A standardized testing protocol and scoring rules were created. Major clinical features such as; skeleton anomaly, mental retardation, psychomotor retardation were scored "2". Minor clinical features such as; visual disorder, dermatological manifestations and progressive hearing impairment were scored "1". Six points and over were accepted as a risk for MPS.

Results: Out of 64 patients with score 6 and over, 59 (92.18%) diagnosed a type of MPS by enzyme and/or mutation analysis. On the other side, 9 out of 59 patients confirmed diagnosis of MPS had scoring 5 or less. Sensitivity, specifity, positive and negative predictive values of the scoring system were 86,7%, 90,5%, 92,2% and 84,2% respectively.

Conclusion: Recently developed MPS specific PSSS seems to be reliable and could be useful in future investigations and case finding studies.

THE APPLICATION OF PROTON NUCLEAR MAGNETIC RESONANCE (1H-NMR) SPECTROSCOPY IN THE DIAGNOSIS OF INBORN ERRORS OF METABOLISM

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Objectives: The timely and efficient diagnosis of inborn errors of metabolism (IEMs) remains challenging in third world countries due to limited awareness of these disorders as well as logistical and technical restrictions in the biochemical diagnosis thereof. The vast capacity of 1H-NMR spectroscopy in the diagnosis of IEMs has shown promise in various centres of the world. The aim of our study was to implement a similar approach at the National Metabolomics Platform of South Africa located at the North-West University, Potchefstroom. The study consisted of the evaluation of 52 anonymized proficiency urine samples provided by the European Research Network for evaluation and improvement of screening, diagnosis and treatment of IEMs (ERNDIM).

Methods: Preparation of samples for 1H-NMR analysis involved centrifugation, followed by the addition of a deuterated

buffer (pH 7) containing an internal standard to the supernatant, before transfer to a 5mm NMR glass tube. Analysis proceeded on a Bruker Avance III HD 500 MHz NMR spectrometer. One dimensional NMR spectral data was qualitatively analysed by two NMR analysts. Interpretation involved comparing ERNDIM sample spectra with pure compound library spectra, and the subsequent evaluation of several regions including organic acid, amino acid as well as creatinine and guanidinoacetoacetic acid, carbohydrate, purine and pyrimidines.

Results: The accurate identification of galactose-1-phosphate uridyltransferase deficiency as well as several organic acidemias including propionic acidemia, methylmalonic acidemia and isovaleric acidemia, which are commonly found in Sub-Saharan Africa, were demonstrated in this study. The additional identification of creatine anabolic deficiencies and purine/pyrimidine related disorders, which are currently not screen for in routine metabolic laboratories in Africa, were promising. Limitation existed in the identification of moderately elevated amino acids and subsequent diagnosis of amino acidemias. Identification of complex carbohydrate related disorders, including lysosomal storage diseases were mostly unsuccessful, although the spectra showed abnormalities in the carbohydrate region.

Conclusion: NMR shows benefit as a screening tool for prevalent IEMs in Africa. It furthermore may serve as complementary application in combination with routine metabolic testing services. Advantages include a prerequisite small sample volume, minor sample preparation requirement and the screening for prevalent disorders. Disadvantage may include increase instrumentation expenses and limited expertise in interpretation of NMR spectra in the developing world.

A METABOLOMICS INVESTIGATION OF THE MITOCHONDRIAL A3243G MUTATION

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The mitochondrion is the primary site for cellular energy generation, which is achieved by five enzyme complexes: the respiratory chain (complex I-IV) and ATP synthase (complex V), collectively known as the oxidative phosphorylation (OXPHOS) system. Mitochondrial function is reliant upon the coordinated expression of two genomes, mitochondrial DNA (mtDNA) and nuclear DNA (nDNA). Mutations in either genome lead to impaired energy metabolism and abnormal mitochondrial function. One such a mutation is the m. A3243G mutation found in the MT-TL1 gene of the mtDNA coding for mitochondrial tRNALeu(UUR). This mutation affects mitochondrial protein synthesis, leads to a decrease of respiratory chain complexes steady-state levels and ultimately affects respiration rate. The mutation was first identified in 1990 where it was linked to mitochondrial myopathy, encephalopathy lactic acidosis and stroke like episodes, better known as MELAS. Since then various other phenotypes have also been linked to this mutation including progressive external ophthalmoplegia (PEO) and maternally inherited diabetes-deafness (MIDD). However, the mechanism behind this mutation resulting in different phenotypes remains elusive. Here we used a urinary metabolomics approach to investigate metabolic differences between various m.A3243G phenotypes in an effort to unravel possible mechanistic differences.

A multiple platform metabolomics approach was followed to explore the urinary metabolome of 161 patients diagnosed with the m.A3243G mutation as well as 63 healthy controls. Because different metabolomics analytical platforms complement each other, six analytical platforms was utilized rather than just one to investigate a larger portion of the metabolome. The analytical platforms utilized included nuclear magnetic resonance (NMR), gas chromatography coupled to time-of-flight mass spectrometry (GC-TOFMS), liquid chromatography coupled to triple-quadrupole mass spectrometry (LC-QQQ) and three untargeted platforms using liquid chromatography with ion mobility, coupled to time-of-flight mass spectrometry (LC-IM-QTOFMS).

By using univariate statistical analyses, it was possible to identify urinary metabolites associated with the different phenotypes investigated. These profiles not only included known metabolites that have previously been linked to mitochondrial disease, but also metabolites not previously associated with the disease. The different metabolic profiles obtained for the various m.A3243G mutation phenotypes clearly points towards mechanistic differences between the phenotypes. To conclude, mechanistic differences were identified for different m.A3243G phenotypes and the value of using a urinary metabolomics approach to investigate metabolic differences in mechanistic studies was highlighted.

10 YEARS OF E-RARE: EUROPEAN PROGRAMME FOR RESEARCH ON RARE DISEASES. ACHIEVEMENTS AND PERSPECTIVES

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At present only few European countries fund research on rare diseases through specific dedicated programmes. Therefore, the funding of transnational collaborative research is the most effective joint activity to enhance the cooperation between scientists working on rare diseases in Europe and beyond and thus reducing fragmentation of research in this field.

The E-Rare consortium was built to link responsible funding organizations and ministries that combine the scarce resources for rare disease research and thus enable the participation of many researchers to transnational projects via Joint Transnational Calls (JTCs). Today, E-Rare is composed of twenty-five partners -- public bodies, ministries and research funding organizations -- from seventeen countries: AT, BE, CA, CH, ES, FR, DE, GR, HU, IT, IL, LV, NL, PL, PT, RO, TK. E-Rare is also a member of IRDiRC and participates actively in implementation of its objectives.

The calls performed since 2007 have shown that funding of projects on rare disease research in a coordinated way is clearly possible and needed as there is a significant interest for collaboration between rare disease researchers in Europe. In the seven joint calls 1021 projects were submitted of which 98 projects were funded with a total budget of 78 million Euros and with 449 research groups involved. Projects cover a wide range of medical areas and they have clear impact on patients' life. New causative disease genes were discovered that have a major impact on diagnosis and potential treatment of patients with a rare disease. The better understanding of the natural history of disease through registries and the harmonisation through guidelines will improve treatment of patients. The creation of animal and cellular models lays the basis for future research into diseases mechanisms and therapeutic options.

To enhance its contribution to excellent and sustainable research results, E-Rare established collaboration with a number of European medical infrastructures and with the European Medicine Agency (EMA), with the aim to customize their services to the demand of rare disease researchers. In order to inform about provided services and to link scientists and infrastructures, E-Rare developed a dedicated portal (www.erare.eu/infrastructures) and it promotes the use of European infrastructures within its calls for projects. In addition, Eurordis -- Rare Diseases Patients Europe -- accompanies E-Rare for many years but since 2014 the organization became a full partner of the consortium and contributes actively to development of new models of funding and implication of patient organizations in research.

Countries involved in E-Rare already demonstrated their steady commitment to rare diseases research funding and willingness to align their strategic agendas with the recommendations provided by IRDiRC. Thus, it is time now to scale up and extend strategic and funding activities of E-Rare into concerted, joint planning complemented by activities ranging from research to coordination and networking, including training, demonstration and dissemination and support to third parties. At the occasion of E-Rare Strategic Workshop (March 2016) the consortium initiated negotiations for the future, more integrated initiative.

CAN WE FIND NATURAL CLUSTERS OF TUBEROUS SCLEROSIS COMPLEX ASSOCIATED NEUROPSYCHIATRIC DISORDERS? A PILOT FEASIBILITY STUDY

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Objectives: Tuberous Sclerosis Complex (TSC) is a genetic disorder with multi-system involvement. The lifetime prevalence rates of TSC-associated neuropsychiatric disorders (TAND) are in the region of 90% in an apparently unique, individual pattern. This 'uniqueness' poses significant challenges for psycho-education and intervention planning. To date, no studies have inspected whether there may be natural clusters of TAND. The purpose of this pilot study was a) to investigate the practicability of identifying natural TAND clusters, and (b) to identify an appropriate multivariate data analysis technique for larger-scale studies.

Methods: TAND Checklist data were collected from 56 individuals with a clinical diagnosis of TSC (n= 20 from South Africa; n = 36 from Australia). Exploratory cluster analysis was performed using R, the open-source statistical platform.

Methods examined included hierarchical clustering (single linkage, complete linkage, average linkage, Ward, McQuitty), and two non-hierarchical clustering methods, PAM and FANNY.

Results: Ward was recognised as the most suitable analysis method to identify potentially clinically-meaningful TAND clusters. Eight distinct clusters were identified- two 'impact/impairment' clusters, and six 'behavioural' clusters. The 'behavioural' clusters included an 'ASD-related' cluster, a 'mood & memory' cluster, a 'language & scholastic' cluster, an 'anxiety & inattention' cluster, an 'externalization' cluster, and a 'hyperactivity/impulsivity/inflexibility' cluster. Intellectual ability and impact clusters showed strong correlation, and the behavioural clusters showed distinct patterns of co-occurrence across intellectual ability groups. For instance, the normal intellectual cluster did not co-occur with the ASD-related or externalizing clusters, but co-occurred with the language & scholastic cluster in 42% and with anxiety & attention in 22% of cases.

Conclusion: These results suggests that natural TAND clusters may be identifiable using Ward hierarchical cluster analysis.

IDENTIFICATION OF A NOVEL MPV17 FOUNDER MUTATION IN BLACK SOUTH AFRICAN PATIENTS WITH MITOCHONDRIAL NEUROHEPATOPATHY, USING A NON-STANDARD DIAGNOSTIC EXOME SEQUENCING APPROACH

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Objectives: Molecular diagnosis of complex heterogeneous disorders like autosomally inherited forms of mitochondrial disease can at best be daunting and extremely expensive and time consuming. Often a number of sequential molecular tests (including full gene screens) are pursued in an attempt to find a diagnosis. Here we describe the identification of a novel MPV17 founder mutation using a non-standard exome data analysis approach.

Methods: DNA from two patients with suspected mitochondrial hepatopathy, in whom all other obvious causes of liver disease had been excluded, were extracted from peripheral blood. Both patients presented with strikingly similar phenotypes, including early onset liver disease, prolonged jaundice, raised lactate, hypotonia, hyporeflexia, hypoglycaemia and failure to thrive. Diagnostic consent was obtained from the parents of the affected patients.

Exome sequencing was performed on DNA from both patients. Complete exomic data were temporarily stored in a secure environment and variation call files (.VCF) were analysed for any obvious mutations in genes associated with mitochondrial dysfunction. However, rather than doing full exome analysis, only genes involved in mitochondrial DNA depletion disorders were analysed manually in Microsoft Excel, according to a pre-established hierarchy of possible involvement, with DGUOK and MPV17 having top priority. Genes were chosen based on their association with clinical features seen in our patients and their involvement in mitochondrial disease.

Results: Manual analysis of .VCF files generated by exome sequencing revealed a single homozygous, novel nonsense mutation in the MPV17 gene in exomes of both patients. The mutation c.C106T (p.Q36X), introduces a stop codon in exon 3, and is predicted to result in a severely truncated protein. Results were confirmed with Sanger sequencing of exon 3 of the MPV17 gene.

Conclusions: Exome sequencing has become cost effective over the past few years and is routinely used in overseas settings. Access to exome sequencing services is easily obtainable and affordable. However, the data analysis infrastructure, bioinformatics support and access to appropriate genetic counselling regarding incidental findings is not. Especially in the resource strained public health laboratory environments of developing countries like South Africa.

Using a gene for gene analysis approach of exomic data rather than expensively sequencing each gene sequentially by Sanger sequencing, we successfully and quickly diagnosed two patients with suspected mitochondrial hepatopathy with the same, novel nonsense mutation in exon 3 of the MPV17 gene. Further diagnosis of 11 more patients followed in the space of about 8 months.

This approach to exome data analysis can be valuable as a cost and time efficient first line screening method in complex rare disorders like mitochondrial disease.

IMPROVED GENETIC DIAGNOSIS OF MITOCHONDRIAL DISEASE AT THE INHERITED METABOLIC DISEASES MOLECULAR LABORATORY OVER THE PAST 18 MONTHS

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Objectives: Mitochondrial disorders as a group are phenotypically and genotypically heterogeneous. With 37 mtDNA genes and more than a thousand nuclear genes involved in mitochondrial function, molecular diagnosis of the condition can be challenging.

A previous retrospective audit of more than 1 000 requests for mitochondrial genetic testing over about 25 years at the National Health Laboratory Services (NHLS) Inherited Metabolic Diseases (IMD) laboratory highlighted serious concerns regarding diagnostic approaches for mitochondrial disorders in South Africa. Amongst these, were inappropriate requests, lack of clinical information, lack of consultation with mitochondrial experts by requesting clinicians and incorrect laboratory referrals.

Since describing these concerns, new measures were implemented by the laboratory to improve clinical liaison and encourage appropriate testing strategies, which included clinician interaction and education as well as expansion of the available test repertoire.

The aim of this study was to perform a retrospective analysis of all mitochondrial requests to this centre over the past 18 months in order to assess the effectiveness of the above strategies.

Methods: Results of all mitochondrial requests from November 2014 to April 2016 (n=86) were retrieved from our existing database and the data analysed descriptively. The percentage of confirmed diagnoses was determined and compared with that seen before changes were implemented.

Results: Analysis revealed that 17% of mitochondrial results issued by this laboratory between June 2015 and May 2016 confirmed mitochondrial disease (compared with 6% described in 2014). Of these positive cases, 46.6% were diagnosed with MPV17 neurohepatopathy, 26.6% with mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) and 26.6% were positive for large mtDNA deletions.

Conclusions: This analysis revealed an increase in the positive rate for mitochondrial disease at the NHLS IMD lab following implementation of the new diagnostic strategy, highlighting the importance of appropriate clinical liaison particularly when diagnosing complex rare disease.

CYSTINOSIS A TREATABLE GENETIC CONDITION

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Objective: Cystinosis is an autosomal recessive genetic disorder. Incidence has been reported as 1 case per 100000- 200000 live births and it has been found worldwide in all ethnic groups. [1]It involves lysosomal storage of the amino acid cystine due to a defect in the membrane transport protein, cystinosin. There are three types of cystinosis. Nephropathic or classic infantile cystinosis (NC), the most severe form, inevitably leading to terminal renal failure in the first decade of life, and it is the major identifiable cause of renal Fanconi syndrome (FS) in children.[2]. CTNS gene which codes for cystinosin is mapped on chromosome 17p13 and common mutation found in SA black population is c.971-12G>A. Our aim is to discuss a patient diagnosed with Cystinosis and a genetic approach in management and care.

Methods (Case report): A 2 year and 10 months old boy was referred to our Genetic Clinic from Chris Hani Baragwanath Academic Hospital by the paediatricians for investigation of severe growth failure associated with dysmorphic features and severe developmental delay. He is second son of non-consanguineous young parents who previously lost an older son at about same age with severe malnutrition and regression of milestones.

On Examination: Weight = 5.5 kg (<< 3rd centile), Height= 66 cm (<< 3rd centile) and HC= 44.5 cm (<< 3rd centile). Birth parameters were not available to compare. Clinically he looked chronically ill and wasted in moderate respiratory distress on nasal prongs oxygen. He was noticed to have dysmorphic features including low set ears, frontal bossing, flat nasal bridge, epicanthic folds, narrow pigeon chest, features of rickets and supernumerary dysplastic teeth. Also found to have 6-8 cm hepatomegaly but no palpable spleen and digital clubbing. Neurologically was alert but irritable and hypotonic with normal reflexes.

Investigations and results:

• FBC: Normal

• U&E: Deranged in keeping with Renal Fanconi syndrome.
• LFT: ALP 581 (↑)|GGT 38 (↑)
• Urine reducing substance -- negative; GALT -- Negative, HIV Negative
• Cardiac echo and Abdominal sonar- no abnormalities noted
• X-rays- severe osteopenia, rachitic rosary ribs; widening of the metaphyses (Rickets)

Final Diagnosis: White cell cystine (↑) elevated; Cystine crystals noted on eye examination in keeping with Cystinosis. Genetic analysis- A heterozygous c.971-12G>A mutation was detected in CTNS gene

Outcome: Patient responded well on Oral Cysteamine therapy and eye drops. Mother was offered genetic counselling.

Conclusion: Cystinosis requires a multidisciplinary approach. Early diagnosis and treatment can prevent complications and improve outcome. New-born screening, if available, can allow earlier initiation of metabolic therapies. Genetic diagnosis is important and allows appropriate counselling for future pregnancies.

A CASE REPORT AND PHENOTYPIC REVIEW OF 1P36.33 MICRODUPLICATION SYNDROME AND THE INCIDENTAL FINDING OF TRIPLE X SYNDROME IN THE FAMILY

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Objectives: This case report aims to (1) present the ultrasound, clinical, cytogenetic and molecular genetic findings related to this rare chromosomal rearrangement, (2) further delineate the phenotypic spectrum of 1p36 microduplication syndrome, which is under reported on in clinical literature and (3) discuss the incidental karyotype finding of triple X syndrome and its implications for genetic counselling.

Case description: We describe a 24-year-old woman in her first pregnancy seen for prenatal genetic counselling following an abnormal 30-week ultrasound scan, which revealed intrauterine growth restriction, strawberry sign, micrognathia, 2 vessel cord, overlapping fingers and unilateral raised index finger. Amniocentesis showed a normal (46, XX) karyotype and an antenatal MRI displayed an absent corpus callosum.

In the neonatal period, the female infant was observed to be dysmorphic, hypertonic and microcephalic. Brain ultrasound showed absence of midline structures and a hypoplastic cerebellum. An atrial septal defect and pulmonary stenosis were confirmed with echocardiography.

A multiple ligation-dependent probe amplification (MLPA) test for subtelomeric copy number variants detected a duplication of genetic material at 1p36.33 targeted by the TNFRSF18, GNB1 and GABRD probes. Constitutional deletions/duplications at 1p36 are a known cause of multiple congenital abnormalities and intellectual disability.

Parental karyotype investigation incidentally identified that the mother of the patient had triple X syndrome (47, XXX).

Case discussion: Unlike the deletion syndrome of the same genomic region, 1p36 microduplication syndrome is not well-described in the literature with only a few documented cases, highlighting the importance of clinically and cytogenetically characterising those affected in the aim of better understanding this rare chromosomal rearrangement.

We also describe how further investigations for implications for recurrence, may reveal incidental findings and add to the complexity of genetic counselling for rare chromosomal conditions.

"WHERE DID IT COME FROM?": PARENTS' UNDERSTANDING OF THE CAUSE OF THEIR CHILD'S HEREDITARY HEARING LOSS

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Objective: Hearing loss (HL), which can lead to deafness, is a significant public health issue particularly in the developing world. Often referred to as the "silent epidemic", the highest prevalence of disabling HL is greatest in developing countries like South Africa (6 per 1000 live births). Genetic aetiology accounts for 50% of prelingual HL in children,

with 70% of these being nonsyndromic, with varying modes of inheritance, age of onset and severity. The aim of this study was to explore parents' perceptions and understanding of the cause of their child's HL to determine the role of genetic testing and genetic counselling services in this population.

Methods: Semi-structured interviews were conducted with eleven parents of children who attended a deaf school in Cape Town, or who had previously been seen at the genetics clinic at Red Cross War Memorial Children's Hospital. Participants were selected using purposive sampling. Data collected during these interviews then underwent thematic content analysis.

Results: Data related to the understanding of putative genetic aetiology of the child's HL was explored, as well as misconceptions regarding the cause, feelings of guilt and interest in genetic testing. Several parents were unable to identify the cause of their child's HL, or attributed it to something that they may have done during pregnancy. Most of the parents were interested in pursuing genetic testing as it would allow them to have a reason for their child's HL. Many of the parents had misconceptions about recurrence risks.

Conclusions: Without appropriate genetic testing for HL in South Africa, many parents are left without a definitive diagnosis for their child's HL. The majority of genetic causes of HL are the result of recessive genes. Unaware that they may carry a genetic change that leads to deafness, parents often fail to identify the cause of their child's deafness as hereditary. Parents struggled to find a reason for their child's condition experiencing guilt. Accurate understanding of the cause of their child's condition, through appropriate genetic counselling can assist in relieving and normalizing feelings of guilt. These findings are valuable in providing insight into parent's understanding of their child's HL and the potential role of genetic counselling services for the population.

EPIDEMIOLOGY OF GRANULOMATOSIS WITH POLYANGIITIS MORTALITY IN SPAIN: SPATIAL AND TEMPORAL DYNAMICS

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Objective: Granulomatosis with polyangiitis (GPA) or Wegener's granulomatosis is a rare disease of the immune system, caused by an inflammation of small- and medium- sized blood vessels and it affects commonly the respiratory tract. The objective of this research was to examine spatial and temporal variability on GPA mortality in Spain in a long-term period that could help assist in health care policies in affected patients.

Methods: GPA deceases were extracted from mortality statistics collected by the National Statistics Institute selecting the codes 446.4 (years 1984-1998) and M31.3 (1999-2013) corresponding to the International Classification of Diseases, 9th and 10th respectively. Five-year period and annual sex- and age-specific adjusted rates for the standard European population were calculated. Temporal trends were assessed through Joinpoint regression analysis. In spatial analysis, Smoothed Standardized Mortality Ratio and Posterior Probability at a district level were estimated for the period 1999-2013, taking into account contiguity between spatial areas. Finally results were displayed on ArcGiS Geographic Information System software.

Results: A total of 568 deaths due to GPA were recorded in the period 1984-2013 (55.6% corresponding to males and 44.4% to females). Global adjusted rate was 0.036 (95% IC: 0.033-0.039) per 100,000 inhabitants: males 0.046 (95% IC: 0.041-0.051 and females 0.028 (95% IC: 0.024-0.033). Joinpoint analysis showed a significant annual growth in mortality rates of 20.4% between 1984 and 1992 (p-value < 0.001) and it has remained stable after that year. Male rates have been higher than females, with a maximum male rate of 0.080 (95% CI: 0.045-0.138) per 100,000 inhabitants in 1994. In five-year periods, 1984-1988 showed the lowest rate with 0.015 (95% CI: 0.010-0.022) per 100,000 inhabitants and the highest in 1999-2003: 0.044 (95% CI: 0.036-0.053) per 100,000 inhabitants. Geographical differences in death risk between among districts have been observed in isolated locations but no spatial pattern is observed. Results show significant high risk in regions in the North (Galicia and Basque Country) and South (Seville and Cadiz).

Conclusions: After a significant growth in mortality, rates are remaining steady in recent 15 years of the period. This could be explained by the earlier detection and immunosuppressive therapies for affected patients seem to slow the progression of the disease, thus leads to stabilized mortality rates. Reasons determining geographic differences in GPA mortality should be studied deep in the future.

THE DETECTION AND IDENTIFICATION OF DISEASE-CAUSING VARIANTS IN RARE DISEASES WITH A SEMI-AUTOMATED BIOINFORMATICS PIPELINE

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Information required elucidating the aetiology of mitochondrial disease in African populations is still lacking. The genetic diagnosis of rare diseases is based on criteria and information from other populations, mostly European, and is compounded by issues such as the substantial genetic variety in the African population and shortcoming of sequence data processing and interpretation. Next-generation sequencing (NGS), the latest technology, allows for improved diagnoses on a genetic level. With NGS sequencing, there are usually vast amounts of data, containing rich information regarding the patients and the genes involved in rare diseases. It could be a daunting and time consuming task for clinicians to process these data. Here we present a pipeline that is specifically developed for variant identification, variant annotation, and variant mining. This semi-automated bioinformatics pipeline make use of freely available open-source developed software. Manual scripting allows for the incorporation of different software, in order to identify novel, reported and possible pathogenic variants. We developed this pipeline with the use of Ion torrent NGS data in a cohort of 200 patients diagnosed with a mitochondrial disorder. On average we identified 700-800 variants per patient. From these variants we identified ~200 novel and ~500 previously reported variants. The pipeline also allowed for identification of 2 possible pathogenic variants in 35 patients. In conclusion, the technology for sequencing will only get more advanced and the opportunity to sequence patients with a rare disease more available. The processing of such data could be time consuming and labour intensive. With a proper purpose-written bioinformatics pipeline, pathogenic variants could be identified systematically, allowing for more efficient genetic diagnosis.

A CASE STUDY OF OSSEOS MANIFESTATION OF ROSAI-DORFMAN DISEASE

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This is a single case study of a 56 year old female that presented at Helen Joseph Hospital with a painful swollen right proximal forearm with no clear history of trauma.

Physical examination yielded a painful swollen proximal forearm with a poorly circumscribed mass of about 7cm by 7cm by 4cm. The arm was neurovascularly intact with no skin manifestations or wounds.

Radiological evaluation via plain films as well as CT scan revealed a suspected malignant process involving the right proximal radial neck with bone loss and soft tissue involvement. Initial radiography reports suggested a malignant process and a biopsy was suggested.

Open biopsy was subsequently done and histological results were as follows:

- Features in keeping with osseous Rosai-Dorfman disease

Immunohistochemical staining S100 showed positive nuclear staining in the lesional cells.

The patient is currently symptom free after the biopsy and is awaiting definitive surgical management at Helen Joseph Hospital.

BIOBANKS PLATFORM: COLLECTIONS OF SAMPLES OF RARE DISEASES FOR BIOMEDICAL RESEARCH IN SPAIN

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Objectives: The Biobanks Platform is a network of Spanish Biobanks that aims to build a biological samples catalogue with high quality clinical and epidemiological data, and to make this available to biomedical researchers. A collaborative program was engaged to focus on Rare Diseases (RD) collections.

Methodology: A working group on RD was created to develop specific actions directed to construction of a catalogue of samples focused on the availability of collections of those rare diseases that are being studied in the context of national and international projects, especially in European networks.

Results: The Working group on RD established a set of actions with the main goal of building a catalogue of RD biological samples to make this available to biomedical researchers:

1. Collect information from each Biobank about the RD biological samples already available in the Biobank Platform: Questionnaires were elaborated and distributed to 52 institutions, and 10 biobanks communicated availability of RD collections. This catalogue of RD samples of more than 5200 patients has been annotated with the ICD-10 disease codification, but other disease codification is also available (Orphan Number, OMIM, UMLS, MeSH, MeDRA and SNOMED CT).
2. Define the minimal data set of associated data that needs to be available for RD research with biological samples: An analysis was conducted with the information about the data already available in the biobanks of the Biobanks Platform, and analysis of the data sets of other international collaborative RD networks (RD-CONNECT). A consensus of this dataset has been established, and MIABIS code was adopted to promote international data sharing.
3. Conduct a survey directed to research investigators to request information about the needs of RD biological samples for ongoing or future research projects.

Conclusion: Biobanks Platform and RD working group create a harmonious cooperative framework for the benefit of the RD scientific community, in order to enhance RD research.