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Rapid NGS Diagnostic Workshop

A Virtual Event

4th & 5th February 2021

9.30am – 12.30pm each day

Delegate Information Booklet

#RND2021

Ymchwil Iechyd a Gofal Cymru Health and Care Research Wales

Ariennir gan Lywodraeth Cymru Funded by Welsh Government

Rapid NGS Diagnostic Workshop

PROGRAMME

Day 1

9:30 - 9:40 **Introduction**
Dr Hywel Williams, Cardiff University School of Medicine

Session 1: Rapid NGS Diagnostics

Chair: Dr Hywel Williams, *Cardiff University School of Medicine*

9:40 - 10:10 **Rapid Genome sequencing - Informed care for critically ill children**
Dr Stephen Kingsmore, Rady Children's Institute for Genomic Medicine, San Diego California

10:10 - 10.40 **Delivering a national paediatric rapid genomics program: the Australian experience**
Professor Zornitza Stark, Australian Genomics Health Alliance, Melbourne

10:40 – 11:00 BREAK & Sponsor Presentations

Chair: TBC

11:00 – 11:30 **Implementation of the Wales' Infants and childreN's Genome Service**
Dr Sian Corrin, *All Wales Medical Genomics Service, Cardiff*

11:300 – 12:00 **Early testing for acutely ill children: the national NHSE&I R14 Rapid Exome Sequencing Service**
Dr Julia Baptista, *Royal Devon and Exeter NHS Foundation Trust & University of Exeter*

12:00 – 12:30 **Discussion & Day 1 Round-up**
Dr Hywel Williams, *Cardiff University School of Medicine*

Day 2

9:30 – 9:40 **Introduction**
Dr Hywel Williams, *Cardiff University School of Medicine*

Session 2: Rapid Prenatal Screening

Chair: Elaine Kenny, *PhD, Director of TrinSeq, CEO of ELDA biotech*

9:40 – 10:00 **Impact of NGS on prenatal diagnosis**
Dr Natalie Chandler, *Great Ormond Street Hospital, London*

10:00 – 10:20 **Prenatal Diagnosis in the era of Genomic Medicine**
Dr Suzanne Drury, *Congenica Ltd*

Session 3: Clinical Implications

Chair: Professor Angus Clarke, *Cardiff University School of Medicine*

10:20 – 10:400 **Clinical aspects of WINGS**
Nicola Taverner, *All Wales Medical Genomics Service*

10:40 – 11:00 **Rapid genomic testing in critically ill children: A new paradigm for genomic testing & Managing risk and uncertainty, a perspective from the literature**
Dr Isabelle Delon PhD FRCPath, *NHS East Genomic Laboratory Hub, Cambridge*

10:40 – 11:00 BREAK & Sponsor Presentations

Session 4: Addressing Current Issues

Chair: Dr Michael Hubank, *Head of Clinical Genomics, Royal Marsden Hospital, London*

11:20 – 11:40 **Use of transcriptomics for undiagnosed patients**
Dr Lamia Mestek-Boukhibar *The Zayed Centre for Research into Rare Disease in Children, (UCL), London*

11:40 – 12:00 **Rapid whole genome sequence data analysis - Dragen**
Joseph Halstead, *All Wales Medical Genomics Service, Cardiff*

12:00 – 12:20 **Genomic analysis in consanguineous cohorts**
Ian Berry, *Central Laboratory of the Yorkshire & North-East Genomic Laboratory Hub, Leeds*

12:20 – 12:30 **End of Conference Round-up**
Dr Hywel Williams, *Cardiff University School of Medicine*

LIST of SPEAKERS

Dr Stephen Kingsmore

Rady Children's Institute for Genomic Medicine, San Diego California

Dr Kingsmore is President/CEO, of Rady Children's Institute for Genomic Medicine, San Diego California. He is a pioneer in the field of rapid diagnostics of critically ill children with his seminal paper published in 2012 – Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. This paper transformed our view of the clinical application of genomic sequencing and subsequent papers have shown how he has been able to reduce the time-to-diagnosis down to just 19 hours.

Dr Kingsmore completed his undergraduate degree and medical training at Queens University, Belfast. He then moved to the United States to work, first at Duke University, North Chapel and then to the University of Florida, to Kansas University and he is now President/CEO, of Rady Children's Institute for Genomic Medicine at San Diego California.
He is a pioneer in the field of rapid diagnostics of critically ill children with his seminal paper published in 2012 – Saunders et al. Rapid whole-genome sequencing for genetic disease diagnosis in neonatal intensive care units. This paper transformed our view of the clinical application of genomic sequencing and subsequent papers have shown how he has been able to get the time-to-diagnosis down to just 19 hours.

Rapid Genome Sequencing-Informed Care for Critically Ill Children

Abstract:
Implementation of rapid genome sequencing is occurring for management guidance for infants and children with single locus genetic disorders. Dr Kingsmore will give an update on his latest work and future directions

Professor Zornitza Stark

Victorian Clinical Genetics Services and the Australian Genomics Health Alliance, Melbourne

Professor Zornitza Stark is a clinical geneticist at the Victorian Clinical Genetics Services and the Australian Genomics Health Alliance. She completed her medical training at the University of Oxford, and paediatric training at the Royal Children's Hospital in Melbourne. Zornitza is passionate about the implementation of genomic technologies into healthcare, particularly as a first-tier test to transform the diagnosis of rare disease.

Delivering a national paediatric rapid genomics program: the Australian experience

Abstract:

The evidence for diagnostic and clinical utility of rapid genomic testing in critically ill paediatric patients is compelling, but how do we translate single-centre academic experience to a national program? The Australian Genomics Acute Care Flagship study has established a national rapid genomics network that has now tested over 250 patients with an average time to result of just 3 days. The program has a strong focus on interdisciplinary evaluation of outcomes to inform future healthcare system implementation in Australia and beyond.

Dr Sian Corrin

Consultant clinical scientist and rare disease lead at All Wales Medical Genomics Service

Consultant Clinical Scientist Sian Corrin, FRCPath. manages the AWMGS laboratory constitutional services team. The laboratory and clinical teams work closely with those in the areas of obstetrics and gynaecology, pathology, clinical biochemistry, clinical haematology, cardiology, paediatrics, neurology and immunology and researchers to help direct testing strategies, aid in the interpretation of genomic testing and to develop cutting edge genomic services, ensuring highest quality of care for patients.

Implementation of the Wales' Infants and childreN's Genome Service

Abstract:

In July 2017, Welsh Government published the 'Genomics for Precision Medicine Strategy' with the aim of improving 'healthcare provision for the people of Wales'. Due to the emerging body of research showing that rapid whole genome or whole exome sequencing for critically ill infants and children can yield a diagnosis in around 40% of cases, the All Wales Medical Genomics Service (AWMGS), prioritised this test for implementation. It was anticipated that establishing the Wales Infants' and ChildreN's Genome Service (WINGS) for critically ill babies and children with unexplained diseases would result in patients receiving a fast, meaningful DNA result that would significantly improve their management, resulting in shorter hospital stays, fewer invasive procedures and, for some conditions, better longer-term health outcomes.

AWMGS Genetic Consultants, Bioinformaticians and Clinical Scientists have been working in partnership with specialist Paediatric Consultants and Cardiff University to develop the UK's first diagnostic rapid WGS service for paediatric patients as part of a national programme within the NHS.

Here we describe the clinical validation, implementation of the clinical and laboratory pathways and the results of the first cases.

Dr Júlia Baptista PhD DipRCPath

Royal Devon and Exeter NHS Foundation Trust & University of Exeter

Julia is a Principal Clinical Scientist at the Exeter Genomics Laboratory leading the national exome service for NHS patients with rare genetic diseases.
A keen educator, Julia is a member of the European School of Genetic Medicine providing courses in genomics and cytogenetics to the international healthcare community for over a decade and she is an honorary lecturer in Genomic Medicine at the University of Exeter.
Julia is interested in how genomic testing, especially in early age, can improve outcomes for patients and their families and in how rare genomic variation impacts on human health and disease.
Julia is also the South West Genomic Laboratory Hub Rare Disease Scientific Lead for Genomic Education and is a board member of the European Society of Human Genetics.

Early testing for acutely ill children: the national NHSE&I R14 Rapid Exome Sequencing Service

Abstract:

The Exeter Genomics Laboratory implemented a diagnostic rare disease exome pipeline in 2013 and in October 2019, it launched the new NHSE nationally commissioned rapid exome sequencing service for acutely unwell children.
In its first year, 519 children have been tested and a genetic diagnosis identified in 37%. With a focus on multidisciplinary team working, this service is a model of how translational medical research and close multidisciplinary working across the NHS can revolutionise patient care, improve patient outcomes and empower families by providing relevant genetic information.

Dr Natalie Chandler, PhD FRCPath

Great Ormond Street Hospital, London

Natalie Chandler is a Senior Clinical Scientist at the London North Genomic Laboratory Hub at Great Ormond Street Hospital, London UK where she manages the translational research team and prenatal exomes service. Her primary interests are in providing and expanding prenatal clinical diagnostic services. This includes non-invasive prenatal diagnosis for single gene disorders and rapid exome testing on invasive samples.

Impact of Next Generation sequencing on prenatal diagnosis

Abstract:

Next generation sequencing technologies have enabled rapid advances in prenatal diagnosis for genetic conditions. This includes non-invasive prenatal testing for common trisomies, non-invasive prenatal diagnosis for single gene disorders and rapid trio exome sequencing for fetuses with structural anomalies. Our laboratory has translated these technologies into UKAS accredited Clinical services which will now be embedded in the Genomic Medicine Service initiating in April 2021.

I will present how these services will impact prenatal testing pathways with particular focus on the prenatal exome sequencing service which initiated in October 2020. I will discuss our experience of the first four months of service and some of the challenges addressed to be able to offer this service in a timeframe applicable to prenatal setting.

Dr Suzanne Drury

Congenica Ltd

Dr Suzie Drury is Lead Translational Scientist; Prenatal Genomics & Personalised Health at Congenica Ltd. She has over 19 years' experience in translational research and the implementation of new technologies for clinical use, including fetal exome sequencing, non-invasive prenatal diagnosis of for single-gene disorders and rapid genome sequence for the PICU patient. In 2015 she was awarded the Malcolm Ferguson-Smith Young Investigator Award for her work on exome sequencing for prenatal diagnosis of fetuses with sonographic abnormalities.

Prenatal Diagnosis in the Era of Genomic Medicine

Abstract:

- Prenatal exome sequencing can impact prenatal management and inform pre- and post-natal treatment
- With careful patient ascertainment, exome sequencing has a high diagnostic yield in cases of fetal structural abnormality
- Using a single workflow to identify multiple variant types aids streamlined diagnosis
- Non-invasive prenatal testing for multiple single gene disorders can be used to identify pathogenic de novo mutations in cell-free fetal DNA

Nicola Taverner

All Wales Medical Genomics Service, Cardiff

Nicola Taverner is a genetic counsellor at the All Wales Medical Genomics Service, and part of the MSc Genetic and Genomic Counselling programme team at Cardiff University. She started out as a lab scientist, before undertaking the MSc Genetic Counselling at Cardiff University. She has worked as a genetic counsellor since 2007, initially for the West Midlands Regional Genetics Service in Birmingham before moving to work in Cardiff. She has worked on the MSc programme since 2014, and is the lead for the modules covering genetics, genomics, bioinformatics and variant interpretation. She is the Chair of the Association of Genetics Nurses and Counsellors (AGNC), the UK professional body, and has a strong interest and involvement in education and in advocating for patients and families.

Impact of rapid diagnostics on patients and families: the WINGS experience

Abstract:

- Benefits and challenges of rapid diagnostics for patients and families.
- Genetic counselling issues and challenges

Dr Isabelle Delon PhD FRCPath

NHS East Genomic Laboratory Hub, Cambridge

From an academic developmental biology background, Dr Delon joined the East Anglian Medical Genetic service 10 years ago, after a PostDoc at The Gurdon institute (Cambridge University-UK) and a PhD at the Institute for Developmental Biology at Toulouse University (France), working on the mechanisms of cytoskeletal rearrangements during morphogenesis and evolution. Specialising in rare disease testing in children, she worked as part of the Next Generation Children (NGC) Project Team with Prof Lucy Raymond, managing the front-end pipeline in the diagnostic laboratory and the clinical interpretation of results after MDT with the research team; Dr Delon gained FRCPath with a dissertation focused on the clinical experience through the project. She recently completed a consultant clinical scientist training (Higher Specialist Scientist) and is leading the paediatrics section of the rare disease service at the NHS East Genomic Laboratory Hub.

Rapid genomic testing in critically ill children: A new paradigm for genomic testing & Managing risk and uncertainty, a perspective from the literature

Abstract:

Over the last five years, rapid genomic testing for critically ill children has been implemented around the world and delivered many successes of life-saving diagnosis demonstrating the clinical utility of the approach. I come back to lessons learnt from the Next Generation Children project, a translational research project run between the University of Cambridge and the NIHR Rare Diseases Bioresource, Cambridge University Hospitals and Illumina, showcasing the change in paradigm represented by this new testing method. I explore the themes from the extensive literature that has arisen from many projects, focusing on the current thinking around managing risk and uncertainty before testing, in testing procedures and when a result becomes available. As a novel step towards the implementation of genomic medicine, rapid testing for very ill children presents opportunities and risks to be harnessed by clinicians, scientists and health system functions.

Dr Lamia Mestek-Boukhibar

The Zayed Centre for Research into Rare Disease in Children, (UCL), London

Dr Lamia Mestek-Boukhibar is a research associate at the Zayed Centre for Research into Rare Disease in Children (UCL). She graduated with a D.Phil in Genetics from Oxford University in 2010. Lamia occupied a postdoctoral position at UCL and a brief one at Imperial College London before she joined the Great Ormond Street Institute of Child Health UCL in 2016 where she worked on the application of rapid whole genome sequencing in the diagnosis of critically ill children. Lamia received funding from the NIHR GOSH BRC to focus her research on addressing yet another unmet clinical need that is the diagnostic gap in rare disease patients.

Bridging the diagnostic gap in rare disease patients

Abstract:

The application of next generation sequencing (NGS) has revolutionized genomic medicine. It has proven clinical utility in the diagnosis of rare diseases and provides unprecedented opportunities for novel gene discoveries. Making a genetic diagnosis in rare disease patients enables coordinated clinical management, genetic counselling and paves the way for possible personalized therapies. However, despite the applications of NGS, many rare disease patients remain without a diagnosis. Here we describe a multi-faceted approach to address this unmet clinical need and bridge the diagnostic gap in a group of rare disease patients. We first describe the Rapid Paediatric Sequencing project (RaPS) to briefly illustrates our experience in setting up rapid whole genome sequencing for the diagnosis of critically ill children. We highlight the need to address the undiagnosed cases and describe our strategy to solve them. This multifaceted approach comprises 1) data re-analysis, 2) data sharing, 3) comprehensive bioinformatics pipelines, 4) reclassification of VUS variants and 5) the application of RNA sequencing in addressing the pathogenicity of the non-coding genome. This multifaceted approach increased the diagnostic rate from 28% to 40% and highlights the need for a holistic approach in the diagnosis of rare disease patients.

Joseph Halstead

Lead Bioinformatician for Constitutional Services at AWMGS

Bioinformatics Challenges in Rapid WGS

Abstract:

All Wales Medical Genomics Service (AWMGS) recently launched a rapid WGS service for critically ill paediatrics known as WINGS. Successfully delivering the service required overcoming multiple complex bioinformatics challenges around variant calling, clinical variant filtering and data management. The use of an Illumina Dragen server combined with several novel in house bioinformatics tools allowed these bioinformatics challenges to be overcome. WINGS has delivered accurate results and has embedded the bioinformatics tools and skills required for the roll out of further

Ian R Berry FRCPath

Central Laboratory of the Yorkshire & North-East Genomic Laboratory Hub (Y&NE GLH), Leeds

Ian Berry is a Clinical Scientist working in the Central Laboratory of the Yorkshire & North-East Genomic Laboratory Hub (Y&NE GLH) in Leeds. He has an interest in developmental disease, inherited cancer and skeletal genetics, and has lead development and implementation of exome sequencing in Leeds for the last six years. His work has particularly focused on the development of informatics

techniques for variant prioritisation and pathogenicity assessment, gene-agnostic analysis methods in singletons, and implementation of rapid exome sequencing for fetal-onset skeletal disorders. He is due to take up a new role as Lead Scientist for Neurogenetics in the Bristol Genetics Laboratory, South West GLH, in February 2021.

Genomic analysis in consanguineous cohorts

Abstract:

Many rapid NGS approaches for rare disease focus on trio or singleton analysis using methodologies developed for patients anticipating a high burden of de novo disease and/or compound heterozygous inheritance of recessive disease variants. In contrast, the disease burden in consanguineous groups is dominated by recessive disease caused by the inheritance of identical-by-descent (IBD) variation, both founder and private. This imposes a number of differences to analytical and clinical practice, which we will explore using our cohort of 250 patients (mostly from Northern England) with early-onset developmental disorders. Key observations from this group include:

- Rare homozygous loss-of-function variation explaining phenotype in the vast majority of explained cases, with significant implications for the efficiency and performance of analytical pathways.
- High incidence of recessive "mimics" of dominant/de novo disorders prevalent in non-consanguineous groups, with significant implications for referral behaviour and differential diagnosis.
- Atypical recessive presentations of genes predominantly associated with dominant inheritance.
- Impacts of this atypical pattern of aetiology on the identification and confirmation of new gene-disease associations.

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THEY ARE INVALUABLE IN INFORMING FUTURE MEETINGS

The forms are included at the end of this booklet and have also been sent to you separately

MANY THANKS

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Dr Sahar Mansour
Professor in Clinical Genetics, St George's Hospital NHS

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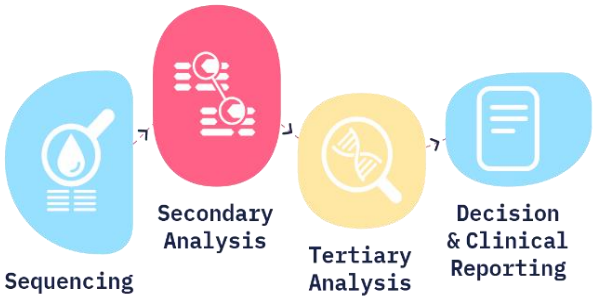

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Rapid NGS Diagnostic Conference

4th & 5th February 2021 **9.30am – 12.30pm each day**

DAY 1 – Thursday 4th February 2021

Evaluation Form

Please evaluate each session giving a mark out of 5 (**5=Excellent, 1=Poor**) and adding any comments or suggestions in the spaces provided.

Session	Mark	Comments
Dr Stephen Kingsmore *Rapid Genome Sequencing…*		
Professor Zornitza Stark *Delivering a national paediatric...*		
Dr Sian Corrin *WINGS Study*		
Dr Julia Baptista *Early testing for acutely ill children…*		
Dr Hywel Williams *Discussion & Day 1 Round-up*		

- **How do you rate the overall quality of the information offered today? Please highlight**

1	2	3	4	5
Poor	Mediocre	Satisfactory	Good	Excellent

- **How do you rate the relevance of today's information to your work needs? Please highlight**

1	2	3	4	5
Poor	Mediocre	Satisfactory	Good	Excellent

- **Will any of today's information have an impact on your work? Please highlight**

1	2	3	4
No, not at all	Not sure	Yes, a little	Yes, a lot

- **Do you think it would be a good idea to hold this event annually? Please highlight**

1	2	3
No	Not sure	Yes

If no, how often do you think it should be held?

Where did you find out about this conference & what do you think is the best way for us to reach interested parties?

If you would like to add comments about the event or make suggestions for future meetings, please use the space below:

Rapid NGS Diagnostic Conference

4th & 5th February 2021 **9.30am – 12.30pm each day**

DAY 2 – Friday 5th February 2021

Evaluation Form

Please evaluate each session giving a mark out of 5 (**5=Excellent, 1=Poor**) and adding any comments or suggestions in the spaces provided.

Session	Mark	Comments
Dr Natalie Chandler *Impact of NGS on prenatal diagnosis*		
Suzanne Drury *Prenatal Diagnosis in the era of Genomic Medicine*		
Nicola Taverner *Clinical aspects of WINGS*		
Dr Isabel Delon *Rapid genomic testing in critically ill children*		
Dr Lamia Mestek-Boukhibar *Use of transcriptomics for undiagnosed patients*		
Joseph Halsted *Rapid whole genome sequence data analysis - Dragen*		
Ian Berry *Genomic analysis in consanguinous cohorts*		

- **How do you rate the overall quality of the information offered today?** **Please highlight**

1	2	3	4	5
Poor	Mediocre	Satisfactory	Good	Excellent

- **How do you rate the relevance of today's information to your work needs?** **Please highlight**

1	2	3	4	5
Poor	Mediocre	Satisfactory	Good	Excellent

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1	2	3	4
No, not at all	Not sure	Yes, a little	Yes, a lot

If you attended yesterday and completed the Evaluation Form, there is no need to fill in the following section again

- **Do you think it would be a good idea to hold this event annually?** **Please highlight**

1	2	3
No	Not sure	Yes

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Many thanks for taking the time to complete the evaluation form.
The information collected will be used to inform future events.

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