The Royal College of Pathologists
Pathology: the science behind the cure

Symposium on Pathology in Wales

Abstracts for programme

Welcome and Introduction
Dr Esther Youd, Chair of the Wales Regional Council

This symposium is aimed at RCPath fellows, members, trainees, medical students and others interested in the range of pathology in Wales. Delegates will hear presentations about the forefront of pathology and share some of the great things going on in Wales. They will meet the President Dr Suzy Lishman, President-Elect Professor Jo Martin and other Honorary Officers and find out what the College does in Wales.

Dr Youd is the Chair of the Wales Regional Council. The Council acts as a conduit for communication between the regions' members and the College headquarters. It monitors local medical and scientific workforce statistics to keep these up to date.

Meeting:	**Symposium on Pathology in Wales**
Lecture Title:	Digital histopathology – the Wales experience
Lecturer Name:	Dr Muhammad Aslam
6 Learning Points	1. Leadership in a major multi-site project, including business case development and key stakeholder buy-in process 2. Technical and process quality in digital pathology implementation, for lab managers and scientists 3. Medical diagnostic learning from the digital pathology implementation and verification process 4. Learning from centralization experience 5. Limitations of digital pathology 6. Future and vision
Abstract	The merging of three North Wales hospitals into a single health board lead to the pathology departments forming a single unit resulting in formulation of one of the largest labs in the country, serving a population of nearly 0.7million. The surgical pathology department supports three acute hospitals, community hospitals and surgeries widely spread in an area of about 6,172 square kilometres, making it slightly larger than the country of Brunei, or the island of Bali. This resulted in introducing geographical, transport, and workload challenges. To address, significant investment was made in IT development, including digital pathology. A scanning system was installed in 2015, and through 2016 a first phase verification study was carried out on 3001 cases, to confirm suitability of digital pathology for routine diagnostics with the support of NHS ETTF. Here we discuss lessons learned from the implementation, and the future of digital pathology in Wales NHS.
References	1.Validating whole slide imaging for diagnostic purposes in pathology: guideline from the College of American Pathologists Pathology and Laboratory Quality Center. Pantanowitz L, Sinard JH, Henricks WH, Fatheree LA, Carter AB, Contis L, Beckwith BA, Evans AJ, Lal A, Parwani AV; College of American Pathologists Pathology and Laboratory Quality Center. Arch Pathol Lab Med. 2013 Dec;137(12):1710-22. doi: 10.5858/arpa.2013-0093-CP. Epub 2013 May 1. Review. 2.The Diagnostic Concordance of Whole Slide Imaging and Light Microscopy: A Systematic Review. Goacher E, Randell R, Williams B, Treanor D. Arch Pathol Lab Med. 2017 Jan;141(1):151-161. doi: 10.5858/arpa.2016-0025-RA. Epub 2016 Jul 11. Review. PMID: 27399211 3.Validation of digital pathology imaging for primary histopathological diagnosis. Snead DR, Tsang YW, Meskiri A, Kimani PK, Crossman R, Rajpoot NM, Blessing E, Chen K, Gopalakrishnan K, Matthews P, Momtahan N, Read-Jones S, Sah S, Simmons E, Sinha B, Suortamo S, Yeo Y, El Daly H, Cree IA. Histopathology. 2016 Jun;68(7):1063-72. doi: 10.1111/his.12879. Epub 2015 Dec 6. PMID: 26409165 4. RCPATH consultation document on digital pathology
Declaration of interest	NIL

Meeting:	**Symposium on Pathology in Wales**
Lecture Title:	The Future of Immunotherapy in Myeloma
Lecturer Name:	Dr Ceri Bygrave
6 Learning Points	1.Overview of Myeloma 2. Difficulty around Cure in Myeloma 3.Why Immunotherapy is applicable to myeloma 4.Monoclonal antibodies - data 5.Other therapeutic approaches 6.
Abstract	Myeloma is an incurable malignant clonal disorder of plasma cells, it is also an example of an immune deficient disease where hypogammaglobulinaemia is a major problem and infection is one of the commonest causes of death. This talk will give an overview of what myeloma is, how it is treated and how treatment has been revolutionised in recent years. It will also discuss the rationale for harnessing the immune system in myeloma in order to improve disease response and outline some of the techniques that have been used to do this.
References	1. Donato et al, Haematologica 2014:4;96:1512-1520 2. Lammerts van Burren et al, Blood 2012:124:3474 3. Dimopoulous et al, NEJM 2016: 375:1319-1331 4. Palumbo et al, NEJM 2016: 375: 754-767 5. Lonial et al, NEJM 2015 6. San Miguel, ASH 2015
Declaration of interest	None

Trainee project 1

Comparing Clinical Decision Making in H&I Laboratories with EQA Interpretative Scenarios

Deborah Louise Pritchard

UK NEQAS for Histocompatibility and Immunogenetics (H&I) has operated an interpretive educational scheme since 2014. Three clinical scenarios are distributed yearly covering solid organ and haematopoietic stem cell transplantation (HSCT) and platelet transfusion. Each case provides clinical information and laboratory findings. Cases require results' interpretation and decisions and advice to be formally reported.

These scenarios allow a comparison of decisions and advice between centres and have been reported by some 70% of H&I laboratories in the UK and Ireland. Responses are not assessed, but are anonymised and shared with participants. Some aspects of the cases have shown excellent agreement, e.g. HSCT unrelated donor selection and HLA matched platelet selection for platelet refractoriness. While others, e.g. HLA specificities to list as 'unacceptable antigens' in kidney transplantation, show more variation.

This scheme aims to improve the quality and consistency of reporting by highlighting difference in H&I practice that could affect patient care.

Trainee Project 2

Genetic Mechanisms in Colorectal Polyposis

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Familial Adenomatous Polyposis (FAP), MUTYH-Associated Polyposis (MAP) and Polymerase Proofreading-Associated Polyposis (PPAP) are syndromes of adenomatous polyposis, and are due to mutations in *APC*, *MUTYH, POLE* and *POLD1*. Up to 90% of patients with a phenotype of typical FAP have a pathogenic *APC* germline mutation identified through sequencing of coding exons and deletion/duplication analysis via MLPA. Of those with an attenuated phenotype, only 10-15% have an *APC/ MUTYH* mutation detected.
The aim of this study is to identify novel constitutional mutations predisposing to multiple colorectal adenomas.

Techniques including ultradeep sequencing, qPCR, cDNA sequencing and whole exome sequencing have been employed. Putative pathogenic variants have been validated in 8 genes, including *APC*.

The results of this study will lead to a better understanding of unusual inherited variants associated with colorectal polyposis. This will allow improved genetic diagnosis, more accurate genetic counselling and optimum clinical surveillance/intervention for affected individuals and their families.

Trainee project 3

Quality improvement in histopathology services: Evaluating effect of short cycle processing on turnaround times for diagnostic H&E slide production.

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Department of Cellular Pathology, Singleton Hospital, Swansea

Purpose of the study: To evaluate the effect on turnaround times of short cycle processing on the production of diagnostic histopathology slides. Short cycle turnaround times were compared with those from standard overnight processing cycles. The aim was to determine whether this could reduce time to produce slides and result in use of processing machines not currently used during the day. This aim is in keeping with lean principles of quality improvement.

Methods: Sixty-two endometrial biopsy specimens were divided into paired samples, which were randomised to standard processing cycles of 12.5 hours versus short cycle processing cycles of 2, 3 or 4 hours. The principal investigators were blind to allocation of each half of the sample. The time and date of specimen receipt in the laboratory was recorded on Trak/LIMS and compared with time and date sent to the pathologist to determine turnaround time in production of slides. Statistical significance was set at a 5% level.

Summary of Results: The greatest reduction in turnaround time was in the 3 hour short cycle processing group which produced slides in 41.3 hours compared with an average standard processing time of 63.1 hours (p=0.026). The 2 hours processing group produced slides in 57.4 hours (p=0.230) and 4 hour processing in 50.3hours (p=0.221).

Conclusions: This study has shown that short cycle processing can decrease time to produce diagnostic histopathology slides. Improved efficiency in laboratory processing is likely to enhance the patient experience through reduced waiting times for diagnosis. The next phase of this quality improvement project is to assess the quality of histochemical and immunohistochemical staining in accordance with published standards.

Meeting:	**Symposium on Pathology in Wales**
Lecture Title:	Medical examiners & changes to death certification
Lecturer Name:	Dr Jason Shannon, Cwm Taf UHB & SRO for Medical Examiner implementation in Wales
6 Learning Points	1. Medical Examiners in Wales will be at the forefront of the Mortality Review System being developed in Wales. 2. Putting Quality Improvement at the centre of the job description for Medical Examiners offers the potential for increased recruitment in an already depleted workforce whilst not detracting from their other statutory duties. 3. Any system which examines deaths in relation to healthcare settings must take into account the role of the Medical Examiner to avoid duplication and conflict.
Abstract	Medical Examiner implementation provides the opportunity to improve death certification and bereavement care in Wales and the UK. In Wales, the mortality review process is well established and the implementation of the Medical Examiner System is complimentary not contrary to its stated aims. The Welsh mortality review system is designed to offer reassurance about most deaths not being linked to the provision of healthcare whilst identifying the minority where improvement opportunities can be identified in an open and transparent way. We aim to use Medical Examiners and their officers in Wales to act as the sieve to determine which cases require further review by Health Boards as distinct from a sampling methodology. The appointment, and terms and conditions of Medical Examiners as well as the fee setting and collection are devolved to Welsh Government (1) and provide potential opportunities to do things in a different way more appropriate to the people of Wales.
References	1. https://consultations.gov.wales/sites/default/files/consultation_doc_files/161107medical-examiners-consultation-documenten_0.pdf
Declaration of interest	I am a Consultant Pathologist with 14 years of experience employed by Cwm Taf University Health Board. I have interests which include autopsy pathology with a role in teaching trainees working towards gaining the Certificate of Higher Autopsy Training. I am both Health Board and National Clinical Lead for Mortality Review with responsibility to Welsh Government and the Welsh Medical Directors. I am Senior Responsible Officer for Medical Examiner implementation in Wales with responsibility to Welsh Government and the Chief Medical Officer for Wales. My national roles are not renumerated.

Meeting:	**Symposium on Pathology in Wales**
Lecture Title:	The Genomics Strategy for Precision Medicine in Wales
Lecturer Name:	RhianWhite FRCPath
6 Learning Points	1. Over the last six months, approximately 120 stakeholders from academia, industry, the third sector, the NHS and the public have attended a series of events across Wales. These events have informed the development of this Strategy. 2. However, it is not, and should not be, a static document. Rapidly emerging technologies will mean that regular review will be required. 3. A steering group will be established to develop a more detailed implementation plan. The group will regularly monitor progress and publish annual reports against key actions highlighted in this Strategy. 4. This Strategy outlines the initial steps necessary to develop the genomics for precision medicine infrastructure in Wales and lays the foundations for the routine application of genomic technologies to support precision medicine approaches in Wales. 5. In doing this, it enables patients and the public of Wales to benefit from better healthcare and underpins a bright future for the application of cutting-edge genomic technologies in NHS Wales.
Abstract	New genetic and genomic technologies have the potential to revolutionise medicine and public health. This Strategy sets out the Welsh Government's plan to create a sustainable, internationally competitive environment for genetics and genomics to improve health and healthcare provision for the people of Wales. In March 2016, the Welsh Government published a Statement of Intent (SoI) outlining the key principles that would underpin the development of a Genomics for Precision Medicine Strategy. Since March, the Taskforce has consulted widely with stakeholders through a series of workshops, focus groups and 1:1 meetings, and feedback and comments from these meetings has informed the development of the Strategy. The Strategy outlines the key initial actions, as part of a 5-10 year plan, that will: • Develop internationally-recognised medical and public health genomics services in Wales – that are innovative, responsive and well-connected to the major genetics and genomics initiatives that are evolving worldwide. • Develop internationally-recognised research in genomics and excellent platforms for precision medicine, with All-Wales leadership and coordination and strong links to clinical genetics. • Be outward-looking, and actively seek out partnerships that can strengthen genomics and precision medicine services and research in Wales, with a focus on those partnerships that will bring the biggest benefits for patients. • Develop the NHS and research workforce in Wales, in recognition that this investment will have the biggest impact on our ability to realise the potential of genomics and precision medicine for patient benefit.

References	1. Welsh Government (2016). Statement of Intent for Genomics and Precision Medicine. http://gov.wales/docs/cabinetstatements/2016/Genomicsstatementofintenten.pdf 2. Welsh Government (2016). Taking Wales Forward. http://gov.wales/docs/strategies/160920-taking-wales-forward-en.pdf 3. Welsh Government (2016). Statement of Intent for Genomics and Precision Medicine. http://gov.wales/docs/cabinetstatements/2016/Genomicsstatementofintenten.pdf 4. NHS England, (2016). Improved outcomes through personalised medicine: Working at the cutting edge of science to improve patients' lives, Leeds. 5. Genomics England, (2015). A Framework for Industry Engagement. https://www.genomicsengland.co.uk/wpcontent/uploads/2015/03/A-framework-for-industry-engagement_march2015.pdf 22 6. European Medicines Agency, (2015). Framework for interaction between the European Medicines Agency and industry stakeholders, London. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500195081.pdf
Declaration of interest	none

Meeting:	**Symposium on Pathology in Wales**
Lecture Title:	Pathogen whole genome sequencing – the Cryptosporidium journey
Lecturer Name:	Rachel Chalmers
6 Learning Points	1. Cryptosporidium is a gastrointestinal protozoan parasite that is transmitted anthroponotically and zoonontically, as well as through food and water, causing a high burden of illness especially in the severely immunocompromised and in young children. 2. Cryptosporidium is an example of a pathogen (protozoan parasite) that is difficult to culture and is present in low abundance, so it presents challenges to the preparation of high quality DNA for whole genome sequencing. 3. The journey started with the publication of just 3 annotated genomes, generated after multiple passage in experimental animals.....not an ideal process for widespread application. 4. New reference genomes are needed to improve the accuracy of annotation and to better represent the genetic variation of the parasite for source tracking and epidemiological investigations as well as discovery of potential new vaccine and therapeutic drug targets. 5. The national Cryptosporidium Reference Unit has developed and improved parasite capture, cleaning and amplification processes that can be applied to Cryptosporidium and related parasites such as Cyclospora, enabling the production of good quality genomes from diagnostic stools. 6. The new genomes have been put to good use for the identification of diagnostic and genotyping markers, and development of specific bioinformatics pipelines for mass sequencing projects that can be used for outbreak investigations.

Abstract	The parasitic protozoan Cryptosporidium is a major cause of moderate to severe diarrhoea globally, causing a high burden of illness especially in the severely immunocompromised and in young children[1.] However, effective drug treatments are lacking and there is no vaccine[2]. Additionally, targeting interventions to limit exposure is complicated by the multiple transmission routes: person-to-person, animal-to-person, and via vehicles such as contaminated food or water. Diagnosis remains limited to presence/absence of the genus with species identification and genotyping available only as reference tests. Improved molecular tools for disease source tracking and epidemiological investigations, as well as discovery of potential new vaccine and therapeutic drug targets, could be enabled by mining genomes but this is hampered by the biology of Cryptosporidium. This parasite is difficult to culture and is present in relatively low abundance in the complex matrix of faecal matter, so it presents challenges to the preparation of high quality DNA for whole genome sequencing. For some years just 3 annotated genomes, generated after multiple passage in experimental animals, were available[3]. New reference genomes are needed to improve the accuracy of annotation and to better represent the genetic variation of the parasite[2]. Here in Wales, at the national Cryptosporidium Reference Unit, we have developed and improved processes enabling the production of good quality genomes directly from diagnostic stools[4], both for Cryptosporidium and other related parasites such as Cyclospora. The new genomes have been put to good use for the identification of diagnostic and genotyping markers, and development of specific bioinformatics pipelines for outbreak investigation, mass sequencing projects, and contribute to the information available for other projects based on mining genomes for potential vaccine and therapeutic drug targets.
References	1. Kotloff KL et al. Burden and aetiology of diarrhoeal disease in infants and young children in developing countries (the Global Enteric Multicenter Study, GEMS): a prospective, case-control study. *Lancet* 2013; 382: 209–22. **2.** Checkley, W et al. Cryptosporidiosis: Global Burden, Novel Diagnostics, Therapeutics and Vaccine Targets. Lancet Infectious Diseases. Published Online September 30, 2014 http://dx.doi.org/10.1016/S1473-3099(14)70772-8 3. http://cryptodb.org/cryptodb/ 4. Hadfield SJ et al. Generation of whole genome sequences of new *Cryptosporidium hominis* and *Cryptosporidium parvum* isolates directly from stool samples. BMC Genomics 2015; 16: 650. https://www.ncbi.nlm.nih.gov/pubmed/26318339 5. Pérez-Cordón G et al. Discovery of new variable number tandem repeat loci in multiple *Cryptosporidium parvum* genomes for the surveillance and investigation of outbreaks of cryptosporidiosis. Experimental Parasitology 169 (2016) 119e128 https://www.ncbi.nlm.nih.gov/pubmed/27523797
Declaration of interest	None

A word from the President and the President Elect
Dr Suzy Lishman, RCPath President & Professor Jo Martin, RCPath President Elect

Dr Suzy Lishman was elected President of the Royal College of Pathologists in 2014, having been an officer for nine years. As President her priorities have been improving two-way communication with members, collaboration with other organisations and political engagement. Suzy is working closely with her successor, Professor Jo Martin, to ensure a smooth handover in November.

Prof Jo Martin is President-Elect of the Royal College of Pathologists. She is a clinical academic pathologist with a specialist interest in gut motility and leads education and training across Barts Health NHS Trust. She was previous NHSE National Clinical Director of Pathology. She is keen to build on the great work in public and member communications, and in getting the great work that pathologists do, and the many skills they offer, recognised more widely.