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Statement: The Ulster Medical Journal is an international general medical journal with contributions on all areas of medical and surgical specialties relevant to a general medical readership. It retains a focus on material relevant to the health of the Northern Ireland population.

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Ulster Med J 2020;**89(1):**1-2

Editorial

The Final Frontier

Dr John Purvis

When I was young, I very much enjoyed reading and watching science fiction – every week, it seemed quite straightforward to dial in warp factor 9 and reach another star in a matter of minutes. The technology varied from programme to programme – jumpgates, stardrives and of course, in the UK, Doctor Who could travel through both space and time, perhaps a little unreliably but always with great charm. Maybe when I grew up, I might also travel to the stars.

The Apollo programme certainly gave some encouragement as grainy images were beamed from the surface of the Moon. Many were optimistic. After all, wasn't it just 66 years from the flight of the *Kitty Hawk* to the landing of the lunar module *Eagle* in 1969? Where would we be after 100 years or 150 years?

There were some problems however, lunar dust is jagged and sharp to a level not seen on Earth where wind and wave smooth away the edges. Static electricity also causes the dust to adhere to everything and it wasn't long before the lunar astronauts reported respiratory issues and the joints in their spacesuits began to seize as the dust seeped in.

On the way to the Moon, the astronauts also reported occasional bright flashes of light even when their eyes were shut. We now know this was due to cosmic rays – high energy ionized atomic nuclei flung off at near light speed by neutron stars, galactic cores and supernovae explosions as well as our Sun- most of these are hydrogen nuclei – protons - but some are much heavier atoms and have considerable potential for cellular damage as they power through our insubstantial bodies on their cosmic journey. We often think of space radiation exposure in terms of medical X-rays but its more like standing inside the particle accelerator at CERN.

Its now 2020 and NASA has discounted a 3-year journey to Mars in favour of developing a programme for sustainable missions to the Moon. I think this is a wise choice – we really know very little about how the human body can survive out there.

A Mars mission would entail potentially lethal exposure to solar particle and radiation storms – the Apollo crews were fortunate that their missions took place during a quiet phase of the Sun's 11-year activity cycle – the odds for a long Mars return trip are not so good. The spaceship's ability to recycle water and oxygen, scrub CO2 and deal with human waste would need to be superb – not many spare parts out there! Humans also expire significant quantities of ammonia and methane which can become toxic in an enclosed environment over time unless chemically scrubbed.

We don't have the capacity to build centripetal sections or a gym into any potential Mars vessel which means that the astronauts would have to physically adapt from years of zero-G to a full Martian 1/3 G on landing – they might have to spend days in their craft acclimatising before they could walk on the Martian surface.

The plan for the Moon is to build a smaller version of the International Space Station (ISS) called the Gateway in an orbit that covers the entire surface of the Moon. From the Gateway, reusable landers can be dropped down anywhere on the lunar surface. Its hoped that robotic missions could land some habitation and infrastructure modules to gradually build up a Moonbase in the same way that the ISS was assembled. If things go wrong or there is a medical emergency, evacuation from the Moon should be possible in 2 or 3 days whereas once set in orbit, a Mars mission would be committed to the entire flight – no coming back for a kidney stone.

An opportunity arose in 2015 for NASA to investigate some of the medical aspects of a long-term mission when 50-year old veteran astronaut, Scott Kelly undertook a year-long stay (340 days) on the ISS. His identical twin brother, Mark who had a similar career stayed on Earth and served as the control.[1]

It was fully appreciated that this is a study with 1 subject in each arm but of the 533 people who have flown in space – few have had available identical twins!

It should be stressed that the ISS orbits within the Earth's magnetic field which is an effective shield against radiation and high energy particles. Nevertheless, Scott accumulated an effective dose of 146.34 mSv equivalent to 54 years of background exposure in the UK or 22 CT scans of the chest.[2]

The twins submitted themselves to extensive blood, saliva, excretory, opthalmological and cognitive tests. NASA divided the results by potential risks to the astronauts.

LOW RISK

Immune function as measured T-cell response by a flu vaccination was well preserved during spaceflight. Chromosome telomeres lengthened in flight which is suggestive of decreased risk of aging, chronic disease and cancer but the authors speculated this might reflect the intense exercise regimen and healthy diet provided on station – Scott's brother on Earth didn't follow the same regimen. Changes in gut microbiota were relatively minor.

MEDIUM RISK

There was increased urinary excretion of collagen components in flight suggesting loss of connective and support tissue in microgravity.

Microgravity is associated with hypernatraemia, risk of dehydration and kidney stone formation – Aquaporin 2 (AQP2) is a protein that regulates water reabsorption in the kidneys –urinary levels were elevated in flight and may prove a useful marker in the future for identification of astronauts at risk.

Although chromosome telomeres lengthened in flight, they tended to *persistently shorten* on return to Earth suggesting increased risk of aging, chronic disease and cancer.

HIGH RISK

About 40% of astronauts have reported problems with their vision during or after flight – this is of significant concern to NASA. Intravascular fluid shifts cranially in microgravity leading to optic disc oedema, globe flattening, choroidal folding and retinal cotton wool spots. NASA calls this Spaceflight Associated Neuro-ocular syndrome (SANS). It is thought to get worse with repeated exposure – Scott showed additional changes during this mission. In some astronauts, the changes are irreversible.

Lack of gravity induces a shift of body fluid towards the head, this is associated with a reduced blood pressure but increase in cardiac output. Vascular stiffness and carotid intima/media thickness increased associated with vascular disease – long term consequences are uncertain.

Finally, Scott exhibited some impairment of judgement in tests performed post-flight. These recovered, but NASA has concerns that a crew landing on Mars after a long journey may be both physically weakened and cognitively impaired at first.

CONCLUSIONS

Overall, it looks as though long duration human spaceflight may be more hazardous than we initially thought. My boyhood dreams have faded, perhaps I should learn to love the Earth a bit more instead.

FINAL THANKS

As this is my last Editorial, I wish to thank my Editorial Assistants, Marie and Kathy, my sub-editor, Mary Crickard and my contacts at Dorman and Sons, Peter and Mike. Thank you to my predecessors, Professors Barry Kelly and Patrick Morrison for their valuable insights and finally thank you to the UMJ Editorial Board and UMS Council for giving me the wonderful opportunity of editing UMJ for the last 5 years.

John Purvis

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We pass on our sincere thanks to all our referees for 2019

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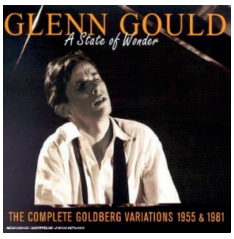
Book Case

PROFESSOR PASCAL MCKEOWN PICKS SOME PIANO WORKS

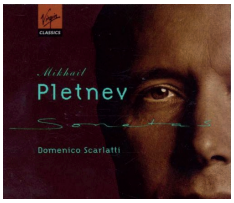
There is something profoundly therapeutic about sitting at a piano and playing music. Cristofori (1655-1731) from Padua is credited with the development of the modern piano. Prior to this, the main keyboard instruments were the harpsichord and the clavichord. As such, whilst these recommendations relate to 'piano works', you may find it interesting to explore recordings of these pieces on other instruments.

JOHANN SEBASTIAN BACH (1685-1750): GOLDBERG VARIATIONS



This piece was originally written for the harpsichord. As it is one of the most recorded of Bach's works, which one should you choose? Possibly Glenn Gould who recorded it twice but at very different tempi – the 1955 recording lasts just over 38 minutes, whereas the 1981 recording lasts 51 minutes! If you listen closely you may also hear Glenn Gould humming along. Alternatively, Rosalyn Tureck's masterful recording is played at a very slow pace (just over 90 minutes). Indeed, Jacque Loussier's jazz trio has also made a recording of it and there are other transcriptions of this work for string quartet or orchestra.

DOMENICO SCARLATTI (1685-1757): SONATAS



Scarlatti is reported to have written over five hundred sonatas for the harpsichord. They demonstrate amazing inventiveness. The broadcaster and music writer, Jeremy Siepmann, has stated: '..in the main the fast sonatas are dominated by the dance… while the slower ones derive their rhythmic character from the nature and span of human breath, and have much of their inspiration in song'. My suggestion is to listen to a selection of these sonatas in the remarkable recording by Mikhail Pletnev.

JOHN FIELD (1782-1837): SONATAS

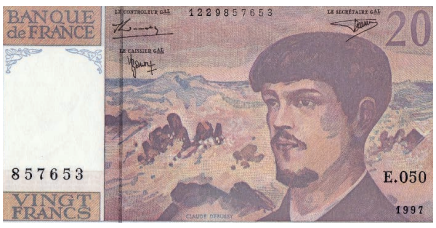
Field is credited with the development of the 'nocturne' - interestingly, he even gets a mention in Tolstoy's War and Peace. However, I recommend his Sonatas, in particular in the recording by the Irish pianist, Miceal O'Rourke.

FREDERIC CHOPIN (1810-1849): WALTZES

Chopin wrote mainly for the piano and composed a wide range of pieces, including mazurkas, waltzes, preludes, nocturnes, and sonatas. He was greatly influenced by his Polish roots and by the Irish composer, John Field, in particular with regard to the development of the nocturne. His collection of waltzes is a wonderful display of virtuosity – you may already be familiar with the so-called 'Minute' waltz as it is used as the theme tune for the BBC Radio 4 programme 'Just a Minute'.

CLAUDE DEBUSSY: (1862-1918): PRELUDES

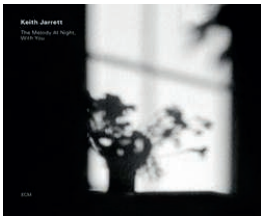
Debussy published his first book of preludes in 1910, with individual pieces based on legends, poems and quasi-religious themes. As an introduction to this music you may wish to consider 'La fille aux cheveux de lin' (The girl with the flaxen hair) or 'La cathedrale engloutie' (The submerged cathedral).



DMITRI SHOSTAKOVICH (1906-1975): 24 PRELUDES AND FUGUES

In 1950, Shostakovich visited Leipzig to take part in a festival of Bach's music. At that time it was not common for Soviet musicians to travel abroad. However, this visit to Leipzig, where Bach had spent a large period of his life and written the second part of his Well-tempered Clavier (a set of pieces in all twenty-four major and minor keys), inspired Shostakovich to compose a very different set of preludes and fugues.

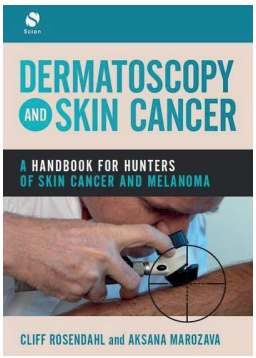
KEITH JARRETT (1945 -): THE MELODY AT NIGHT, WITH YOU



Keith Jarrett is a composer who is internationally renowned for his jazz music as well as his recordings of classical music. In this album he has recorded improvisations from a wide range of sources. My personal favourite is his transcription of the traditional American folk song, Shenandoah.

Book Reviews

DERMATOSCOPY AND SKIN CANCER: A HANDBOOK FOR HUNTERS OF SKIN CANCER AND MELANOMA



Cliff Rosendahl and Aksana Marozava. First edition. Banbury, UK: Scion Publishing Ltd; 2019. 386 pages. ISBN 9781911510338. RRP £37.99.

Dermoscopy (sometimes referred to as dermatoscopy) has become a well-established tool for skin lesion assessment in secondary care. It is becoming more commonplace in primary care, yet training for many clinicians can be largely self-directed. This new textbook provides an invaluable resource for new and improving students of dermoscopy both to read and reference. It offers a methodical and comprehensive guide to understanding dermoscopy and using it to assess skin lesions.

The authors intentionally concentrate on the recognition of skin malignancies and are practical in focus; they provide instruction for clinicians on the systematic examination of the skin, and on dermoscopy decision aids to assist in determining how lesions should be safely and appropriately managed.

As a student of dermoscopy myself, I found two features of the book particularly commendable.

First is its simplicity: the writers assume no previous familiarity with dermoscopy, but begin by thoroughly addressing the fundamentals of the science behind dermoscopy and skin microanatomy. They clearly define the terms used to describe dermatoscopic findings, helping the novice to understand and adopt terminology used in the field.

Secondly is its images: the range of high quality pictures is impressive, and paired dermatoscopic and clinical photographs of the same lesions allows readers to compare the salient features from both perspectives. The large number of images allows an appreciation of the variation that exists between lesions of the same diagnostic type, which is important in preparing for dermoscopy use in clinical practice.

Later chapters discuss the specific dermatoscopic features of many types of lesions, and are admittedly more complex, but these are not essential material for the successful use of the simpler dermoscopy decision aids. For novices or generalists whose everyday practice does not include large volumes of skin lesions, these chapters are useful for reference but may be more difficult to fully absorb.

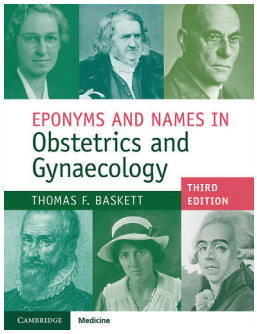
The attention given to some benign lesions is more limited, but this is admittedly not the primary purpose of the authors, whose main focus is skin cancer. Therefore while an excellent book for generalists, those wishing to become dermoscopy experts may wish to consult additional texts. However, the breadth of material included and the clarity of writing have created a book that I suspect will be highly influential in its field, with the potential to become a standard reference for students of dermoscopy.

Dr Jonathan Fee

General Practitioner

Dr Fee has collaborated with Cliff Rosendahl in secondary research.

EPONYMS AND NAMES IN OBSTETRICS AND GYNAECOLOGY



Thomas F Baskett, 540 pages, Publisher: Cambridge University Press 2019, ISBN 978-1-108-42170-6, RRP £ 99.99

Throughout the history of medicine, eponyms have been used to honour the individuals who played a major role in identifying either anatomical structure, pathophysiology of a disease or discovering a new technique. Very few specialties have a more extensive eponymous background than obstetrics and gynaecology although the fascinating work done by the great individuals behind those names is often forgotten or unappreciated. Thomas F Baskett fills this gap by uncovering the stories behind some of the greatest figures in the specialty in whose steps we follow through his book " Eponyms and Names in Obstetrics and Gynaecology.

Educated at Belfast Royal Academy and graduated from Queens University Belfast in 1964, Thomas Baskett emigrated to Canada in 1970. In addition to working as the professor of Obstetrics and Gynaecology at Dallhousie University in Halifax, he has served as president of the Society of Obstetricians and Gynaecologists of Canada and the Canadian Gynaecological Society. His interest in history of medicine developed in 1990s leading to completing the Diploma in History of Medicine from the Worshipful Society of Apothecaries of London in 1997 and he was the 2008 History Fellow of the American College of Obstetricians and Gynaecologists.

Eponyms and Names in Obstetrics and Gynaecology brings a human touch back to the specialty and provides due recognition to the pioneers in the field. The book makes the names of some of the significant characters memorable through the context and portraits provided. This is one of the two books he published on the subject and is the only one currently available.

The book provides biographical data as well as the outline of the work of 391 pioneers in the field of obstetrics and gynaecology and related specialties such as paediatrics from 34 countries. Not only the outline of work, quotations from

the original work giving an insight into the language used in different eras are also included with a portrait or photograph of the individual and related instrument when appropriate. Where available, the original and related references are provided with a bibliography of linked references to assist readers interested in more details on individual subjects.

It has been enlightening to read the stories behind some of the famous names and procedures in the field of obstetrics and gynaecology, ranging from Apgar score, Bandl's contraction ring, Burns Marshall Manoeuvre, Fits-Hugh and Curtis syndrome, Sheehan's syndrome to Wertheim's hysterectomy. This book provides an insight into the evolution of the specialty not many doctors in training are familiar with, and this would definitely be a guide to whoever is interested in making their teaching sessions to trainees or medical students more entertaining.

Dr Janitha Costa

Consultant Obstetrician.

Game Changers

THE ERA OF MANAGEMENT OF COLORECTAL LIVER METASTASES

Mr Gareth Martel, Mr Tom Diamond

Department of Hepatobiliary Surgery, Mater Hospital, Crumlin Road, Belfast BT14 6AB

Colorectal malignancy represents the second most common cause of cancer related mortality in the UK. The majority of mortality relates to metastatic disease, most commonly colorectal liver metastases (CRLM)[1].

For several decades it has been recognised that CRLM do not necessarily equate incurable disease. Previous resection criteria required low burden disease limited to one lobe. This is no longer the case; the gloves are off when it comes to liver metastases.

There are two simple criteria for CRLM resection. Resection must be technically feasible with adequate margins and sufficient remnant liver (minimum 30% volume) and the patient must be fit enough to undergo liver resection. Even where there is unlikely to be sufficient remnant volume this does not preclude the possibility for resection. Techniques including chemotherapy to reduce tumour burden, ablation for small lesions and portal vein embolization to produce future liver remnant hypertrophy are used to render more advanced disease operable. Even CRLM with low burden lung metastases can be resected in combination with lung resection, with good reported outcomes[2]. Where curative treatment is not possible selective internal radiation therapy (SIRT) can offer excellent palliation.

5 year survival rates following CRLM resection are reported as high as 48%[3]. When disease recurs the criteria for further resection remain the same, with excellent outcomes reported from repeated resection. Ultimately we are entering a new era in the management of CRLM; no longer should development of CRLM be considered a terminal event as we attempt to cure or convert this into a chronic condition.

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EPICARDIAL ACCESS FOR VENTRICULAR TACHYCARDIA ABLATION – A BUBBLE IN THE LAGAN?

Dr Nick Cromie

Department of Cardiology, Belfast City Hospital, Lisburn Road, BT9 7AB

Scar related ventricular tachycardia (SRVT) is a significant cause of morbidity and mortality in patients with structural heart disease. While implantable cardioverter-defibrillators have been shown to be effective in preventing sudden death due to ventricular arrhythmias, they are not able to prevent recurrent episodes, but rather treat these arrhythmia when they occur. Antiarrhythmic drugs have demonstrated some efficacy in preventing VT. SRVT ablation is often the only treatment option in patients in whom medications are not tolerated or are ineffective.

SRVT can originate from the surface of the heart (endo or epicardial) or be midmyocardial. Endocardial SRVT can be approached for ablation via the transvenous or intra arterial route, however epicardial access is more difficult. Traditional epicardial access is obtained percutaneously using a subxiphoid or transpericardial puncture to obtain access for a guide wire in which to insert a steerable sheath. Due to the moving heart and small epicardial space major complication rates are high (reported at 5% in high volume centres).

The transcoronary vein exit procedure was recently described by Silberbauer et al.[1] Coronary vein exit into the pericardial space is achieved using a stiff coronary artery wire. A microcatheter is then passed over the wire into the pericardial space to facilitate CO2 insufflation. The CO2 creates an air gap or 'bubble' that is easily visualised under fluoroscopy. Subsequent percutaneous subxiphoid anterior access, using a microneedle puncture, is then achieved reliably and safely.

Did this 'bubble' come up the Lagan, I think not!

1. Coronary Vein Exit and Carbon Dioxide Insufflation to Facilitate Subxiphoid Epicardial Access for Ventricular Mapping and Ablation: First Experience. Silberbauer J, Gomes J, O'Nunain S, Kirubakaran S, Hildick-Smith D, McCready JACC Clin Electrophysiol. 2017 May;3(5):514-521

Ulster Med J 2020;**89(1):**7-10

James Logan Prize Essay

The Challenges of Managing Bone Pain in Cancer

Carenza Glithero

Accepted: 9th September 2019

PREFACE

James Alexander Logan, a second-year medical student at the Barts and The London School of Medicine and Dentistry, died in February 2001 after a painful illness. A Trust was set up in his name in 2003 to promote education in the recognition and treatment of cancer pain and it provided funds for an annual essay prize, open to those undergraduate medical students of Queen's University, Belfast, who had completed their fourth year palliative care teaching. The first competition took place in 2010 and the winning entry appeared in the Ulster Medical Journal in 2011.

The Trust itself was dissolved in 2014 but the essay prize continues and the Trust's website can still be accessed at http://www.jameslogantrust.org.uk/

INTRODUCTION

With advances in cancer treatment significantly improving survival, it is increasingly vital to consider the impacts on the quality of life experienced by cancer patients. One factor is pain, with bone pain the most common cause among cancer patients.[1,2] Bone pain typically results from metastases, especially from lung, breast, kidney and prostate cancer.[1] Up to 70% of patients with advanced cancer have bone metastases, however only a third will be symptomatic.[3-5] The presence of bone metastases confers a poor prognosis with median survival of several months.[6]

Bone cancer typically results in a constant baseline pain punctuated by intermittent episodes of severe pain.[1,4] While the pain may be non-specific, occurrence at night, at rest, or on movement should raise the index of suspicion and provoke further investigation.[7] Episodic or incident pain may occur spontaneously or be provoked by moving or bearing weight on the affected bone.[1,4] In up to 55% of cancer patients bone pain is undertreated, resulting in additional suffering for patients with a limited life-expectancy.[8]

This essay will review the challenges of managing bone pain in cancer, reviewing the mechanisms involved, current available therapies and ongoing issues in management.

BONE PAIN IN CANCER

The underlying mechanisms behind the generation and maintenance of cancer-associated bone pain are complex, and a lack of understanding has long hindered the management of affected patients.[9] Bone pain in cancer has both an inflammatory nociceptive and a neuropathic element.[1,4] Metastases to bone alter the normal balance between resorption and formation, causing subsequent changes in the peripheral and central nervous systems.[4,10]

Cancer cells promote bone destruction through the expression of κ-B ligand (RANKL) which binds to RANK receptors on osteoclasts, promoting their differentiation into mature osteoclasts.[1,2] The osteoclasts then resorb bone via an acidic resorption zone, resulting in pathological fractures, hypercalcaemia and severe pain to the patient via the stimulation of TRPV1 and ASIC3 channels expressed by nerve fibres.[1,9,11]

Continuous peripheral stimulation promotes neuroplastic change in the dorsal root ganglion neurones, increasing sensitivity and lowering the pain threshold, resulting in hyperalgesia.[2] Inflammatory mediator release stimulated by the tumour cells further contributes to sensitisation of peripheral nerve endings.[2,4] Direct damage to nerve endings by cancer invasion compounds the neuropathic component of cancer bone pain.[4]

Bone metastases weaken bone and leave patients prone to fractures.[2] These result in sudden and severe pain and may significantly impair patients' mobility. Patients may also experience stress fractures, which are commonly missed clinically and difficult to control pharmacologically.[2]

ASSESSMENT

Inadequate assessment is one of the most commonly reported factors in the undertreatment of cancer pain.[5,12,13] The assessment of a patient with cancer bone pain should include a detailed pain history and the use of a structured pain assessment tool, such as the visual analogue scale or numerical rating scale.[14] The impact on the patient's life of the pain should also be explored, in addition to previous analgesic use and the patient's choice.[14] Where appropriate, an examination may be carried out to identify areas of tenderness indicative of the source of pain.[14] Investigations must be considered in the context of the patient's condition; only those which are likely to alter management should be performed and, in patients nearing the end of life, only if the pain may be due to a reversible cause.[14]

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MANAGEMENT

The World Health Organisation recommends a three-step ladder to treat cancer pain, according to the intensity of the pain.[15] Firstly non-opioids (aspirin, non-steroidal anti-inflammatory drugs (NSAIDS), paracetamol), then mild opioids (codeine), followed by strong opioids (morphine) if required.[15,16] The ladder also promotes the use of adjuvants at all stages where indicated for neuropathic pain or other symptoms, and a 'step up, step down' approach to changes in pain intensity.[16] Despite being generally efficacious, pain in many bone cancer patients cannot be adequately controlled using this approach.[2]

Several systematic reviews have found that while paracetamol is well tolerated, it does not provide any significant analgesic relief in cancer pain, especially when added to strong opioids.[4,17,18] However, no subgroup analysis on cancer induced bone pain was performed in these studies.[4]

Given the major role of inflammation in cancer induced bone pain, it is reasonable to assume that NSAIDs would be particularly efficacious compared with other pain syndromes, however to date the evidence for this is limited.[4,17,19] Side effects including gastric ulcers and nephrotoxicity limit the clinical use of NSAIDS.[2]

Systematic reviews of the use of Tramadol and Codeine in cancer pain found minimal if any benefit, with significant nausea and vomiting associated with tramadol.[20,21] Again, there was no subgroup analysis for bone pain, and it is common to miss this step in the analgesic ladder with cancer induced bone pain and to progress directly to low dose strong opioids.[4]

Several small randomised trials found no difference in either the efficacy nor side effects between intermediate and standard release morphine.[22] Opioids commonly cause constipation, so co-prescription of a laxative should be considered.[4] Alternatively, transdermal opioids may be used which are less likely to cause constipation.[4] Around 75% of patients with cancer pain achieve good analgesia with strong opioids.[4,23]

Incident pain is more difficult to control.[4] The timing of analgesia is challenging since the pain manifests within 5 minutes and in around half of patients resolves within 15 minutes.[4] Fast acting fentanyl preparations provided statistically superior analgesia when compared with oral morphine in a meta-analysis of the management incident pain.[4,23] However, due to the higher number needed to treat (18 compared with 12) and greater cost they are currently recommended as a second line treatment, if intermediate release morphine fails.[4,24]

The use of adjuvant drugs including anti-depressants and anti-convulsants may enhance analgesia with strong opioids, especially in patients with an element of neuropathic pain.[4] However the current evidence is of poor quality and provides insufficient evidence on the efficacy and associated side effects.[4,25,26] Two randomised controlled studies have found no sustained analgesic benefit from the use of steroids in cancer pain.[4,27,28] There is currently insufficient evidence to support the use of lidocaine patches in bone pain in cancer.[4]

Radiotherapy is the gold standard for pain relief in symptomatic bone metastases.[29] A systematic review found 60% of patients experienced a meaningful reduction in bone cancer pain, with 25% being pain free.[30,31] These results were achieved with both single and multiple dose radiotherapy, meaning that a single dose can provide effective pain relief with minimal side effects in frail patients.[4]

Studies investigating metastasises to bone, especially from prostate cancer, have found that radioisotopes may be beneficial in palliation of diffuse bone cancer pain.[4] However, severe adverse effects including leukocytopenia and thrombocytopenia were common.[4,32-34]

Bisphosphonates reduce cancer-related bone pain and complications by inhibiting the function of osteoclasts.[1,4,35] A 2002 Cochrane review examined the evidence for the use of bisphosphonates in pain secondary to bone metastases.[36] While bisphosphonates provided some analgesic benefit, it was inferior to that of strong analgesics or radiotherapy, and as such the report recommended the use of bisphosphonates only where palliation and radiotherapy were insufficient to control a patient's pain.[36]

Novel agents including Osteoprotegrin and Denosumab inhibit osteoclast function by preventing the binding of RANK to its ligand, the stimulus necessary for osteoclast proliferation and maturation.[1,37] Multiple studies have demonstrated reduced osteoclast function, tumour-related fractures and bone cancer pain with both bisphosphonates and RANK targeting therapies.[1,9,37-40]

Prophylactic fixation of metastatic bone lesions can provide good long-term palliation of pain and maintenance of function in patients with a good performance status.[4,41] Functional outcomes are superior with prophylactic fixation compared with stabilisation after fracture, and patients who may benefit can be identified with either the Mirel's criteria.[4,42-44] Furthermore, some bone primary tumours and metastases may be excised with curative intent.[44]

A Cochrane review of acupuncture in cancer pain identified some studies demonstrating pain reduction, however none were large enough nor sufficiently well-designed and the report concluded there was insufficient evidence to assess efficacy.[4,45] There was also insufficient evidence to recommend the use of TENS (transcutaneous electrical nerve stimulation), although one small feasibility study

demonstrated reduced verbal pain scores in cancer bone pain with TENS compared with placebo.[4,46]

CONCLUSION

The range of subtypes of bone pain in cancer patients, its changing nature and varied incidence complicate pain management. With limited understanding of the nature of bone pain, the lack of high quality evidence on the efficacy of many treatments and difficulty of balancing analgesic benefit with the side-effects of such therapies, treatment decisions are challenging. However, with adequate assessment and a multifaceted approach, pain management can be optimised to improve the quality of life of cancer patients.

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Grand Rounds

Critical Care Neurology for Junior Doctors; Four Key Management Strategies

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INTRODUCTION:

As with all acutely unwell patients, the management of those with neurological insults should focus on promoting adequate oxygenation and perfusion to the compromised organ system. Brain injuries can be classified as either primary or secondary and can be ischaemic, traumatic, metabolic, inflammatory or multifactorial in aetiology. Prior to implementing targeted treatment based on a specific cause however, it is important to know how to provide general neurological protection. This protection involves improving oxygenation and perfusion of brain tissue and relies on four main management strategies: 1) Maintaining mean arterial pressure, 2) Reducing intracranial pressure if raised, 3) Optimising oxygen delivery and 4) Reducing oxygen demand. This article will adopt a case study and explore underlying physiology to illustrate how intensive care principles for neurological protection can be used in a ward-based environment by any junior doctor.

CASE SCENARIO:

A 27-year-old male presents to the Emergency Department with lethargy, vomiting and a widespread non-blanching maculopapular rash. He is diagnosed with bacterial meningitis and is treated with appropriate antibiotics and steroids. He later complains of headache and has one tonic-clonic seizure. On examination he is drowsy, confused and his left pupil is dilated and non-reactive to light. His observations are as follows; blood pressure 86/45mmHg, heart rate 110bpm, temperature 38.7°C and oxygen saturations 86% on room air. How should a clinician approach the management of this critically unwell man? Using the steps outlined below one can protect against further neurological damage by using simple measures to promote adequate blood and oxygen supply to the brain.

1. MAINTAINING MEAN ARTERIAL PRESSURE:

Considering that perfusion to the brain relies on the cerebral perfusion pressure (CPP=MAP-ICP), it is usually reasonable to assume that optimising the mean arterial pressure should lead to an increase in cerebral perfusion.[1] Cerebral perfusion pressure should be maintained between 60mmHg-100mmHg, but as it is not feasible to calculate this exactly in a ward environment it is important to understand and apply the main principles of the equation. As mean arterial pressure is calculated using the systolic and diastolic blood pressures (MAP=SBP+2DBP/3), it is also safe to assume that by manipulating blood pressure you can increase the mean arterial pressure, to a target of over 65mmHg.[2] Therefore the key to management of this critically unwell patient is to monitor the blood pressure and treat any identifiable cause of hypotension, such as hypovolaemic shock (e.g. gastrointenstinal blood losses), distributive shock (e.g. sepsis, neurogenic shock), obstructive shock (e.g. tamponade, pulmonary embolus) and cardiogenic shock (e.g. myocardial infarction, cardiac failure). By administering intravenous fluids, packed red cells, antibiotics or by treating a tamponade or myocardial infarction you can increase the mean arterial pressure, thereby increasing perfusion to the brain and providing critical neurological support.

2. REDUCING INTRACRANIAL PRESSURE:

An equally important component of cerebral perfusion regulation is an appropriate intracranial pressure. The Monro-Kellie doctrine states that the skull is a rigid compartment with three main components of blood, cerebrospinal fluid and brain tissue, each of which can increase or decrease in volume to a certain degree without causing significant rises in intracranial pressure.[3] However, when such compensatory mechanisms are overwhelmed, intracranial pressure can rise, causing compression of arterioles and consequently a reduction in cerebral perfusion. Intracranial pressure should ideally be less than 15mmHg, but on a ward having this specifically monitored is not practicable. It is therefore crucial to recognise symptoms and signs of rising intracranial pressure (Figure 1) which include but are not limited to; headache, vomiting, visual disturbance, absence of pupillary reaction to light and perhaps most importantly, altered mental status. If one recalls the equation for cerebral perfusion pressure, treatment of increased intracranial pressure can salvage the brain tissue from the effects of hypoperfusion. Temporary reduction in intracranial pressure can be achieved

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by using hypertonic saline or mannitol but ultimately treatment must address the underlying cause such as surgical debulking of cerebral metastases or treatment of meningitis with antibiotics. Knowledge and application of the principles of the cerebral perfusion pressure equation can allow for general protective measures to be instigated whilst definitive therapy is awaited.

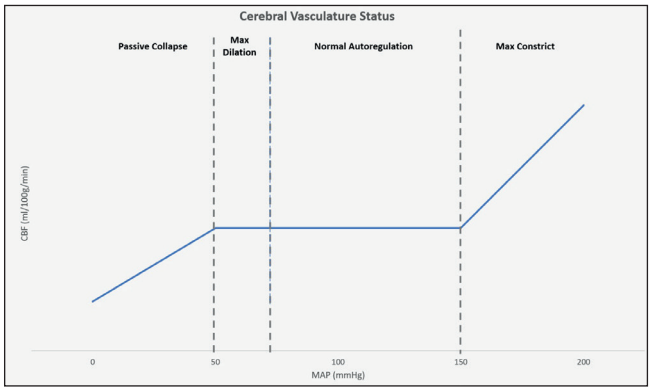

Figure 1: Graph displaying relationship between mean arterial pressure, cerebral blood flow and autoregulation of cerebral vasculature.

3. INCREASING OXYGEN DELIVERY:

In addition to perfusion, oxygenation is another essential component of critical neurological support. As above, using a simple equation can demonstrate how manipulation of various physiological processes can equip junior doctors with the key principles to maintain oxygen supply to the brain. The oxygen delivery equation can guide our management here as it lists some key components that can be manipulated on the ward;[4]

$DO2=CO \times (1.34 \times Hb \times SaO2 + (PaO2 + 0.003))$

DO2 is oxygen delivery

CO is cardiac output

1.34 is the oxygen binding capacity of haemoglobin

Hb is haemoglobin in g/l

SaO2 is haemoglobin oxygen saturation

PaO2 is partial pressure of oxygen

0.003 is the amount of dissolved oxygen in blood.

It is not essential to remember the specifics of the equation, however the understanding that cardiac output, haemoglobin level and oxygen saturation contribute to oxygen delivery allows the junior doctor to take ward-based actions that can improve oxygenation of vulnerable brain tissue. Cardiac output relies on heart rate and stroke volume, therefore using vasopressors or increasing preload with volume expansion can increase this. Transfusion of packed red cells to increase haemoglobin if anaemic or in the setting of acute blood loss as well as providing supplemental oxygen if saturations are low are other ways of increasing oxygenation. These are simple measures that can be taken by applying the principles of the oxygen delivery equation.

4. REDUCING OXYGEN DEMAND:

To ensure appropriate oxygenation to the brain one must also consider any increased oxygen demands that are present at the time of insult. These include fever, seizures, anxiety, agitation, pain, shivering and excess stimulation. A sensible approach reducing oxygen demand is to reduce stimuli, particularly in the first 24-48 hours of the injury. Antipyretics can be given and targeted temperature management (maintaining body temperature between 32 and 36 degrees Celsius) may be employed in situations such as in post-cardiac arrest.[5] Anticonvulsants may be required if seizures are present, including the use of benzodiazepines to terminate status epilepticus. Patients often require sedation if distressed or agitated and investigations must be undertaken to establish the cause, for example inadequate control of pain. In summary one should be mindful about any bodily processes that are energy-requiring and potentially superfluous and bring about their minimisation where possible, to reduce their effect of the oxygen demands of the brain.

5. WORKED CASE SCENARIO:

If we return to the above case of bacterial meningitis, we can see that each of the four principles can be applied here in order to maximise perfusion and oxygenation of brain tissue. The patient has a reduced mean arterial pressure, the underlying cause likely being vasodilatation from sepsis-induced bradykinin and prostaglandin release. He is also exhibiting signs of increased intracranial pressure, this likely arising from vasogenic oedema caused by inflammation of the meninges. He has also dropped his oxygen saturations due to an imbalance of delivery and demand. We can therefore increase perfusion to his brain by giving intravenous crystalloids to expand his intravascular volume. Prescription of mannitol might also be considered upon consultation with senior colleagues in order to reduce his intracranial pressure whilst being wary of dropping his blood pressure further. We can increase his oxygenation by giving supplemental oxygen through a non-rebreather mask and can reduce his oxygen demands by controlling his pyrexia with paracetamol and his seizures with anti-epileptic medication. These measures can be implemented on the ward whilst awaiting senior support and can be crucial in preventing irreversible neurological damage and potentially life-altering consequences.

CONCLUSION

Using the above principles and treatment strategies, junior doctors can feel empowered to employ basic measures to improve oxygenation and perfusion to the brain, thereby protecting it whilst waiting for senior advice on definitive management. To improve perfusion to the brain we must consider mean arterial pressure and intracranial pressure and to improve oxygenation we must increase delivery and reduce demands. These four key strategies can be utilised on the ward, by any junior doctor and in doing so can protect

this vital organ in the critically unwell patient whilst awaiting further support.

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Short Report

Natural history of a fibrous cephalic plaque and sustained eight decade follow-up in an 80 year old with tuberous sclerosis complex type 2.

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ABSTRACT

Introduction: Fibrous cephalic plaques (FCP) are a characteristic manifestation of tuberous sclerosis complex (TSC) and occur in one third of cases. Their natural history and long term course is unknown, as is the outcome of long term follow-up of TSC cases in old age.

Phenotype and methods: We describe an 80 year old with TSC due to a c.2784dupC TSC2 mutation, who was diagnosed in infancy with an FCP and was regularly followed up at the TSC clinic over 8 decades with regular epilepsy treatment and renal monitoring.

Results: Regular clinical photography and clinical records document the plaque at different ages. The FCP naturally resolved at 74 years. Facial angiofibromas also faded with time in the last decade. His epilepsy and renal abnormalities remained under control with careful surveillance and monitoring.

Discussion: Natural aging in the eighth decade causes progressive laxity of collagen and leads to natural resolution of FCPs. This novel finding with a unique 80 year follow up yields valuable insights into the aging changes within FCPs and facial angiofibromas as the pathways linking facial angiofibromas and FCP's through the TGF-β1 pathway are now being elucidated.

Conclusion: We present a clinical odyssey showing the natural progression and history of FCPs in TSC and comment on the mechanistic pathways allowing potential interventions in this disfiguring condition. TSC cases can be successfully managed and complications – particularly in the brain and kidney, can be avoided over an entire lifetime. This is encouraging for long term prospects for patients with TSC.

INTRODUCTION

Fibrous cephalic plaques (FCP; also known as forehead plaques) are a characteristic manifestation of tuberous sclerosis complex (TSC). [1,2] They occur in around a third of cases, often in childhood, and vary in size and position.[3] Their natural history is unknown, as often they are removed in early life, either surgically or by laser treatments, for cosmetic reasons. Histopathological examination shows that they are composed of bundles of reticular collagen with decreased elastic fibres, and are histologically similar to skin angiofibromas and fibrofolliculomas. We describe the clinical course of a large FCP in a patient with TSC2 over an 80 year period. Reports of long term follow-up of TSC cases over several decades are unknown and potential complications – particularly in the brain and kidney, can be avoided over an entire lifetime. Survival for more than 80 years is encouraging for long term prospects for patients with TSC.

PATIENT PHENOTYPE

The patient, aged 80 years on most recent examination in 2018, had an onset of tonic- clonic seizures at eleven months old, following earlier appearance in infancy of a large cephalic plaque (Figure 1). He had subsequently regular clinical follow-up at 1-2 yearly intervals since 1955. On examination at 18 years, he had multiple large facial angiofibromas, an FCP in the right temporo-parietal area, measuring ~90mm on its longest axis, multiple

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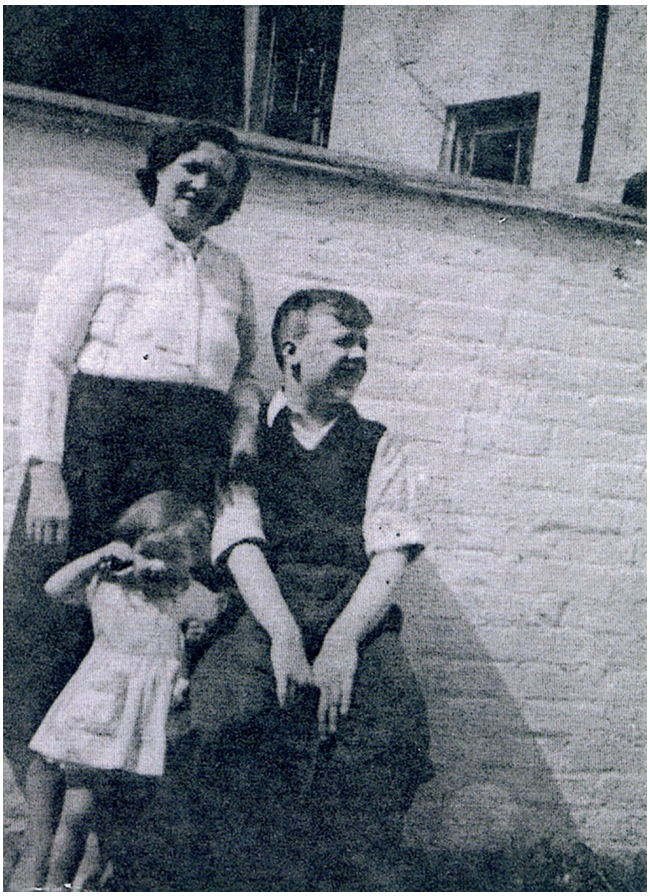

Fig 1. The patient aged 15 with his mother and younger sister, showing the large FCP in the right temporal region.

hypopigmented macules on his trunk and some groin skin tags. He had severe learning difficulties, no speech and had limited understanding and the ability to perform some simple commands. He also had well controlled epilepsy. Examination at 41years noted the cephalic plaque on the right temple measuring 92x90mm (from scale photographs) on its longest axis, and multiple facial angiofibromas (Figure 2a,b). He was kept indoors in residential accommodation as he disliked the outdoors. Regular ultrasound of his renal tracts to monitor angiomyolipoma formation confirmed slow growing angiomyolipomas bilaterally (40mm diameter largest lesion at age 70 and 79mm at age 80). Regular computed tomography of brain to monitor development of cortical tubers and potential sub-ependymal giant cell astrocytoma and other intracranial complications, showed some only periventricular calcification but at the last scan attempt, at age 75, he was too agitated and no further scans were attempted with the agreement of his family. Genetic testing confirmed a c.2784dupC mutation within the TSC2 gene. At 80 years he was having 1-2 partial seizures per week, controlled with Levetiracetam (Keppra), and clonazepam, and his angiofibromas had lessened in intensity, redness and size (Figure 3a) compared to age 41. His cephalic plaque had a residual diameter of 88x87mm with a small ridge remaining at the frontal border and the majority of the plaque area is now confluent with the scalp skin (Figure 3b). The shrinkage of the plaque commenced around seven years ago and has now resolved entirely leaving a small anterior ridge. Parental testing was not possible as both parents were deceased but had no evidence of any features of tuberous sclerosis on examination in late life, and recent mutation testing of other siblings has been normal so this may be a de novo mutation.

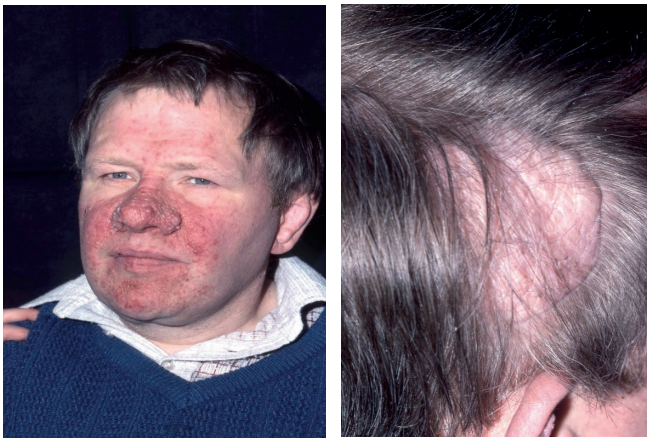

Fig 2. Frontal and right lateral views of the patient aged 41 showing severe angiofibromas (2a) and the FCP (2b).

Fig 3. Frontolateral and right lateral views of the patient aged 80 showing less vascularization of the angiofibromas (3a) and resolution of the FCP (3b).

DISCUSSION.

FCPs are a characteristic feature of TSC and form part of the 2012 diagnostic criteria. [4] Their natural history is unknown as terminology has changed over the decades and most cases where the lesions are large (>50mm diameter on the longest axis) are now generally treated by early surgical removal, vascular laser therapy or laser CO_2 ablation. Recently, topical sirolimus preparations have shown some effect on shrinkage. [5] Some plaques may previously have been described in the literature descriptions of skin lesions in TS as shagreen patches – collagenomas or connective tissue nevi which tend to occur predominantly on the lower back. [6] FCPs are more common in patients with TSC2 mutations, and may be more likely to occur on the left side of the body, as are some other TSC-related skin lesions. Our patient had a TSC2 mutation and right-sided FCP, with more intense angiofibromas on the right side, along with some large right nasal angiofibromas. Some evidence suggests that cilium laterality genes in mice

may account for a left-sided preference. [7] The histological features of FCPs are similar to skin angiofibromas and folliculomas. Angiofibromas are another common feature in TSC. Fibrofolliculomas are a common presentation in Birt-Hogg-Dubé syndrome, but have only rarely been described in TSC - both tend to cluster more commonly in the peri-nasal area. [8] Our patient has been followed up at clinics from 18 years of age giving a rare clinical odyssey visible over eight decades. [9] The resolution of the forehead plaque suggests that there is a finite lifespan for these lesions and natural collagen decay as part of the aging process may have hastened resorption of the collagen naturally. There is some evidence that sun exposure worsens lesions in TSC, including the facial angiofibromas. Sun protection advice is now routine, with sunscreen applied to sun exposed areas, particularly the peri-nasal region of the face – an area which may get more sun exposure. Our patient had difficult behaviour (he lay down and just refused to get up) when taken outside, so was generally kept indoors. This may have contributed to the improvement in his FCP and his angiofibromas, as he had less exposure to UV radiation over time, compared with the normal population.

The natural history of the FCP suggests that interventions that induce collagen decay, such as radiation therapies or other skin treatments, may be a beneficial adjunct in these disagreeable lesions. The use of mTOR inhibitors may increasingly help management of these lesions and may alter their natural history. Therapeutic steroid use, including triamcinolone acetonide, has recently been shown to improve collagenomas and may act by reducing transforming growth factor β1 (TGF-β1) in fibroblasts and increasing basic fibroblast growth factor (bFGF), which may inhibit fibroblast mitosis and collagen synthesis. [10] Research into the early clinical use of these treatment modalities and therapeutic targets in combination might help future management of patients with these displeasing lesions. Patients who decline to have the FCP's removed surgically either because they are not aware or bothered by the lesions or would be unco-operative because of behavioural difficulties, can be reassured that they are generally self-limiting over time. Until recently there has been a high mortality rate in cases of TSC – particularly in cases with learning disability. Regular renal ultrasound showed non-progressive cysts and very small angiomyolipomas and cranial imaging showed no progression of his periventricular calcification and no complications due to any intracranial tumours. This case shows that increasingly TSC patients can live a normal lifespan and using the latest consensus guidelines on surveillance and management [11], careful regular monitoring of the brain (particularly for sub-ependymal giant cell astrocytomas) and renal tracts (particularly for angiomyolipomas) and management of learning difficulties can allow achievement of a normal lifespan with regular but minimal monitoring to avoid complications. [12] His epilepsy was manageable and occasionally newer therapeutic options became available and were tried effectively, however he continues to have weekly seizures. Evidence shows that careful early treatment of epilepsy is a major factor in the diminishment of seizures with age and in the prevention of learning difficulties. Wei *et al* [13] have shown that if the first AED is effective, then patients may outgrow their seizures with age. In our patient, early onset of the epilepsy in an era when therapeutic options were very limited has probably not allowed optimum efficacious treatment of the seizures (compared to today's treatments) with resultant persistence of his learning difficulties. With refactory seizures associated with cognitive disability [11], this is something we hope will become less common with strong adherence to more modern guidelines.

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Clinical Paper

Who's at The Door? – Surface Contamination of Door Frames in a Single-Bedded In-Patient Adult Cystic Fibrosis (CF) Unit

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Keywords: cystic fibrosis, cross infection, infection control, environment, microbiology

ABSTRACT

The Gram-negative bacterium, *Pseudomonas aeruginosa*, is a major respiratory pathogen in patients with cystic fibrosis (CF), with an associated increase in morbidity and mortality. Consequently, infection prevention and control (IPC) plays an important role within health care in order to minimize the risk of cross-infection of this organism amongst patients and the hospital environment. It was the aim of this study to examine bacterial contamination of the health estate of CF in-patients' single-bedded rooms and related environments (n=40). Twelve bacterial genera were identified, six being Gram-positive (*Brevibacterium, Dermacoccus, Micrococcus, Rothia, Staphylococcus* and *Streptococcus*), and six being Gram-negative (*Acinetobacter, Citrobacter, Klebsiella, Moraxella, Pantoea* and *Pseudoxanthomonas*). None of the organisms identified were considered of particular clinical significance to CF patients. The CF lung and associated sputa may be important reservoirs of *Pseudomonas aeruginosa*, with potential for spill-over into the health care estate. In the aftermath of the *Pseudomonas* neonatal outbreak at Altnagelvin and the Royal Jubilee Maternity Hospitals, where there was heightened IPC awareness regarding the presence of this bacterium, it is encouraging to note its absence from the CF-health care estate examined.

INTRODUCTION

In late December 2011 and early 2012, there were outbreaks of *Pseudomonas aeruginosa* infection at the neonatal unit at Altnagelvin Hospital, Londonderry, as well as at the Royal Jubilee Maternity Service, Belfast, which tragically led to the death of four babies.[1] The subsequent Independent Review examined the fabric and design of neonatal units throughout Northern Ireland and made several recommendations relating to the fabric and design of estate to support good principles of infection prevention and control.[2]

Whilst *Pseudomonas aeruginosa* is an uncommon cause of bacteraemia in babies, around one or two cases have been reported each year in Northern Ireland for babies under 1 year old, it is however a commonly isolated pathogen from patients with cystic fibrosis (CF).[2] CF is the most common lethal genetic disease affecting mainly Caucasian populations, with an approximate frequency of 1 in 2500 live births and a genetic carriage rate of approximately 1 in 25 persons. The pathophysiology of the disease stems from a genetic defect of the CFTR protein, which transports chloride ions through ion channels in the cell membrane. Absence or limited functionality of these ion channels results in the accumulation of sticky sputum/mucus, which traps a variety of different micro-organisms. Failure to be able to expel trapped bacteria leads to their accumulation in the airways of the lungs of CF patients, resulting in chronic infections, which are largely responsible for high morbidity and mortality in these patients.[3]

Pseudomonas aeruginosa (*P. aeruginosa*) and *Burkholderia cenocepacia* (*B. cenocepacia*) are two important bacterial pathogens in patients with cystic fibrosis (CF), resulting in chronic lung infections with significant morbidity and mortality.[4] Both of these bacteria have been isolated from a wide variety of environmental sources, including waters.[4]

The importance of these bacteria has driven the implementation of stringent cross-infection strategies,

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particularly in the in-patient setting. The development of and adherence to robust infection prevention and control (IPC) guidelines for cystic fibrosis (CF) has helped minimize the transmission of respiratory pathogens within this patient population.[5,6] One key component of such IPC guidelines is the in-patient management of CF patients in well-ventilated single rooms of adequate size, each with their own ensuite facilities. People with CF understand the infection risks from physical interaction. Yet, on occasion adults with CF may speak to other patients but position themselves in the open doorway of an inpatient room in an attempt to reduce this risk. Fomite surfaces therefore have the potential to become contaminated, as their positioning breaches the "3 foot rule".[7] Given the importance of the need to prevent cross-infection between CF in-patients, whilst they are treated in their single bedded ensuite rooms with i.v. antibiotics, building design strategies targeting and promoting such infection prevention need to be developed and adopted into new builds. To date, there has been limited interaction between building design teams and cystic fibrosis clinical teams, in setting out what organisms are of key clinical importance. Given the clinical importance of this organism, the tragic historical legacy of its association with neonatal deaths in Northern Ireland, coupled with the heightened awareness of *Pseudomonas aeruginosa* within infection control and prevention, we wished to examine the hospital environment, where this organism is prevalent with in-patients. To date, there is no data to tell if door frames or other CF in-patient fixtures and fittings of similar height may become contaminated with CF respiratory pathogens during such events, through direct contamination at head level, from patients' saliva, respiratory secretions or from handling doors.

METHODS

A study was performed, whereby pre-moistened swabs (Sterilin Ltd, UK) were collected from door frames, as well as from three other locations within an adult CF Unit (n=40), as detailed in Table 1. All doors frames were located in single bedded ensuite rooms that adult CF patients occupy during their in-patient stay which normally lasts two weeks. Door frames were wooden and were sealed with a plastic veneer. After completion of swabbing an area of door frame, swabs were transferred from the Adult CF Unit on transport medium and were immediately plated onto Columbia Blood Agar (CBA; Oxoid CM, Oxoid Ltd., Basingstoke, UK), which were incubated aerobically at 37°C for 48hrs. Resulting colonies were purified and those which were phenotypically different in terms of the colonial morphology, were sub-cultured singly onto fresh CBA plates, in preparation for phenotypic identification by MALDI-TOF analysis.

RESULTS

Microbiological results are shown in Table 1. In total, this study generated 47 bacterial isolates, of which 33 (70.2%) were able to be identified by MALDI-TOF analysis. For the remaining 14 unidentified isolates, clear spectra were obtained, but these spectra were, as yet, not available in the MALDI-TOF database. Overall, no conventional CF bacterial flora, including *Pseudomonas aeruginosa, Burkholderia cepacia* complex organisms, *Staphylococcus aureus*, *Achromobacter xylosoxidans* or *Stenotrophomonas maltophilia*, were isolated from any area. Twelve bacterial genera were identified, six being Gram-positive (*Brevibacterium, Dermacoccus, Micrococcus, Rothia, Staphylococcus* and *Streptococcus*), and six being Gram-negative (*Acinetobacter, Citrobacter, Klebsiella, Moraxella, Pantoea* & *Pseudoxanthomonas*). None of the organisms identified are considered of particular clinical significance to CF patients.

DISCUSSION

In this study, we targeted four fomite areas, as shown in Table 1, with emphasis on door frames and door handles in patients' single-bedded rooms. Sampling purposely targeted these areas at head height to attempt recovery of CF pathogens which could be deposited from patients' mouths, nose and hands onto such surfaces, whilst chatting at the door threshold of patients' rooms. Results indicate that "dry" areas, including door frames and handles, predominantly yield Gram-positive organisms, whereas "wet" areas including sinks and taps, yield Gram-negative organisms. The former finding is in agreement with other studies, which have shown an exclusive predominance of Gram-positive organisms, in "dry" sites/fomites, including ATM machines[8] and monetary coinage.[9] The potential demise of Gram-negative organisms in dry fomites is of particular importance for people with cystic fibrosis. Knowledge of the biology of the processes leading to a reduction of Gram-negatives would allow for a better understanding, especially for IPC purposes. After deposition on fomite surfaces from the patient, the drying process commences for the Gram-negative organism, in the presence of the biological matrix (sputum, saliva) that it is contained in. There is a marked decrease in membrane integrity and redox activity and a concurrent increase in membrane depolarization, which is usually lethal to the bacterium.[10,11] Gram-positive organisms are less susceptible to drying than Gram-negatives, due to the presence of their robust cell wall structure. The work of Nocker and colleagues demonstrated that the killing effect due to desiccation in Gram-negative organisms was amplified in the presence of 150-400 mM sodium chloride.[11] This finding may be significant in cystic fibrosis, where nebulized hypertonic saline solution (0.6 – 0.7% w/v NaCl) is employed as a mucolytic agent to improve muco-ciliary clearance of sputum from the CF lung. Translating IPC guidance is necessary to keep pace with the changing microbiological environments. This knowledge indicates that where fomite surfaces remain wet or moist, this scenario may lead to greater environmental persistence of Gram-negative organisms. Maintenance of dry conditions may lead to the reduction of Gram-negative organisms but have less effect on Gram-positive organisms and spore-forming organisms, such as *Clostridium difficile*. Therefore, where pragmatic, shifting the environmental paradigm from "wet/

moist" to "dry" environments or investing resources to maintain a relative state of dryness, could add value to IPC interventions relating to cystic fibrosis and in general and further lead to reduced environmental persistence of Gram-negative organisms contaminating fomites.

It is reassuring to note the lack of recovery of pathogenic CF bacterial flora from such sites. However, recovery of a spectrum of bacteria from these sites demonstrates these areas have their own bacterial signatures despite regular cleaning. The clinical significance of these organisms remains unknown but with declining rates of *Pseudomonas aeruginosa* within CF populations there is increasing interest in the role of other Gram negative and anaerobic bacteria and their potential for pathogenicity in the CF lung. This emphasizes the need to maintain effective IPC interventions, including keeping doors closed in single-bedded rooms, as well as educating the CF patient and re-emphasizing the need for stringent IPC behavioral precautions amongst people with CF, both in and out of health care facilities, in order to minimize the burden of cross infection with known and future CF respiratory pathogens. In the context of the present study, CF centres should be aware of the latest recommendations from the UK CF Trust[12], with particular reference to the non-tuberculous *Mycobacterium* (NTM), *Mycobacterium abscessus,* including:-

(i) Rooms must be left with the door closed, with at least an hour between patients to allow for dispersion of possible airborne contamination and then cleaned according to local infection control guidelines, (ii) Gloves and aprons must be worn and hand washing with soap and water must be performed before and after contact with each patient and/or their immediate environment, (iii) All other equipment and surfaces must be cleaned and dried between patients, according to local infection control guidelines. To date, there has been little interaction between CF clinical and building design teams.[13] Such early discussions are essential in new builds, namely the construction of new buildings, as well as in retrofits, namely the modification/ adaption of an existing building, which was not present during initial construction, regarding the specific needs of the CF patient environment, which present relatively unique

Area	Number of fomites from which bacteria were isolated	Identification of bacteria
Door frames in patients' single-bedded rooms (n=10)	***5***	*Acinetobacter lwoffi* *Micrococcus luteus* *Pantoea agglomerans* *Staphylococcus epidermidis* *Staphylococcus hominis*
Door handles entering patients' single-bedded rooms (n=13)	7	*Brevibacterium casei* *Dermacoccus nishinomiyaensis* *Micrococcus luteus* *Moraxella osloensis* *Staphylococcus capitis* *Staphylococcus epidermidis* *Staphylococcus hominis* *Staphylococcus simulans* *Streptococcus mitis/oralis* *Rothia dentocariosa* *Unidentified (x1)*
Push devices [automated door release buttons, alarm buttons, door visors, keyboard. mousemat] (n=11)	8	*Dermacoccus nishinomiyaensis* *Micrococcus luteus* *Moraxella osloensis* *Pantonea agglomerans* *Staphylococcus capitis* *Staphylococcus epidermidis* *Staphylococcus hominis* *Unidentified (x1)*
Wet areas [tap, sink drain, showerhead] (n=6)	3	*Citrobacter freundii* *Klebsiella oxytoca* *Pseudoxanthomonas mexicana*

Table 1:
Identification of bacteria isolated at specific locations within the adult cystic fibrosis unit

challenges to such teams, when contemplating designs to minimize the burden of bacteria on surfaces in such units. More data on the employment of materials and architectural design is urgently required to help chose optimal designs to ensure "infection-free by design" solutions are duly implemented.

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DECLARATION OF CONFLICTING INTERESTS

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Clinical Paper

Point of Care Thyroid Ultrasound (POCUS) in Endocrine Outpatients: A Pilot Study

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Key words: point of care, thyroid ultrasound

ABSTRACT

Background: Thyroid ultrasound is used for the assessment and characterisation of thyroid nodules/goitres and to guide diagnostic biopsy, it is normally performed by radiologists. Point of care ultrasound (POCUS) by trained non-radiologists, has the potential to reduce cost, expedite diagnosis and enhance patient satisfaction if embedded in an outpatient clinic setting.

Aim: To perform a pilot of the use of point of care thyroid ultrasound in an endocrine outpatient setting for the assessment of thyroid nodules and goitres.

Methods: Thyroid ultrasound was undertaken with consultant radiologist supervision, over a period of 16 months between January 2017 to April 2018. Using a GE Logic e7 portable thyroid ultrasound machine with 12 MHz linear probe. All scans were performed on patients attending for assessment of thyroid disorders at the Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, Belfast.

Results: Thyroid ultrasound was performed on 40 patients (M:10,F30), mean age 52 years, range 23-77 years, median follow up 14 months, range 6-18 months. Twenty scans were performed to assess thyroid nodules, 13 for investigation of a goitre and the remaining 7 were for patient preference. 39 patients had benign thyroid disease, 1 patient had a confirmed newly diagnosed papillary thyroid carcinoma (PTC). The ultrasound 'U' classification was U1 and U2 (n=37), U3 and above (n=3). Fine needle biopsy (FNA) was performed on 9 patients with one confirmed as a thyroid carcinoma (Thy1;n=2, Thy2;n=6 and Thy 5;n=1). Thyroid ultrasound reporting was broadly similar between radiologist and non-radiologist ($p< 0.01$). Time to scan was reduced during the pilot from the existing model (n=40) of a mean of 52 days (range 7-95 days) to 1 day ($p<0.01$).

Conclusion: With appropriate training and radiology supervision, point of care thyroid ultrasound can be performed accurately and safely in outpatients by an endocrinologist. There are potential benefits in terms of cost savings, time to scan, reduction in clinic visits, and in expediting diagnosis.

INTRODUCTION

Thyroid ultrasound for the assessment of thyroid disorders (nodules and goitres) is typically performed by a trained radiologist or sonographer. More recently in some centres, appropriately trained endocrinologists are performing thyroid ultrasound, often in the context of a 'one stop shop'.[1,2] The rate of incidental discovery of thyroid nodules continues to increase, adding further to the burden on Radiology Departments. Most of these nodules are benign, there appears to be a current need to rationalise this service. The British Thyroid Association (BTA) has recently produced clear guidelines for the investigation of thyroid nodules, in particular the use of an ultrasound (US) classification (U1-U5)-*Figure 1* which describes features indicative of being benign or malignant.[3] The use of such a classification for the prediction of a nodule being benign or malignant helps to determine whether a biopsy should be performed, (U3 to U5 typically requires biopsy). Thyroid cytology reporting of thyroid (FNA) biopsy is with the Thy classification which proceeds from 1 to 5, with Thy1: non-diagnostic, Thy2: non-neoplastic thyroid change such as a nodular goitre or thyroiditis, Thy3: all follicular lesions, Thy 4: abnormal, suspicious of malignancy and Thy 5:diagnostic of malignancy. POCUS (point of care ultrasound) is gaining momentum and an evidence base in other medical specialities as a means of an extension to the clinical examination. There are clear pathways in the UK to safe and effective certification provided there is direct supervision by a consultant radiologist.

Thyroid ultrasound and ultrasound guided biopsy in our centre currently represents a large service commitment to the radiology department, with an average of around 100 scans performed monthly. Against this background, we sought to establish the utility of a pilot of point of care thyroid ultrasound in endocrine outpatients.

PATIENTS AND METHODS

Patients attending the Regional Centre for Endocrinology and Diabetes, Royal Victoria Hospital, Belfast for investigation and management of thyroid disorders were invited to have a point of care ultrasound at their outpatient clinic visit as

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part of the pilot study. Clinical information and laboratory data were obtained from the online medical record NIECR (Northern Ireland Electronic Healthcare Record). A total of forty scans were performed over a 16-month period between January 2017 and April 2018. Indications for scanning were the presence of thyroid nodule/s, goitre and also for patient preference. Thyroid ultrasound was performed using a 12 MHz linear probe GE Logic e7 portable thyroid ultrasound machine (MDI Medical Ltd, Kells Co Meath, Ireland), purchased after a successful in-house business case application. The duration of each scan was around 5-7 minutes. A provisional report of each scan in accordance with BTA guidelines and template for reporting was documented in the patient's notes, each scan and subsequent report was reviewed by a consultant radiologist (*PKE*). In addition, to ensure the accuracy and integrity of the study and for validity of medico-legal documentation all patients had a formal departmental scan which was uploaded/stored onto i-Site (online radiology imaging system), performed by another in house radiologist. Point of care thyroid ultrasound was performed by an endocrinologist (*PCJ*), in accordance with the UK accredited BTA and RCR (Royal College of Radiologists) national training scheme for certification in the use of ultrasound in the management of thyroid disease by non-radiologists. Briefly, this includes a knowledge of neck anatomy, ultrasound technique, interpretation and reporting of images in accordance with BTA US 'U' classification system (Figure 1). Attendance is also required at a national training course in thyroid ultrasound. All patients were examined in the supine position with the neck hyperextended. Using a high frequency linear-array transducer, scanning was done in both transverse and longitudinal planes. Real time images of the thyroid were performed using gray scale and colour doppler techniques. FNA (fine needle aspiration) was performed if indicated.

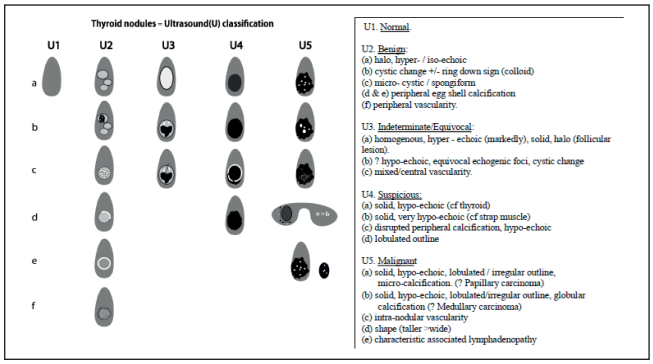


Figure 1 British thyroid association "U" classification

RESULTS

Baseline characteristics

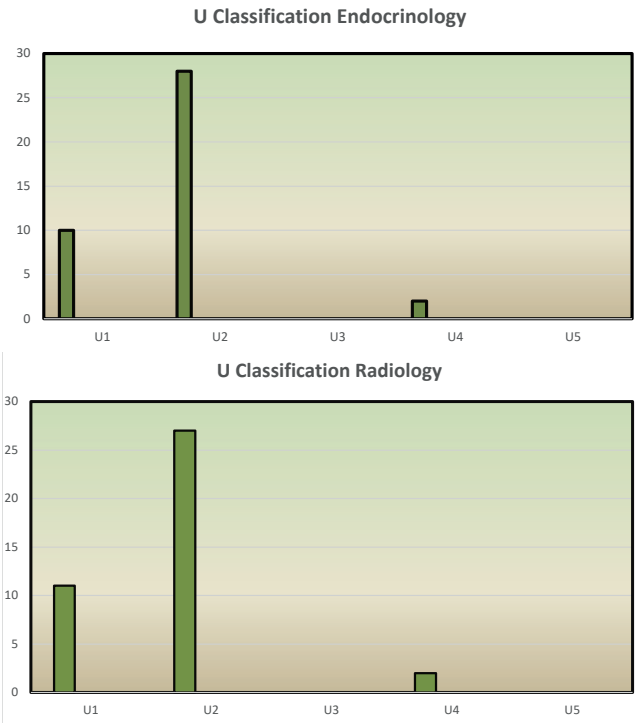
Thyroid ultrasound was performed on 40 patients (M:10,F30), mean age 52 years, range 23-77 years, median follow up was 14 months, (range 6-18 months). Twenty scans were performed for the assessment of thyroid nodules, 13 were for investigation of a goitre and the remaining 7 were for patient preference, *Table 1*.

Table 1 Clinical characteristics, imaging and diagnoses

Variable	N
Age	52 years (mean) range 23-77 years
Gender	F:30, M:10
Indication for scan	Nodule (n=20), Goitre (n=13), patient preference (n=7)
U Score (endocrine-PJ)	U1+U2 (n=37), U3-U5 (n=3)
FNA result	Thy1;n=2, Thy2 n=6 and Thy 5;n=1
Diagnosis	Benign (n=39), Malignant (n=1)

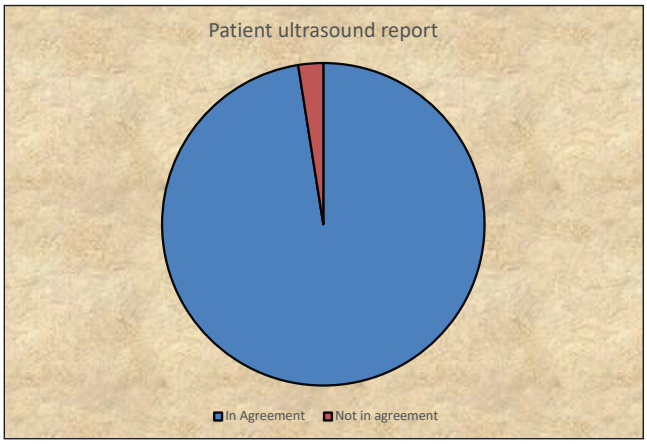
On the initial point of care scanning at outpatient clinic by PCJ, the ultrasound 'U' classification was as follows; U1-normal (n=10) and U2 (n=27), U3 (n=1), U4 (n=2), U5 (n=0) total. Agreement between PCJ and PKE on

Figure 2a Imaging features and agreement between endocrine and radiology reporting



the U classification (*Figure 2a*) demonstrated very good agreement which was statistically significant ($p< 0.01$). The one difference between (PCJ and PKE) interpretation was a U2 nodule (PCJ) interpreted as U1 (PKE) by radiology, this

Figure 2b Comparison of U scoring between the radiologist and endocrinologist



was confirmed as U2 on follow up and formal departmental scan. Formal departmental scanning performed by the in house radiology department (*Figure 2b*) demonstrated good agreement between PCJ and in house radiologists (not PKE) ($p< 0.01$). The one difference (between PCJ and in house radiologists) was between a U2 lesion-in house radiology U4-PCJ. This had been reported as possible U4 previously by radiology but subsequently reclassified to U2, with a subsequent FNA Thy 2;-benign.

OUTCOME OF BIOPSY (FNA)

FNA was performed on 9 patients (Thy1;n=2, Thy2 n=6 and Thy 5;n=1)-*Table 1*. Indications for the 9 FNA's were; five performed due to U scoring, one due to a positive PET result, one for symptomatic relief of a cyst, one on patient request given concerns and the last FNA due to the appearance on CT scanning. At follow up one patient was diagnosed with a papillary thyroid carcinoma (initial POCUS U classification U4 (agreed among PJ, PKE and in house radiologist), and subsequent FNA-Thy 5), this was performed on a patient who did not have an overt goitre or palpable nodule and requested the scan at clinic.

Potential cost and clinic visit savings and time to scan

A comparison of time to scan was made between the current pilot and a selection of 40 consecutive scans who had thyroid US requested at their outpatient clinic visit prior to the start of the pilot. The mean time to scan prior to the pilot was 52 days, range 7 to 95 days, in comparison to the pilot which was done on the day of the scan (52 days v 1 day, $p<0.01$). Potential cost savings are accrued as patients are not required to attend the radiology department for an ultrasound scan. On average in the NHS this costs £60 per ultrasound. Over forty patients this is a potential significant saving of £2400 and can be extrapolated for a larger POCUS service.

DISCUSSION

Real time imaging of the thyroid gland performed as part of a routine evaluation during outpatient clinic can aid in the diagnosis and therapeutic intervention in thyroid disease.[4] Across the UK there has been a recent trend towards the establishment of 'one stop shops' whereby a trained radiologist in tandem with either an endocrinologist and/or an endocrine surgeon performs the scan, typically for the assessment of thyroid nodules and for thyroid cancer screening[5]. The current pilot is a slight departure from previously established models, in that the scan was performed by an endocrinologist under the guidance/mentorship of a trained radiologist as part of the routine clinic visit. The perceived advantage to the patient is the convenience of real time scanning with the potential to improve patient satisfaction (although this was not formally assessed during the pilot) and allow for immediate diagnosis or the need for biopsy if required. In addition to assessing thyroid nodules, thyroid US can also be utilized for the assessment of goiters. For patients, same day imaging at their clinic visit can offer reassurance to patients as it can differentiate what the aetiology of the goitre is. One of the indications for scanning in the current pilot was imaging at clinic if the patient requested it, this has the potential to add to unnecessary workload if the scan was not indicated, however a new thyroid cancer in a patient who was relatively asymptomatic with no clear indication for the use of thyroid ultrasound in this particular case was identified. This raises questions regarding the suitability of screening for thyroid cancer in patients who present with thyroid disorders.

In order for the current pilot to commence certain pre-requisites had to be met by the endocrinologist including; a knowledge of neck anatomy, an understanding of the U classification system, ultrasound technique and reporting of the imaging according to the BTA guidelines. With the advent of portable ultrasound machines, this has meant an increase in the use of ultrasound by non-radiologists in a variety of settings. Recent evidence suggests that clinicians when trained by radiologists can gain similar diagnostic accuracy.[6] With the introduction of the new UK internal medicine curriculum there are potential opportunities to incorporate ultrasound into training. Point of care ultrasound is rapidly gaining an evidence base in other specialities mainly within respiratory and rheumatology specialities, where it is now embedded within the trainee curriculum and there is a clear pathway for obtaining certification to allow for independent use.[7] It has been shown to improve safety during medical procedures and aid in diagnostic accuracy. Advantages of POCUS can include improved patient satisfaction, expediting diagnoses, reducing the need for multiple clinic/imaging visits, cost and time savings, and the potential to ease the work burden for radiologists.[8] Perceived disadvantages can include the expense of obtaining the machine, time constraints for scanning within clinic time, ensuring diagnostic accuracy, obtaining certification, and the perceived taking of business from radiology colleagues, *Table 2*.

CONCLUSION

With appropriate training and supervision by a radiologist, point of care thyroid ultrasound can be performed accurately and safely in outpatients by an endocrinologist. There are potential benefits in terms of cost savings, reduction in clinic visits, and in expediting diagnosis.

Table 2 Point of care thyroid ultrasound-pros and cons

For	Against
• Same day scanning	• Expense of obtaining machine
• Patient centred	• Time constraints
• Non-invasive	• Diagnostic accuracy
• Reduce need for multiple visits	• Obtaining certification
• Cost and time savings	• Taking of business from radiologists
• Expedite diagnosis	• Radiology supervision
• Ease burden for radiologists	• Documentation of scans

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Clinical Paper

Pre-Operative Imaging can Reduce Negative Appendectomy Rate in Acute Appendicitis

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ABSTRACT

Introduction: Acute appendicitis is a common surgical emergency, with a prevalence of 112 per 100,000 people per year in Europe. Negative appendicectomy is defined as a pathologically normal appendix removed from patient suspected with appendicitis. Negative appendectomy rate (NAR) has been reported to be around 15-25%. We aimed to evaluate our unit's negative appendectomy rate and the effect of pre-operative imaging on NAR.

Method: A retrospective study including all patients who underwent both open and laparoscopic emergency appendicectomy in a single district general hospital from 2017-2018. Clinical information including cost was calculated based on the 2017/18 national tariff payment system. Patients under 18 years old were excluded from this study.

Results: Two hundred thirty-two patients were included in this study, of which 69 (29.74%) had a pre-operative CT scan. The mean length of stay was 2.57 days. The sensitivity, specificity, positive predictive value and negative predictive value for CT were 77.8%, 100%, 87.5% and 100%. The negative appendicectomy rate with and without pre-operative CT scan were 7.25% and 22.09% respectively. Based on the 2017/18 national tariff payment system, a CT abdomen and pelvis with contrast and emergency appendicectomy with CC score of 0 cost 92 and 2370 pounds respectively. The total cost of patients who underwent appendicectomy without imaging was £ 322,320. If all patients undergo pre-operative CT, with a reduction of 15% in negative appendicectomy rate, the overall total cost would significantly lower to £ 36,212.

Conclusion: Our study demonstrated that the negative appendicectomy rate could be improved by preoperative imaging. The study also showed that implementation of preoperative imaging for suspected appendicitis cases could save costs, allowing better allocation of resources.

INTRODUCTION

Acute appendicitis is a common surgical emergency, with a prevalence of 112 per 100,000 people per year in Europe[1]. In England alone, it accounts for more than 40,000 hospital admissions annually.[2] Appendicitis is defined by the presence and spreading of inflammation within the inner lining of the vermiform appendix. Its presentation varies with severity but typically includes anorexia, nausea, vomiting and migration of central abdominal pain to the right iliac fossa.[3] Early diagnosis and prompt appendicectomy are crucial to prevent significant increases in morbidity and mortality.[3,4]

Appendicitis is typically diagnosed through clinical presentation and physical examination. It is also important to note that patients at extremes of age can present with atypical and non-specific symptoms, thus, requiring a high index of suspicion.[4] Nonspecific abdominal pain and gynaecological causes in young females can present with similar symptoms. When assessing cases, it is essential to consider potential benefits in implementing imaging: the theorised benefits can be evaluated by measuring negative appendicectomy rate (NAR). NAR is defined as the incidence of pathologically normal appendices removed from patients suspected of having appendicitis.[5] NAR has been reported to be 15-25% previously and evidence suggests that it can be lowered through preoperative imaging.[5] This can, in turn, prevent unnecessary postoperative complications and costs.

The current diagnostic accuracy for appendicitis lies between 76% and 80%, translating to approximately 20% NAR in the UK without preoperative imaging.[6,7] The UK rate of NAR is significantly higher than in the US and Netherlands where imaging, including Ultrasound sonography (USS) and computed tomography (CT) are used routinely.[8,9] Through preoperative imaging, NAR can be lowered to reduce surgical complications, hasten discharge and healthcare costs.[8,10] We evaluated the use of liberal diagnostic imaging to improve

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NAR and to investigate the cost-effectiveness of routine preoperative imaging in patients with suspected appendicitis in our institution.

METHOD

All patients who underwent both open and laparoscopic emergency appendicectomy in a single district general hospital from 2017-2018 were extracted from the theatre system. Information including Preoperative imaging, Inflammatory markers, post-operative appendix histology, length of stay and readmission (if applicable) are collected. The cost of hospital stay was calculated based on the 2017/18 national tariff payment system. Patients under 18 years old were excluded from this study.

RESULTS

Two hundred thirty-two patients were included in this study, of which 69 (29.74%) had a pre-operative CT scan. The mean length of stay was 2.57 days. The sensitivity, specificity, positive predictive value and negative predictive value for CT were 77.8%, 100%, 87.5% and 100%. The negative appendicectomy rate with and without pre-operative CT scan were 7.25% and 22.09% respectively. Based on the 2017/18 national tariff payment system, a CT abdomen and pelvis with contrast and emergency appendicectomy with CC score of 0 cost 92 and 2370 pounds respectively. The total cost of patients who underwent appendicectomy without imaging was £ 322,320. If all patients undergo pre-operative CT, with a reduction of 15% in negative appendicectomy rate, the overall total cost would significantly lower to £ 36,212.

DISCUSSION

Appendicitis is a common cause of abdominal pain, with a lifetime risk of up to 7-8%.[11] While many present with the classic signs, those with atypical presentation present diagnostic uncertainty. Furthermore, routine laboratory markers such as C-reactive protein (CRP) and polymorphonuclear cells (WCC), are not 100% specific or sensitive.[12] The emergency general surgery guide produced by Association of Surgeons of Great Britain and Ireland (ASGBI) recommends that patients with suspected appendicitis, raised WCC or CRP should be sent for imaging or diagnostic laparoscopy.[11] Patients with normal WCC and CRP are considered unlikely to need appendicectomy and are managed conservatively or sent for additional imaging to rule out appendicitis.[11]

While acute appendicitis is an emergency, not all patients undergoing intervention have appendicitis. The hospital costs associated with negative appendicectomies include the operation, surgical consumables, hospital stays and postoperative recovery. A cost analysis of laparoscopic appendicectomy at a UK institution in 2009 revealed that the equipment costs ranged from £111 - £451 and theatre costs of £273 - £1333, producing a total median operative cost of £906.[13] With the addition of £220 per night in ward, this rises to a median total inpatient cost of £1632. This is similar to the 2017/18 national tariff payment system in which emergency appendectomy in patients without significant co-morbidity were coded as £2370. As these merely reflect the costs of the average stay 2.6 to 3.9 days, these figures would increase with complications.[14,15] Furthermore, complication rates of appendicectomies remained around 10% and were remarkably similar between positive and negative cases. Common complications include wound infection, abscesses, or hospital-acquired infections- these can be reduced by avoiding unnecessary surgery.[16,17]

Diagnostic imaging is increasingly used in investigation of right iliac fossa pain and has had success reducing NAR and complication rates.[11,18-20] This includes the most commonly used USS, CT and, less commonly, magnetic resonance imaging (MRI).[21] Mandatory preoperative imaging has been implemented with great success in the Netherlands and in a large multinational trial: NAR dropped from 15% to 3.3% across 62 Dutch hospitals (1975 patients), and NAR reduced to 5.4% in the US group (19327 patients).[22,23] The odds for negative appendicectomy without preoperative imaging was 3.7 (CI 3.0-4.4), even after adjusting for age, sex and white cell count.[23] These results are promising and warrant a review of the evidence to evaluate its implementation.

USS is widely accessible and is often the first line imaging modality used in investigating acute abdominal pain, with the diagnostic criteria being a non-compressible and non-peristaltic structure >6 mm in diameter.[4] A meta-analysis, of 2643 patients across 22 studies, calculated that USS offers a sensitivity of 86.7% (CI 85.4-88.0) and specificity of 90.0% (CI 88.9-91.2) and is generally considered useful, especially in younger populations and complex cases.[21,24,25] Efficacy of USS remains debatable as its specificity can be as low as 74% in other studies.[24] Yu et al. also calculated that the overall NAR with USS is 10.7%, compared to rates of 10%-20% without imaging.[25] The authors identified that preoperative USS might be useful for diagnosis, particularly effective in young, male sex and those with suggestive presentations. The primary limitation of USS is that it is heavily user-dependent; reliability and accuracy are limited by intra-observer variability, user experience and patient anatomy.[26]

Despite these drawbacks, a study of 228 cases on USS with optional CT use, found that preoperative imaging improved patient selection for surgery and effectively reduced NAR from 19% to 5%.[7] A similar study on the use of USS and/or CT reduced NAR from 13% to 7%.[24] While diagnostic performances were similar between USS and CT, CT was associated with a higher perforation rate: perforation rate for only surgery is 29%, 54% with CT (CI 8%-44%) and 71% with both USS and CT (CI 25%-67%). These differences may be attributed to the temporal delays but remain inconclusive as many clinical parameters were not accounted for. While the effects of USS on NAR are yet to be established, USS shows potential in reducing NAR without affecting perforation risk, but more investigation is needed to account for other variables.

The use of USS does not always offer a definite diagnosis of appendicitis and hence requires additional, complementary

modalities such as CT or MRI. CT offers higher sensitivity and specificity, of 84% and 99% respectively, as well as reducing NAR from 13% to 5%.[24] The Surgical Care Outcomes and Assessment Program (SCOAP) collaborative in the US analysed a dataset of 20,000 patients across 60 hospitals and identified that preoperative imaging substantially improved NAR, where CT achieved statistically significant ($P < 0.001$) reduction in comparison to USS.[23] NAR with CT and USS in young adults were 4.6% vs 12% respectively, whereas it was 3.8% vs 8.6% for middle-aged populations. Another multi-centre study on preoperative CT saw significantly lower NAR compared to non-imaged groups (6.6% vs 20.6%, $P < 0.05$).[27] They also observed the vastly different CT utilisation (86.9%, 66.4% and 13.3%) across the centres which provided a statistically significant inverse correlation, rho= -1 ($P < 0.05$), between CT use and NAR. While in the UK, Stephenson et al has introduced a trial by performing a low dose contrast CT in raised inflammatory markers/ inconclusive USS group. They reported a significantly low NAR (4%) with no missed cases of appendicitis.[6]

Regardless of the benefits in reducing NAR, we should also consider the limitations, namely surgical delay and radiation. A UK cohort study of 2510 patients investigated the safety of in-hospital delays in acute appendicitis cases and did not find an association between timing of operation and risk of complicated appendicitis.[2,28] All the calculated ORs were statistically insignificant ($P > 0.30$): 12-24 hours OR 0.98; 24-48 hours OR 0.88; 48+ hours OR 0.82. Another study of 9048 adult appendicectomies, found the mean time from presentation to surgery to be 8.6 hours which was not a predictor of perforation risk (OR 1.0, CI 0.99-1.01).[2] These findings also agree with a meta-analysis of 11 non-randomised studies of 8858 patients; delay of 12-24 hours is not associated with increased complicated appendicitis (OR 0.97; $P = 0.750$).[29] However, delays of >48 hours were associated with increased wound infection and 30-days adverse events, with adjusted OR of 2.24 ($P = 0.039$) and 1.71 ($P = 0.024$) respectively.[28] As these diagnostic scans can be performed almost immediately, additional imaging is unlikely to subject patients to such risks.

Conversely, concerns with CT lies in its use of radiation and its limitation in specific patient groups such as children and pregnant women. This is important as appendicectomy is commonly performed on these groups who are particularly vulnerable to radiation. Appendicitis is both the most common non-obstetric surgical emergency and paediatric surgical emergency, affecting up to 2.1 per 1000 pregnancies and 23.3 per 10,000 10-19-year-olds.[4,24] Radiation dosage delivered by abdominal CT can range up to 10-20 mSv, equivalent to 500-1000 chest radiographs. With a higher portion of dividing cells, children are more radiosensitive and have longer for radiation-induced cancers to develop. An abdominal CT, at 240 mAs, on a patient at age 10 gives a 0.09-lifetime attributable risk of cancer, whereas the same radiation dose at age 35 would be 0.02.[30] Furthermore, a study attributed 1.5-2% of cancers in the US to CT radiation, highlighting the importance of reducing dosage during routine use.

Radiation doses can vary between institutions and countries. A study investigating CT doses, from 151 institutions across seven countries, revealed the median effective dose for abdominal CT to range between 5-32 mSV, where the UK mean was 7.9 mSv.[31] The findings suggest that dose variation is primarily attributed to protocol and machine parameters instead of clinical circumstances, hence, implementation of standardised doses may reduce radiation while maintaining sufficient diagnostic accuracy. In a study comparing high and low appendicitis CT doses (5.2 mSv vs 1.4 mSv in males and 7.1 mSv vs 2.2 mSv in females) no significant difference was found ($P>0.05$).[32] Promising results are achieved by reducing radiation dose using lower tube current, but it also increases image noise and can lower diagnostic accuracy.[33] Up to 22% of emergency abdominal CT resulted in the need for additional diagnostics due to incidental pathologies, including potential malignant adnexal, pulmonary and colorectal lesions.[34] In short, the lack of standardised CT dosage across institutions presents a barrier towards balancing radiation dose and diagnostic performance.

CONCLUSION

In conclusion, our study demonstrates that negative appendicectomy rate can be reduced significantly with the use of preoperative imaging. The clinical potential of various imaging modalities has been demonstrated by successful implementation in the Netherlands and offers a solution to unnecessary operations and expenditure. This study also showed that implementation of preoperative imaging for suspected appendicitis cases would be cost saving, allowing better allocation of resources. Further studies should focus on a standardised CT protocols to minimise the risk of radiation, especially in young adult and females.

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Medical Training

Career Progression of Queen's University Belfast Graduates after Completion of Foundation Programme Training

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INTRODUCTION

In the United Kingdom (U.K.), all medical graduates are required to enrol in a two-year Foundation Programme. The Foundation Programme is designed to allow newly qualified doctors to gain experience and acquire skills in a range of different specialities under supervision.[1] After completion of the Foundation Programme, doctors can choose to enter speciality training. The speciality training takes 3 to 8 years depending on the chosen speciality and time spent out-of programme e.g. to complete research for a higher degree, to enter management/leadership training or to seek overseas clinical experience. Since 2006, the General Medical Council (GMC) conducts a national survey for trainees undertaking a GMC approved training post. This aims to monitor medical education and training across the U.K.[2] Data regarding career progression of junior doctors and their destination are included as part of the survey and available online since 2012.

There is a decreasing trend in the number of junior doctors entering speciality training immediately after completion of the Foundation Programme.[3] In 2018, only 37.7% of foundation year two doctors (FY2s) went directly into specialty training, a year-on-year reduction from 67% in 2012, 64% in 2013, 59% in 2014, 52% in 2015, 50.4% in 2016, 42.6% in 2017.[4] This gap in training can be attributed to several factors including indecisiveness, highly competitive nature of the process and opportunities outside the U.K. or medical field.[5] In this paper, we aimed to evaluate the destination of Queen's University of Belfast (QUB) graduates at the transitional point between FY2 doctors and speciality training and whether there are any differences when compared to other U.K. medical school graduates.

METHOD

The progression reports from 2012 to 2018, which are sub-parts of the national training surveys reports, were obtained from the GMC website.[2] We further examined these reports and extracted the data on career progression of FY2 doctors linked to their medical schools. The report illustrated the recruitment of speciality/core training for doctors completing their two-year foundation training programme. Further shortlisting was made to include trainees obtained their primary medical qualification from QUB.

Comparisons were made between QUB graduates and other U.K. medical school graduates in a) number of graduates making an application to speciality training immediately after completion of foundation programme, b) proportion of FY2 doctors entering directly into speciality training after successfully obtaining an offer from any core/speciality training programme (data specific for QUB graduates only available after 2016) and c) number of graduates making an application to core/speciality training in the seven specialities with the highest number of posts available nationally (Core Medical Training, Core Surgical Training, General Practice, Clinical Radiology, Obstetrics & Gynaecology, Core Anaesthetics Training and Paediatrics)

RESULTS

Year	Number of Foundation Year 2 doctors	
	Queen's University Belfast	National
2012	196	6,831
2013	258	6,977
2014	236	6,949
2015	240	7,304
2016	263	7,226
2017	240	7,220
2018	250	7,075

Table 1: The number of FY2s participated in the GMC National Training Survey each year

The number of medical graduates who completed the survey is shown in Table 1. The number of graduates completing the survey varied each year, ranging from 6,831 to 7,304 (nationally) and from 196 to 263 (QUB).

a) Number of graduates making an application to core/speciality training

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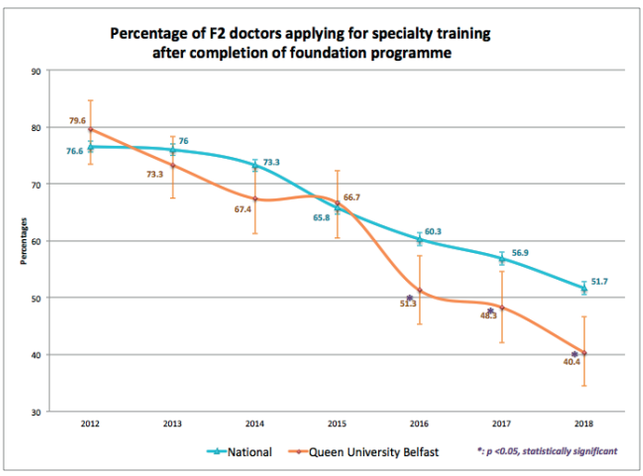

Figure 1: Number of speciality training applications by FY2 doctors graduating from QUB and across the United Kingdom from 2012 to 2018

The percentage of FY2 doctors making an application for core/speciality training programme (C/STP) upon completion of UK Foundation Programme training has significantly decreased from 76.6% in 2012 to 51.7% in 2018. The downward trend is illustrated in Figure 1. This trend is even more marked for FY2 doctors who were QUB graduates with fewer direct applications for C/STP directly than the national

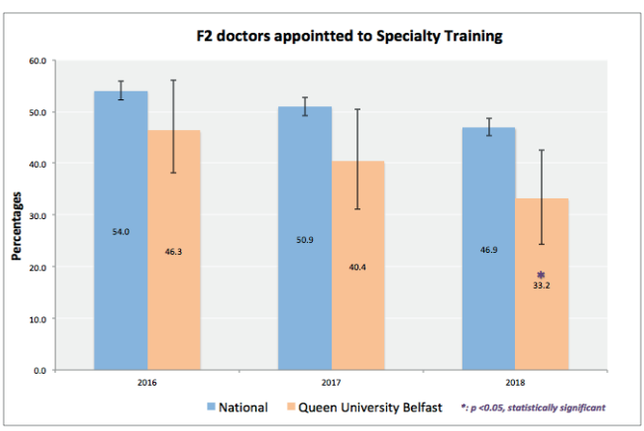

Figure 2: The percentage of FY2 doctors appointed to Specialty Training from 2016 to 2018

level since 2016.

b) The proportion of FY2 doctors entering directly into core/speciality training

The percentage of FY2 doctors entering directly into C/STP was lower than the percentage of FY2 doctors who made applications for C/STP. Results from 2016 to 2018 are shown in Figure 2. There has been a reduction in the proportion of UK FY2 doctors entering directly into a C/STP from 54% in 2016 to 46.9% in 2018. The percentage of FY2 doctors who were QUB graduates entering directly into C/STP has been lower than the national percentage since 2016.

c) Number of FY2 doctors making an application to core/speciality training

In terms of specific speciality application, similar trends were

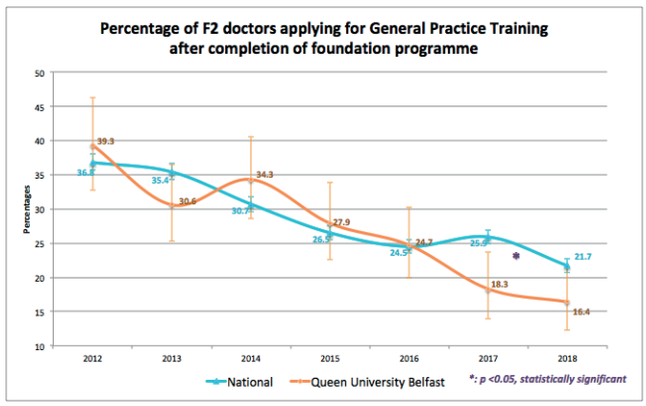

Figure 3: Percentage of FY2 doctors applying for General Practice Training after completion of Foundation Programme training, from 2012 to 2018

shown. There was a national reduction in the percentage of FY2 doctors who were applying for C/STP from 2012 to

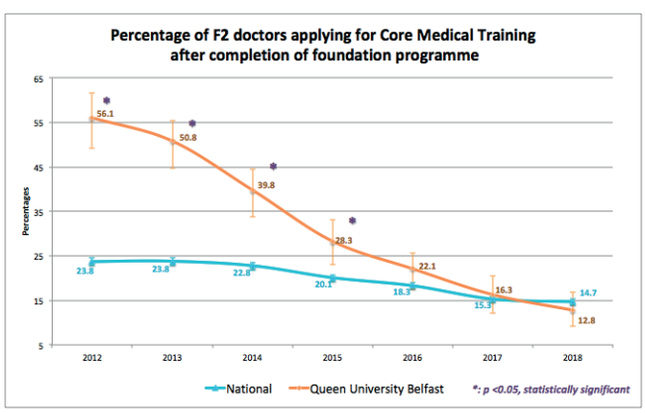

Figure 4: Percentage of FY2 doctors applying for Core Medical Training after completion of Foundation Programme training, from 2012 to 2018

2018. This was seen across the seven specialities we analysed (except for Clinical Radiology). Nationally, General Practice Training received the largest proportion of applications by FY2 doctors, but also showed the most significant reduction in the proportion of applicants from 36.8% in 2012 to 21.7% in 2018 (Figure 3).

At a national level, since 2012, the percentage of FY2 doctors

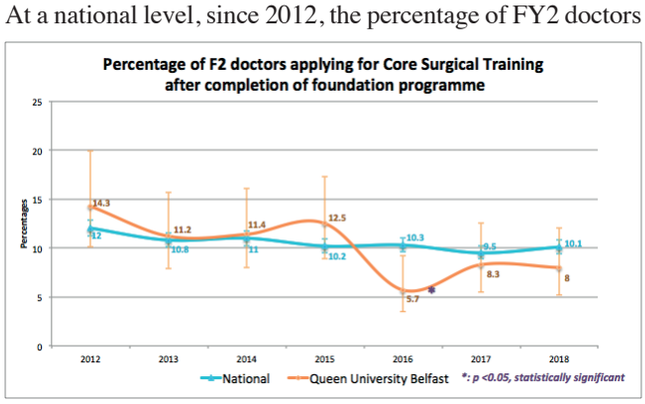

Figure 5: Percentage of FY2 doctors applying for Core Surgical Training after completion of Foundation Programme, from 2012 to 2018

applying for Core Medical Training (CMT) has declined gradually every year from 23.8% in 2012 to 14.8% in 2018 (Figure 4). Of interest, from 2012 to 2015, the percentage of FY2 doctors who were QUB graduates applying for CMT was higher than the national percentage.

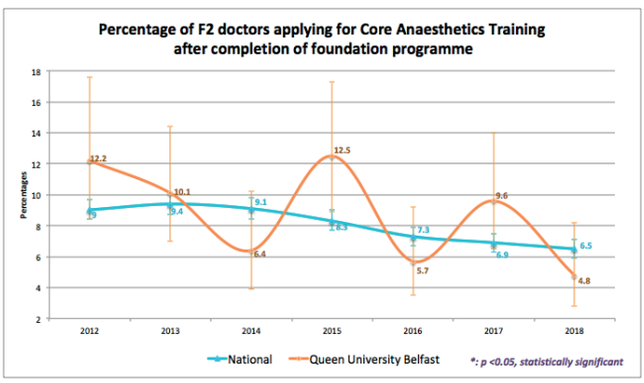

Figure 6: Percentage of FY2 doctors applying for Core Anaesthetics Training after completion of Foundation Programme training

Nationally, Core Surgical Training (CST) has had a consistent proportion of applications from FY2 doctors, approximately

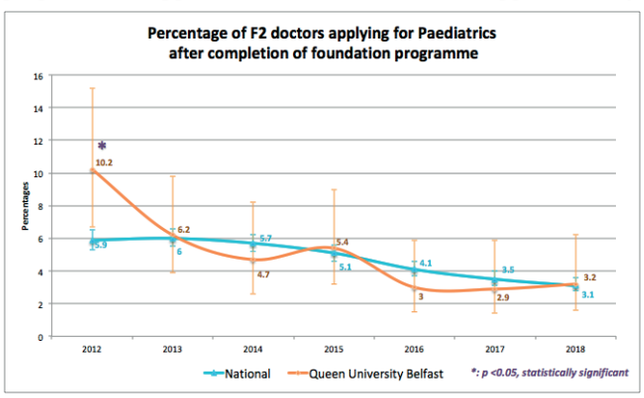

Figure 7: Percentage of FY2 doctors applying for Paediatrics after completion of Foundation Programme training

10% (Figure 5), from 2012 to 2018. The proportion of QUB graduates applying for CST at FY2 stage also displayed a

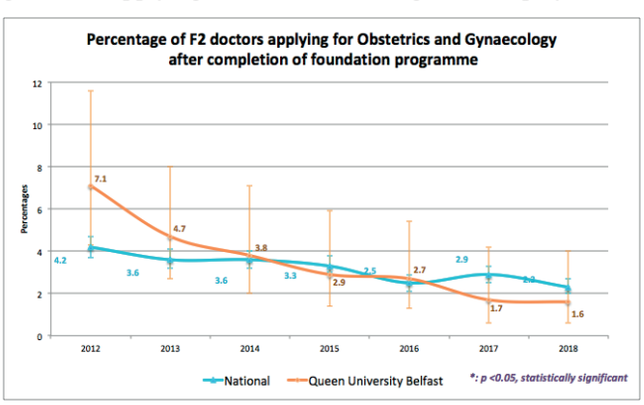

Figure 8: Percentage of FY2 doctors applying for Obstetrics & Gynaecology after completion of the Foundation Programme

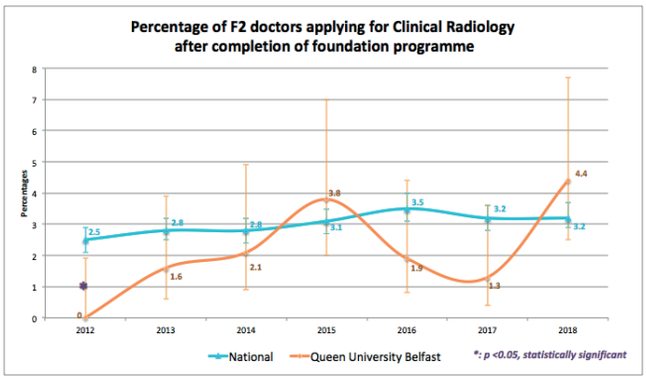

Figure 9: Percentage of FY2 doctors applying for Clinical Radiology after completion of Foundation Programme training, from 2012 to 2018

stable trend around 10 % despite a dip into 5.7% in 2016. The proportion of national FY2 doctors applying for Core Anaesthetics Training (CAT) also decreased from 9% in 2012 to 6.5% in 2018. The percentage of FY2 doctors who were QUB graduates applying for CAT also displayed a declining trend over the same period (Figure 6). No differences are noted in the applications to Paediatrics and Obstetrics & Gynaecology training which are shown in Figures 7 and 8.

The only exception is Clinical Radiology in which an overall increase is seen in the percentage of FY2 doctors making an application. Similar trends are noted in both national and QUB graduates. Details are shown in Figure 9.

DISCUSSION

The GMC National Training Surveys (NTS) have been conducted annually since 2006, and all doctors undertaking GMC approved training posts are invited to complete the survey. More than 75,000 doctors completed the surveys in 2019 across the United Kingdom.[6] The surveys evaluate both trainees' and trainers' satisfaction, and results are available online. The progression reports are part of the NTS and are designed to evaluate trainees' progression from both undergraduate (Primary Medical Qualification) and postgraduate (Training body).

The NHS is facing pressure in sustaining the medical workforce across the healthcare service. Moreover, it also requires ensuring the equitable distribution of trainees across all specialities and geographic locations based on workforce planning.[7] The individual career preferences of junior doctors and the supply of training places are directly responsive to the service needs.[8] An oversubscription in some specialities can prolong the time doctors spend in training due to increased competition for these posts. Conversely, there will still be a future shortage of practitioners in less-popular specialities.

The difficulty of delivering high-quality patient care within the NHS, partially due to underfunding, has contributed to doctors holding an increasingly negative view on the role of junior doctors in the NHS.[9] This negative view has manifested itself in the form of many FY2 doctors either leaving the U.K. or not going into core or speciality training directly

after completing their Foundation Programme training. In a 40-year long series of surveys, it was found that the desire of UK-trained junior doctors to remain in U.K. medical practice was unprecedentedly low in 2015.[8]

The number of FY2 doctors deciding to work outside the U.K. has varied from year to year. A similar trend is seen in QUB graduates with 15.2% and 25.2% decided to work outside the U.K. in 2016 and 2018 respectively.[4,10] Among the popular destinations for U.K. graduates to work after competition of Foundation Programme training are Australia and New Zealand. Sharma et al conducted a cross-sectional survey in 2012 and found that UK-trained doctors who left the U.K. to work in New Zealand had "higher job satisfaction than their UK-based contemporaries" and cited a preferable lifestyle in New Zealand as the predominant factor influencing their decision not to return to the U.K.[9] More recently, in 2015, it was found that FY2 doctors had reasons for leaving the U.K. specific to the challenges of their current roles, such as career decision making, exposure to workplace bullying, and difficulties in raising concerns.[11] Factors contributing to the negative view on the role of junior doctors at this time were difficulty in attending training due to workload (with additional pressure from the European Working Time Regulation), family life, and job seeking.[12]

A break in training can be viewed as a positive initiative.[13,14] Approximate 6-7% of QUB graduates decided to take a career break after Foundation Programme training.[4,6,10] At this critical point of career-decision-making between FY2 and Core/speciality training year one, a "gap year" provides junior doctors opportunities to consider their future options before committing to one speciality carefully. This "gap year' may allow trainees opportunities to acquire more skills, consolidate their existing skills and polish their applications to make them more competitive for CT1/ST1 posts. However, despite the benefits to the individual, the time-out makes workforce planning extremely challenging for the NHS. The progression reports also highlighted that 90% of FY2 doctors had made applications to core/speciality training within 4 years of completing Foundation Programme training. The number of FY2 doctors deemed appointable and entering core/speciality will be lower.[2] In addition to temporal breaks in training, there is a worrying exodus of junior doctors from the NHS to either practice abroad or work in other professions.[7]

There are several limitations to our study. First, the reason for trainees not entering the core/speciality training is not evaluated. Instead, we focused on revealing the trend of trainees applying/entering core/speciality training. Further studies are required to evaluate QUB graduates' career of choice and factors affecting their career progression. Moreover, we did not evaluate trainees' satisfaction in various specialities. Trainees satisfaction are linked to job performance and associated with a lower incidence of burn out. Several small studies concluded that Northern Ireland trainees felt well supported and supervised.[15,16]

CONCLUSION

Our data suggested that QUB graduates were less likely to apply directly to speciality/core training after completion of the Foundation Programme when compared with other medical graduates in Great Britain. This trend seems likely to continue. Further work is needed to encourage more medical graduates from Queen's University Belfast (and other U.K. universities) to apply for core/speciality training after completion of the Foundation Programme.

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Medical History

Psychiatric Day Hospitals

Alec Lyons

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Provenance: Internally peer reviewed

INTRODUCTION

The Psychiatric Day Hospital Movement in the United Kingdom started after the Second World War. One of the first was the Marlborough Day Hospital in London started by Dr Joshua Bierer, who was a great advocate of the "therapeutic community". In this concept, all members of staff, including clerical and domestic staff, could be involved in the treatment of patients and were part of the therapeutic team. Staff would no longer wear uniforms and they would eat together with patients in a communal dining area.

Psychiatric Day Hospitals arrived in Belfast in the 1950's and there were eventually three "stand alone" Day Hospitals in the city which were active between 1955 and 2000. All have now gone. The medical staff who worked in these hospitals are now aged and some are no longer alive. I write my memories of these hospitals before it is too late. As I will soon be 90, my memory may not be 100% as regards detail, but I have a clear memory of the main players. I worked in all three hospitals at different times and they were a major part of my professional life. I think it is important to put my memories on record. Writing this article was triggered by the recent death of Dr Artie Kerr, who worked with me in the Day Hospitals and we also both worked as consultants in the Rathlin Unit, Purdysburn Hospital.

THE HOSPITALS

The first one to open was Clifton Street Day Hospital. It was started by Holywell Hospital, Antrim Management Committee, the reason being that many of their patients came from the Newtownabbey area and as a strict boundary policy operated at that time, Newtownabbey patients had to go to Antrim.

The hospital in Clifton Street was in a three-story house a short distance from Carlisle Circus and a little north of Royal Avenue. The top floor was used as consulting rooms. The first floor was for use by patients and the bottom floor was offices and a reception area. There was a pleasant view from the top floor across to Clifton House, which was directly opposite, and a little to the left was the old Benn Ophthalmic Hospital. The situation of this Day Hospital was very suitable for patients to get to, as several main roads met nearby and there was excellent public transport available. There was no private parking, but it was usually easy to find a space in nearby streets.

Clifton Street Hospital was later taken over by Purdysburn Hospital Management Committee in the late 1960's, but its days were numbered because of the West Link development. It was demolished to accommodate the route of a new dual carriageway which linked motorways across Belfast.

The second Day Hospital to open was Albertbridge Road, which was situated in the heart of East Belfast. The building had been used formerly by the Northern Ireland Mass Radiography Service, but with a decline in the incidence of tuberculosis it was no longer needed for this purpose. It was a substantial building and a considerable extension was built at the rear when Purdysburn Management Committee took it over.

The ground floor accommodation included a large reception area where the medical secretaries were based, and patients also waited there for their appointments. The rest of the ground floor was consulting rooms, kitchen and dining area. The kitchen was small as the meals were provided by the main kitchen at Purdysburn, arriving each day in a hospital van. The first floor was mainly accommodation for the day patients. One area was set aside for the administration of Electroconvulsive Therapy (ECT). An anaesthetist attended for the ECT sessions, usually twice per week.

The Day patients were engaged in various types of occupational therapy and group discussion. Wide use was made of facilities in the community, especially the Rupert Stanley College which was situated nearby and patients attended a number of classes there.

There was a small car park at the rear of the building, but there was ample parking space in the adjacent Lord Street. Albertbridge Road Hospital, like Clifton Street Hospital, was in the centre of the community it served and was easily reached by public transport. It was situated in what was regarded as a strong Loyalist area, but many of the patients came from the Nationalist Short Strand area and I don't recall any problems. As Figure 1 shows, a barricade was erected at the top of Lord Street during the loyalist strike in the 1970's.

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The hospital can be seen in the background and this caused temporary problems for access for a short time, for both staff and patients.

Figure 1. Albertbridge Road Hospital with a barricade at the top of Lord Street in 1972.

The third Day Hospital to open was in Alexandra Gardens (Figure 2) in North Belfast. This was a replacement for Clifton Street Hospital. It consisted of two large semidetached houses. There was ample accommodation on the three floors and there was a large car park at the rear. It was slightly removed from the main area of population, so to facilitate patients' attendance a driver and van were organised by the management committee. Patients were collected at a few pick-up points in the morning and returned to their homes late afternoon.

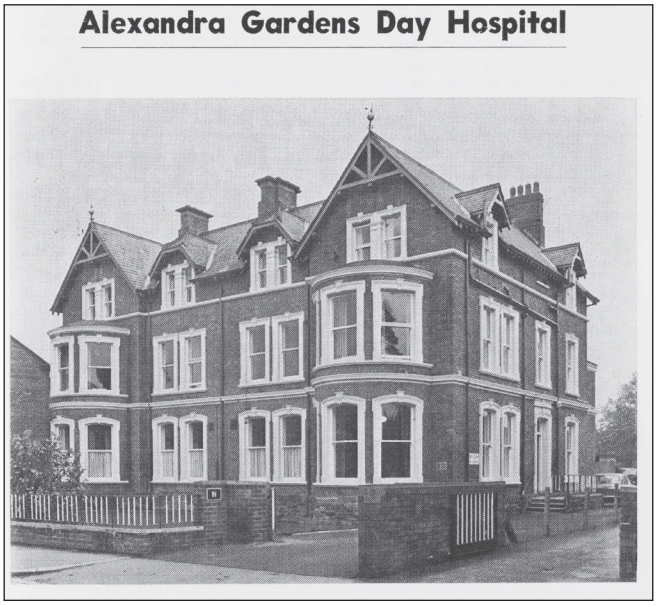

Figure 2. Alexandra Gardens Day Hospital

On the ground floor there was a large reception area and three consulting rooms. Opposite each consulting room there were smaller rooms used by the medical secretaries. Another room was set aside for physical examinations and another for patients' records. At the rear of the building there was a canteen, the meals arriving daily from the main kitchen at Purdysburn Hospital, as was the case with Albertbridge Road Day Hospital.

The first floor consisted mainly of accommodation for patients, providing a range of occupational therapy activities and group discussions. Once again, as in Albertbridge Road Day Hospital, use was made of the existing facilities in the community, which included a nearby church hall. The top floor was used for ECT and a variety of other treatments and was a quiet area often used for relaxation therapy.

THE STAFF

There was a strong medical input with at least two Consultant Psychiatrists working in each Day Hospital. The exception to this was Clifton Street Hospital where initially Dr Roger Whitely was the only Consultant. However, this was changed when Purdysburn Hospital Management Committee took over from Holywell Hospital Management Committee. Dr John Meenan and I were appointed at that time.

Dr Meenan had been a Consultant in the Tyrone & Fermanagh Mental Hospital previously. When Clifton Street Hospital was replaced by Alexandra Gardens Hospital, I was joined by Dr Artie Kerr and Dr Stafford Knox. Dr John Meenan moved to England.

When Albertbridge Road Day Hospital was opened in 1962, Dr Bill Norris was the Administrative Head and I joined him (Figure 3). Much of the consultants' time was taken up by out-patient clinics and the day-to-day running of the hospital was left to the nursing staff and the occupational therapy staff. The consulting facilities were used not only for new referrals, but also for the follow-up of patients who had been psychiatric in patients.

Figure 3. From Left, Dr Bill Norris, Sister Sally Mullan, Dr Alec Lyons and Dr Artie Kerr

The consultants were greatly assisted by other medical staff, particularly those graded as Senior Hospital Medical Officers. (This is now equivalent to Staff Officer Grade). This gave

continuity of care which is of major importance in psychiatry.

One SHMO post in Alexandra Gardens was shared between two women who lived in Bangor and often travelled together (Dr Sheila Leonard and Dr Yvonne Shaw). Another SHMO post at Alexandra Gardens was taken up by Dr Isolda Dolan. Many of the junior psychiatrists in training passed through the day hospitals as part of their rotation.

The day hospital running was largely carried out by nursing staff. There are too many to name, but Sister Sally Mullan and Sister Maureen Macklin stand out. The Macklin family later developed a chain of nursing homes in the Belfast area.

Anaesthetists attended, usually twice per week for ECT sessions. Dr George Bigley came to Albertbridge Road and Dr Kay Browne came to Alexandra Gardens, as well as a number of other anaesthetists at various times. Other types of treatment were given such as relaxation therapy, either with the help of drugs or hypnosis. One of the senior male Charge Nurses became an efficient hypnotist (Mr Declan Dixon).

An attempt was made to develop the concept of the therapeutic community with patients and staff being involved in group therapy. There was communal dining for staff and patients. This was not entirely popular, especially among the senior medical staff. This was the beginning of the "nurse therapist" era and the nursing staff and occupational therapy were very actively involved in treatment.

I worked closely with the social work staff, especially Mr Stanley Heron in Alexandra Gardens and Mrs Muriel Simm in Albertbridge Road. There were regular meetings of all disciplines and also meetings between patients and staff, to which all grades of staff attended.

The pharmacy was supplied from Purdysburn Hospital to all three Day Hospitals and Mr John Ward, Chief Pharmacist, often attended personally. The nursing staff dispensed the medication, which was a little complicated as the patients had access to medication at home and the situation had to be carefully monitored.

THE PATIENTS

The Belfast Psychiatric Day Hospitals were developed as acute treatment units and as an alternative to admission to Purdysburn Hospital where most psychiatric patient beds were situated. There were a few in-patient beds in the Mater Hospital under the care of Dr Pierce O'Malley. The Windsor Academic Unit at the Belfast City Hospital had just recently opened at this time.

Most day patients lived in the locality of the Day Hospital, but there was no rigid boundary policy. The patients usually arrived by public transport about 9.30 am and left about 4.30 pm. They started with daily attendance Monday to Friday and, depending on progress, attendance could be gradually reduced. They would then be followed up as an out-patient.

Most of the acute types of mental illness could be treated at the Day Hospitals including those with early symptoms of schizophrenia. Patients with chronic mental illness were not suitable for Day Hospital Management and were more suited to attend Day Centres where the emphasis was on general support and nurse supervision, with a strong input from occupational therapy staff. Day Centres were managed by Social Services. There was a considerable number of chronic mentally ill patients at this time (1960's) as the large mental hospitals were closing beds and discharging patients into the community.

Certain other types of patients were not suitable for management in the Day Hospitals, such as those living alone with active suicidal thoughts. However, if a suitable family member was available to help, those with severe depressive illness could be managed as day patients.

All the usual treatments were available including ECT, and various types of supportive psychotherapy, both individual and as a group, were a major part of their treatment. This was at the time when the word "counselling" came into vogue. The other recent innovation for treatment of psychotic illness was the administration of medication by intramuscular injection and nursing staff were actively involved with this treatment.

Treating patients in Day Hospitals had many advantages. Firstly, the patient was able to remain at home with their family and other family members could be involved in their treatment. Secondly, there was much less stigma attached to attending a Day Hospital. At that time there was considerable stigma attached to admission to a mental hospital such as Purdysburn, but this was much less with Day Hospital attendance. Also, the Day Hospital was in the heart of the community and it was possible to use existing facilities such as libraries and colleges of further education, and it was planned that the patients would continue to use the facilities when discharged.

SUMMARY

The Day Hospitals were fully active during "The Troubles" in Northern Ireland and were situated in areas of severe civil disturbance. The hospitals treated patients of different political persuasions within their premises and as far as I am aware, there were never any sectarian problems. The Albertbridge Road Hospital was close to the Nationalist area of Short Strand. The Day Hospital was situated in a strong Loyalist area, but patients from the Short Strand seemed happy to attend on most occasions.

The situation was described by Fraser Williamson, a Staff Nurse at Alexandra Gardens Hospital (Figure 2) who wrote a paper entitled "Day Hospitals in a Troubled Community". 1

The Day Hospitals no longer exist. Albertbridge Road is now a GP Health Centre. Clifton Street was closed because of the West Link development and Alexandra Gardens is vacant. Why did they close? Possibly a major factor was the retirement of the consultants who were working in these hospitals (Dr Norris, Dr Kerr, Dr Lyons). At least this was a trigger. The posts were not replaced as specific Day Hospital Consultants. Another factor was the development of the psychiatric units in general hospitals, especially the Mater

Hospital and the Ulster Hospital. Also, the development of multidisciplinary teams to do home visits and treat patients at home was an important development.

It would seem superficially that it would be more economical to treat patients on a daily basis.

However, I am informed that this was not the case and these "stand alone" Day Hospitals were more expensive to run due to the high patient/staff ratio and services having to be provided from the parent hospital.

I have happy memories of working in all three Day Hospitals at different times. I think most of the staff enjoyed their time in these units and got considerable job satisfaction. Relationships between all groups of staff were always cordial and in fact a number of romances developed. At least three marriages followed these romances. One male Senior Social Worker married one of the medical secretaries and they are now living in the south of Spain growing olives! Two senior male Staff Nurses married, one to a Social Worker and one to a Receptionist.

More importantly, the patients appreciated being treated near their homes. The Day Hospitals also fulfilled a teaching role and many medical students and psychiatrists in training passed through these units. Now that there is so much publicity regarding mental health issues, is it time to re-think the value of Day Hospitals?

I wish to acknowledge the advice and encouragement I received from Professor Margaret Cupples in writing this article.

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Letters

STAPHYLOCOCCUS AUREUS ENTEROTOXINS IN PEOPLE WITH CYSTIC FIBROSIS (CF)

Editor,

Staphylococcus aureus (SA) is a Gram-positive bacterium, which produces several enterotoxins inducing nausea. We hypothesize that patients with cystic fibrosis (CF) who are chronically infected with enterotoxin-producing SA in their airways may expectorate sputum containing enterotoxins, especially during sleeping, which may be ingested, subsequently leading to nausea. Therefore, we wished to examine if SA isolates obtained from CF sputum are enterotoxin-producers, which have the potential to cause nausea in their host.

We examined 16 clinical SA isolate from sputum of CF patients (n=16), who were infected with SA. SA cultures were examined for enterotoxins A, B, C, D and E by ELISA assay, in accordance with the manufacturer's instructions (RIDASCREEN® SET Total (R-Biopharm AG, Darmstadt, Germany). Of these, 10 (62.5%) isolates were positive for at least one enterotoxin, with the remaining six isolates negative for enterotoxin(s). There was no statistically significant difference (p=0.8) in lung function (FEV1%) between patients chronically/intermittently colonised with enterotoxin –producing SA strains and non enterotoxin-producing SA strains (Figure 1).

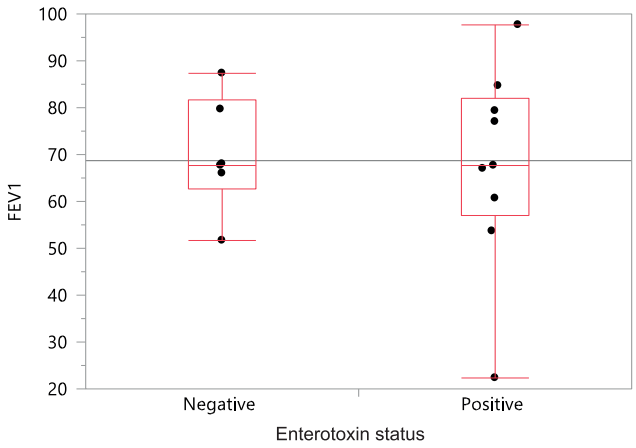

Figure 1: Comparison of lung function (%FEV_1) in patients with cystic fibrosis infected with enterotoxin-producing *Staphylococcus aureus* and non-enterotoxin-producing *Staphylococcus aureus* (p=0.82)

The exact amount of SEs required to produce emesis is not specific, largely due to individual variations in sensitivity to enterotoxins, however a study looking at a staphylococcal gastroenteritis outbreak discovered that doses of around 0.1µg of SEA were sufficient to produce nausea.[1] A review in 2012 found that most studies quoted the total amount of SEs required for symptomatic gastroenteritis to occur to be around 0.1µg, however one exception suggested the figure to be as high as 10-20µg.[2] In terms of numbers of enterotoxin-producing SA required to produce GI symptoms including nausea, this has been estimated to be *circa* 10^5 colony forming units (CFUs) per gram of food[2]. In the CF lung, previous work from our group has shown that with chronic SA infection, the mean number of organisms is 1.01 x 10^7 CFU per gram of sputum.[3]

In our CF population, 46.1% of adults and 44.7% of children are infected/colonised with SA. Data from the current study demonstrated that 62.5% of SA isolates were enterotoxin producers, equating to an occurrence of 28.8% and 27.9% SA enterotoxin-producers in adults and children, respectively. Interestingly, a study of 48 SA isolates from young and healthy Irish students between 1995 and 2004 found that 66.7% of isolates harboured the classical SE genes (SEA – SEE).[4]

Nausea in CF patients can be associated with several aetiologies, including distal intestinal obstruction syndrome (DIOS), chronic inflammation of the GI tract and antibiotic usage, as well as other less frequent causes of nausea, such as eosinophilic esophagitis. Given the relatively high occurrence of SA from sputum in the CF population, the high occurrence of enterotoxin producers within these SA isolates, combined with the frequent reporting of nausea, we are now exploring if this could be contributing to nausea in our CF patient population. Further work is now required to determine the stability of SA enterotoxins produced in the CF lung, particularly their persistence against denaturation by the proteolytic environment within the lung, including their intact passage from the lungs into the GI tract.

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OESOPHAGITIS DISSECANS SUPERFICIALIS – AN UNUSUAL ENDOSCOPIC FINDING

Editor,

Oesophagitis dissecans superficialis (ODS) is a desquamative oesophageal disorder, characterised by sheets of sloughed squamous tissue with normal underlying mucosa.[1] It is extremely rare and benign.[2] We describe a case of ODS and discuss the condition.

An 83-year-old female was admitted to hospital with a 4 day history of vomiting and central cramping abdominal pain.

On abdominal examination, there was epigastric tenderness with intermittent guarding. Abdominal radiograph showed faecal loading.

The impression was gastritis and constipation. A Computed Tomography scan of the abdomen and pelvis was carried out, due to suspicion of ischaemic bowel and showed no acute intra-abdominal pathology. The scan report noted that the stomach fundus appeared slightly thick-walled and advised an oesophago-gastro-duodenoscopy (OGD).

The OGD showed ODS in the oesophagus (Figure 1), and a small hiatus hernia. The stomach and duodenum appeared normal. Biopsies were taken. The oesophagus showed patchy acute mild inflammation with epithelial hyperplasia and parakeratosis. Periodic acid-Schiff stain showed scattered *Candida* organisms. The gastric body mucosa showed some cystic dilatation of glands suggestive of a fundic-type polyp, with no evidence of dysplasia.

The patient was prescribed laxatives and anti-emetics. Over several days, her nausea and constipation resolved.

ODS is a desquamative oesophageal disorder, involving sloughing of the superficial mucosa.[1] It is extremely rare, with one study reporting an incidence of 0.03%.[3] It usually affects adults after age 50 and is slightly more common in women than men.[3]

ODS can be idiopathic or secondary to oesophageal mucosal

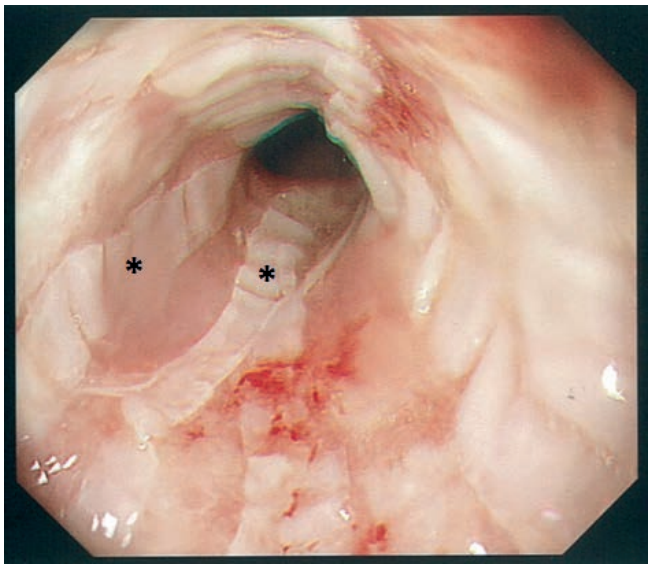

Fig 1. Endoscopic image of the oesophagus, showing sheets of sloughed mucosa (see asterisks), with normal underlying mucosa

injury which may be due to bisphosphonates and non-steroidal anti-inflammatory medications, certain foods, or repeated vomiting.[4] It is also associated with systemic diseases, such as pemphigus vulgaris and coeliac disease.[1] In this case, the patient was not taking any associated medications and did not have any associated systemic diseases.

It is usually asymptomatic and discovered incidentally, which was likely to be the case in our patient. It can occasionally be associated with dysphagia, nausea, bleeding, vomiting, heartburn, epigastric pain, and odynophagia.[2,3] The abdominal pain in our patient's case was felt more likely to be due to constipation rather than her ODS, as the pain improved following successful laxative use.

It has been suggested that meeting 3 of the following endoscopic criteria is consistent with ODS: "(1) strip(s) of sloughed oesophageal mucosa >2cm in length; (2) normal underlying oesophageal mucosa; and (3) lack of ulcerations or friability of immediately adjacent oesophageal mucosa."[1] Biopsies are not always necessary, but should be performed if the patient is symptomatic, a coexisting diagnosis may be present, or the endoscopic features are not classical.[1]

The most common histological findings are parakeratosis and intraepithelial splitting, although these are non-specific.[1] Biopsies may show inflammation, and there may be associated fungal elements.[5] In our patient's case, *Candida* was noted.

Whilst there are no clear guidelines for the management of ODS, it has been reported that stopping any potential causative medications and use of acid-suppressing medications results in resolution. ODS is benign and does not cause permanent damage.[2]

It is important to raise awareness of ODS. One study reported that only 41.5% of cases were correctly identified at endoscopy.[1] Gastroenterologists' unfamiliarity with this condition may cause it to be mistaken for other diseases[3].

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COLLATERAL THINKING

Editor,

We present a rare and challenging case of a patient presenting with ectopic variceal haemorrhage. A 57 year old man with a background of alcohol related liver cirrhosis (Child Pugh A6, MELD 10) presented with 3 episodes of frank bleeding from his umbilicus over a 4 day period. Variceal surveillance with OGD in March 2017 was negative and other significant medical history included alcohol dependence, morbid obesity, type 2 diabetes mellitus and COPD.

Abdominal examination showed caput medusae that had been oversewn in the emergency department; there was no detectable ascites or asterixis. Doppler ultrasound of liver revealed patent hepatic vasculature. Subsequent CT confirmed cirrhotic appearances of the liver with features of portal hypertension, recanalisation of the umbilical vein and varices measuring up to 2cm in diameter within an umbilical hernia (Figure 1 and 2).

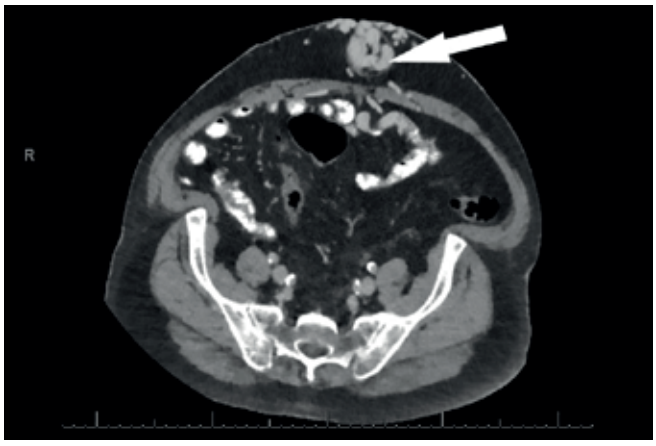

Fig 1. CT showing sizeable umbilical varices (white arrowhead)

Following a further episode of bleeding from the umbilicus 48 hours post-admission, his haemoglobin fell from 113 g/L (130 – 180 g/L) to 62 g/L. He was managed as per gastro-intestinal variceal haemorrhage with transfusion of packed red cells, terlipressin and prophylactic antibiotics.

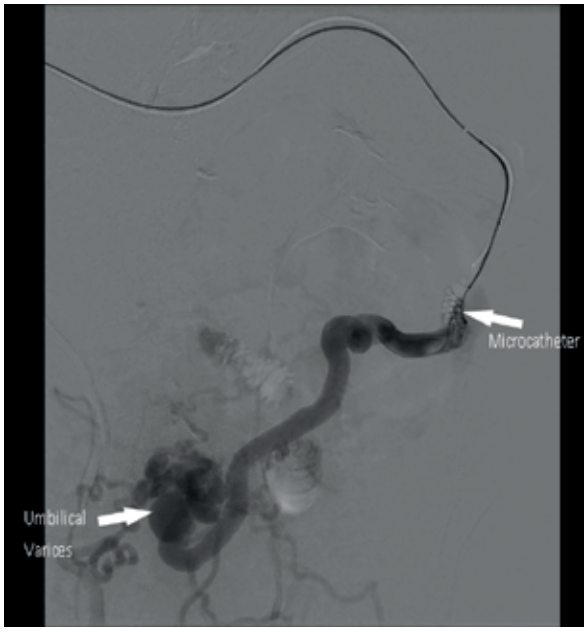

Fig 2. Catheterisation of umbilical varices

To prevent further bleeding a transjugular intrahepatic portosystemic shunt (TIPSS) was arranged. An echocardiogram, performed as part of a pre-TIPSS work-up, established that biventricular function was normal. He remained haemodynamically stable and proceeded to TIPSS (Figure 3) which proved to be technically successful with the aid of CT fusion imaging (Figure 4). A significant hepatic venous pressure gradient in excess of 30 mmHg was recorded prior to stent deployment. Venography demonstrated a large portosystemic collateral vessel which eventually reached the level of the multiple varices at the patient's umbilicus. A

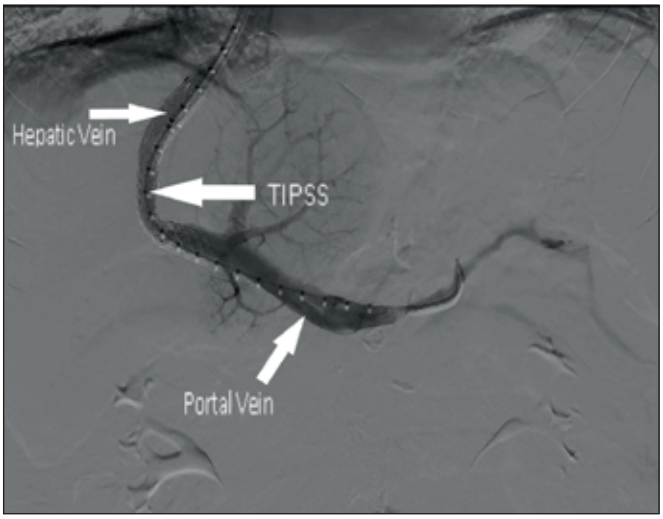

Fig 3. TIPSS insertion

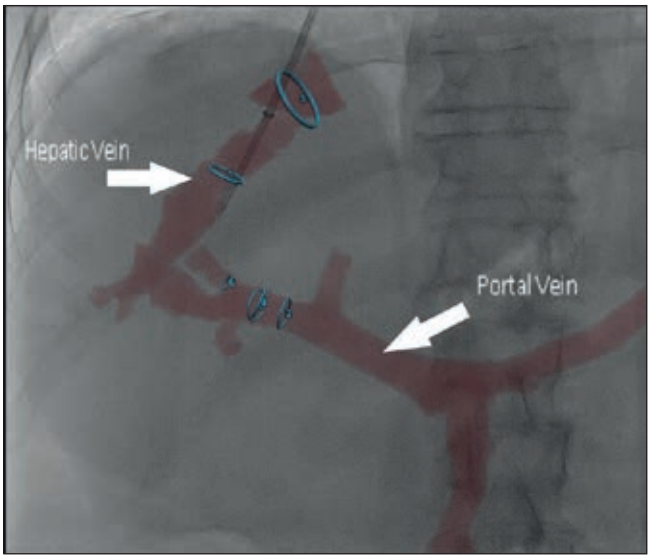

Fig 4. CT guided fusion imaging

microcatheter was negotiated along this allowing coiling and fibrovein foam embolisation (Figure 2). Following TIPSS and embolization (January 2018) bleeding was controlled and the patient was successfully discharged.

To date, liver cirrhosis remains compensated with no post TIPSS hepatic encephalopathy in spite of relapse to low level alcohol consumption. He is currently Child Pugh A5 offering a 1 year survival of 95% and 2 year survival of 85%. No further variceal surveillance is required as portal hypertension has been addressed.

Gastroesophageal variceal bleeding is a common complication of patients with chronic liver disease. Bleeding from any location where there are portosystemic anastomoses and collateral vascular formation is possible.[1] Variceal bleeding from locations other than the gastrointestinal tract (ectopic variceal bleeds) whilst rarely considered, account for up to 5% of all variceal bleeding. In addition, haemorrhage can be massive with mortality reaching up to 40%.[2]

Treatment is generally guided by local expertise due to absence of large studies. Initial interventions such as suture haemostasis and cauterisation have success for only a limited time frame. Medical treatments implemented to lower portal pressure include vasoconstrictors (terlipressin) in the acute setting and beta blockers (propranolol, carvedilol) in the chronic setting.[1, 2, 3]

Radiological interventions such as shunting (TIPSS) and percutaneous umbilical vein embolisation with sclerotherapy have been documented. A greater than 50% reduction in pressure gradient has been demonstrated to protect patients from rebleeding.[1]

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Key Words: Gastrointestinal Bleeding/Alcoholic Liver Disease/Interventional Radiology/Portosystemic Shunting

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PRIMARY PANCREATIC LYMPHOMA

Editor

We present a case of a rare primary pancreatic malignancy which provides a challenging diagnosis given a non-specific presentation and lack of unique identifiers on imaging.

An 80-year-old gentleman presented with painless jaundice (Bilirubin 85 µmol/l, Alkaline Phosphatase 235 U/L, Aspartate Aminotransferase 124 U/L, Alanine Aminotransferase 132 U/L, and Gamma-Glutamyl Transferase 326 U/L).

Abdominal ultrasound confirmed a large mass related to the head of the pancreas. Computed Tomography (CT) chest, abdomen and pelvis showed a pancreatic mass with vascular involvement and presence of a gastric antrum lymph node.

Endoscopic Ultrasound (EUS) with Fine Needle Biopsy (FNB) of the pancreatic mass was performed (Figure 1 and Figure 2). Figure 1 shows a 3.7cm hypoechoic mass with no vascularity on Doppler imaging, suggesting that the mass is not a neuroendocrine tumour. Figure 2 shows the mass infiltrated by a biopsy needle and a smooth non-infiltrative border, atypical of adenocarcinoma.

Histology and immunochemistry of the pancreatic mass confirmed a high-grade B cell Non-Hodgkin's Lymphoma stage IV A.

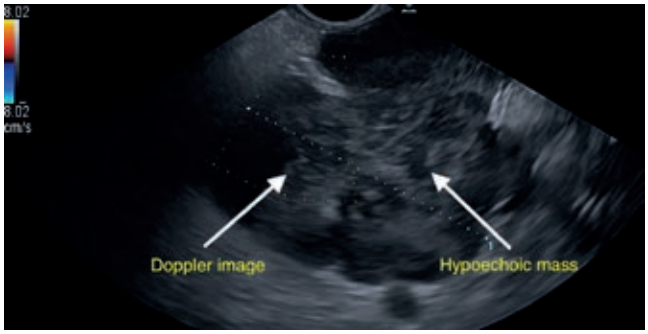

Figure 1

He was referred to haematology for treatment and following cycle 4 of chemotherapy, a follow up Computed Tomography scan of his Chest, Abdomen and Pelvis showed a significant reduction in size of the Primary Pancreatic Lymphoma.

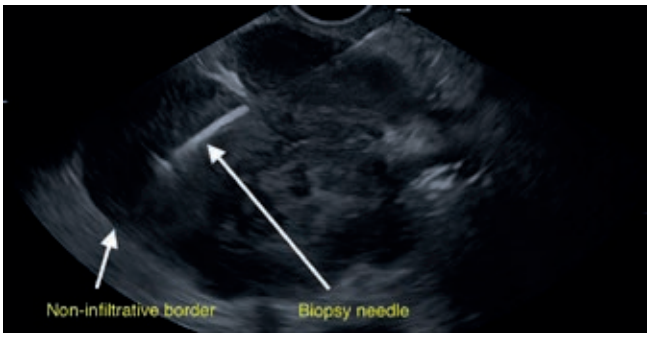

Figure 2

DISCUSSION

Primary Pancreatic Lymphoma (PPL) is a rare subtype of primary pancreatic malignancy, consisting of <0.5% of all pancreatic cancers), usually found in males aged 35-75.[1,2]

The diagnostic criteria for PPL are:

1) Neither superficial lymphadenopathy nor enlargement of mediastinal lymph nodes on chest radiography.

2) Normal leucocyte count in peripheral blood.

3) Main mass in the pancreas with lymph-nodal involvement confined to the peri-pancreatic region.

4) No hepatic or splenic involvement. [3]

They present in similar ways to the head of pancreas adenocarcinoma, with symptoms such as jaundice, pancreatitis, abdominal pain, abdominal mass and diarrhoea, though rarely have typical B-symptoms of Non-Hodgkin's Lymphoma such as night sweats or fevers.[2]

Serum tumour markers are not particularly useful in PPL as they are not always raised, and CT scan can confirm presence of distal node involvement therefore pointing away from a PPL.

Endoscopic ultrasound (EUS) combined with fine needle biopsy (FNB) improves diagnostic accuracy on top of an FNA alone.[2] EUS is less invasive and can characterise the lesions present. Once a FNB has been obtained from EUS, it will be sent for Flow Cytometry (FC) and immunohistochemistry in order to aid diagnosis and treatment.

The treatment for PPL is cycles of chemotherapy under the guidance of a haematologist, without evidence for surgical resection. [4]

The prognosis for PPL is much better than that for pancreatic adenocarcinoma. A case series from 2005 showed a mean survival rate of 69-80 months for patients who received chemotherapy as a first line treatment for PPL.[5]

CONCLUSION

As shown in this case, histological sampling of a pancreatic mass must always be made given the difference in treatment and prognosis between adenocarcinoma and PPL. Given the small amount of tissue involved, samples should be sent for immunohistochemistry and flow cytometry to aid diagnosis and treatment.

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FEASIBILITY OF COLOUR DOPPLER ULTRASOUND FOR DETECTION OF INTRAARTICULAR SACROILIAC JOINT INJECTION: A CASE SERIES.

Editor,

We would like to share our experience of colour Doppler ultrasound (CDU) in the detection of correct needle placement for sacroilliac joint (SIJ) injection during interventional procedures for management of low back pain (LBP).

Injection of steroid mixed with local anaesthetic (LA) is a well-recognised method for both diagnostic and therapeutic management of SIJ pain. Several imaging modalities have been used to guide such interventions in SIJ.[1] Fluoroscopic guidance is still considered as gold standard to confirm needle placement and spread of the dye. The majority of such imaging techniques involve use of ionising radiation. Ultrasound is however being used increasingly.[2] In many interventional pain procedures it is replacing ionising modalities because of the portability allowing the procedure to be performed at bedside without such hazards.[3] However, ultrasound has ta potential limitation in viewing the needle trajectory and the spread of the injectate inside the bony SIJ. CDU can overcome this problem by allowing visualisation of the flow of the injectate.[4] We thus decided to conduct this case study to find out the utility of CDU.

After obtaining approval from ethical committee and informed consent, 10 adult patients scheduled to undergo SIJ injection were included. After positioning the patients in prone position and using proper aseptic cleaning and draping, a low frequency curvilinear ultrasound transducer was used to localise the target SIJ anatomy. After skin infiltration with LA, a 22-gauge Quincke spinal needle was advanced towards the SIJ under ultrasound guidance. Once the needle was seen to enter the SIJ, colour Doppler mode was activated. A 1.5 mL mixture of steroid and LA was then injected. Positve Doppler signal suggesting the flow within the SIJ along with absence of any overflow outside the bony landmarks were noted (**Fig 1**). Then an independent observer who was blinded about the study methodology, confirmed the intra-articular placement of the needle fluoroscopically by injecting radioopaque contrast. Efficacy of the injection in providing pain relief, was assessed at follow up.

Demographic details of the patients are depicted in **Table 1**. CDU flow pattern indicated correct intra-articular injection without any extra-articular flow pattern in all our patients. Subsequent fluoroscopy and dye injection also confirmed correct needle placement. Preprocedural visual analog score (VAS) (6.7±1.05) reduced significantly after the injection

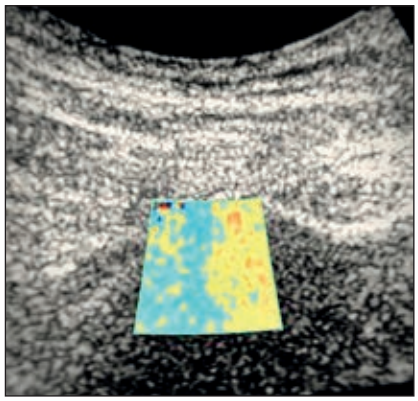

Fig 1: Use of color Doppler flow to locate needle placement.

(2.3±1.03) (p <0.0001) (**Table 2**) confirming the efficacy of the procedure.

In this case series, we found that CDU can be used successfully to confirm correct intra-articular placement of needle and subsequent injectate in SIJ.

Table 1: Demographic data and Pain scores.

		p value
Age (Years)	55.7±11.81	NA
Male	4	NA
Female	6	NA
Pre-Procedure VAS score	6.7±1.05	<0.0001
Post-Procedure VAS Score	2.3±1.03	

VAS: Visual Analog Score. Data expressed as mean±standard deviation or discrete variables wherever application.

This utility of CDU has not been reported to date. Arslan *et al*. used duplex and colour Doppler ultrasound to demonstrate vascularity inside and around the SIJ to diagnose sacroilitis and to monitor the therapeutic response, but they did not perform any SIJ injection using ultrasound.[5]

Table 2: Techniques used for needle placement and confimation of that.

	Intra-articular Doppler Flow Signal	**Extra-Articular Doppler Flow Signal**	**Subsequent Fluoroscopic Confirmation of Needle Placement**
US Doppler Guided Needle placement	Detected in all cases	Not detected in any case	Intra-articular needle placement confirmed in all cases using radioopaque dye.

We thus strongly propose a well powered randomised controlled trial on this.

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Conflict of Interest: The authors report no conflicts of interest.

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SLOW SURGERY?

Editor,

Some of your readers will have heard of slow medicine. This concept was born in Italy in 2011 and aims to make medicine more measured, respectful and equitable.[1] Slow medicine asks health professionals to take their time to allow for a more holistic approach and a careful consideration of new methods and technologies. The movement has expanded, particularly in Europe.[2]

This has got me thinking about the surgical equivalent – slow surgery. For example, my Health Board in Wales, a home nation of the UK, has introduced an orthopaedic lifestyle programme for patients who may need a hip or knee replacement and have a Body Mass Index (BMI) of 35 and over. Patients take part in a 32-week programme of exercise classes at Leisure Centres and receive support from qualified professionals such as physiotherapists and dieticians. The aim is to induce weight loss in order to reduce the complications of surgery, as well as to decrease pain to the point, in some cases, where surgery is no longer needed.

The operational standards relating to referral to treatment times in Wales are that 95% of patients should be seen within 26 weeks, and no patients should wait longer than 36 weeks.[3] Trauma and Orthopaedics is the largest contributor to long waits, with 66% of total waits over 36 weeks in March 2018 being from this surgical specialty; this is followed by general surgery (9%). Therefore, could it be argued that we are practicing slow surgery by default anyway? I am sure that the picture will be similar in other home nations of the UK.

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PLASTIC AND RECONSTRUCTIVE SURGERY JOURNALS: FEASIBILITY OF ACCESS BY SURGEONS AND TRAINEES IN THE UNITED KINGDOM.

Editor,

The current surgical training system expects high levels of knowledge from trainees[1]. This is especially true in plastic and reconstructive surgery which is one of the most competitive specialties. Hence, surgeons in training must be familiar with the current literature in the field.

The resources available to achieve this goal reside mainly in medical journals. Access has been widely revolutionised by the novel electronic platforms.[2] However, limitations imposed by subscription fees are a significant obstacle.

We conducted an electronic survey to assess availability of medical journals, in UK units to surgeons in training and analyse the pattern to make recommendation for improvement. Ten journals were selected using the Scientific Journal Ranking (SJR) index, which is a numerical value used to compare journals according to the number of citations and popularity.[3] (Figure1). A questionnaire was distributed to librarians in the respective units followed by a telephone call to units that did not respond.

We collected responses from 52 units with 100% response rate. 45(86.5%) of them were in England, five (9.6%) in Scotland and one (1.9%) unit each in Wales and Northern Ireland.

The mean was 6.48 journals per unit whilst the overall mode was nine. One (1.9 %) unit had no access while only eight (15.3%) units subscribed to all journals.

The plastic surgery units in London and Scotland had higher access to the selected journals compared with other geographical areas in the UK. The highest number of journals accessible to trainees was in Scotland with an average of 9.2 followed by London with an average of 8.5.

The journal subscribed the most was Plastic and Reconstructive Surgery in 41(78.8%) of the units. The results show significant variation in both the number and quality of journals available to plastic surgery trainees in different units. In order to provide a level playing field, all trainees should have access to at least a core number of relevant journals.

Potential solutions include migrating to free access journals or providing shared access through a central point.

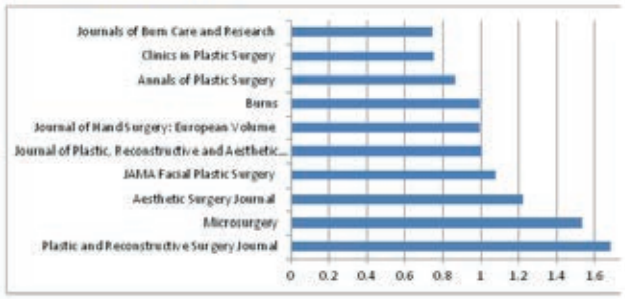
Open access journals, full or hybrid, provide free navigation without restrictions.[4] Funding can take many forms including article processing charges, institutional membership scheme, volunteer labour, sponsorship, institutional subsidies and finances from other sources.[5]

A growing trend is the conversion of subscription-based journals to hybrid open access journals where authors pay an extra charge to make their articles freely available to readers.[4] The development of open access journals may be helped by policy makers through centralised payment

scheme towards the article processing charge.[3] A good example of institutional support is the agreement between UK institutions and Springer to provide free access to more than 2000 subscription journals and an option for open access publication in hybrid journals.[6]

Another option is to provide a themed specialty specific subscription organised by professional bodies to replace the current arrangements that provide area-specific subscription organised by the relevant National Health Service trusts. Partnership between universities and NHS trusts can increase such access.

Chart 1: Plastic and reconstructive Journals included in the study and respective SJR indices 2016



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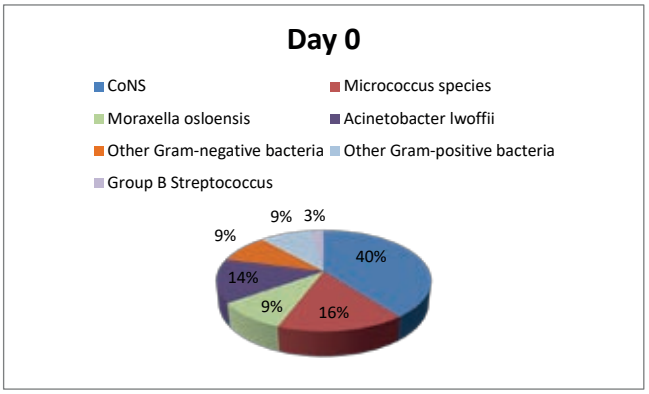
WHO CLEANS YOUR OCTOPUS? AN OBSERVATION OF CLEANING BEHAVIOURS AND BACTERIAL COLONISATION OF TOYS IN A NEONATAL UNIT

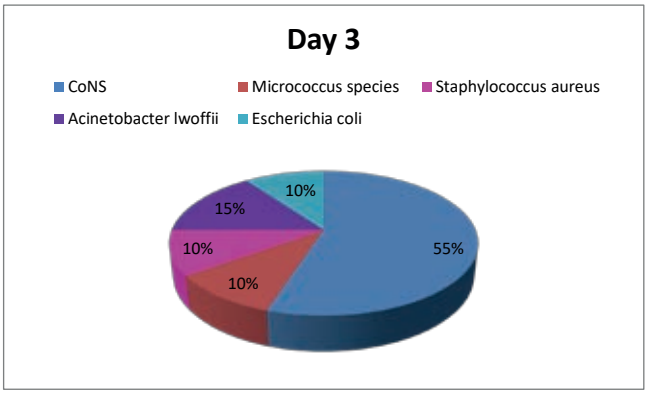
Editor,

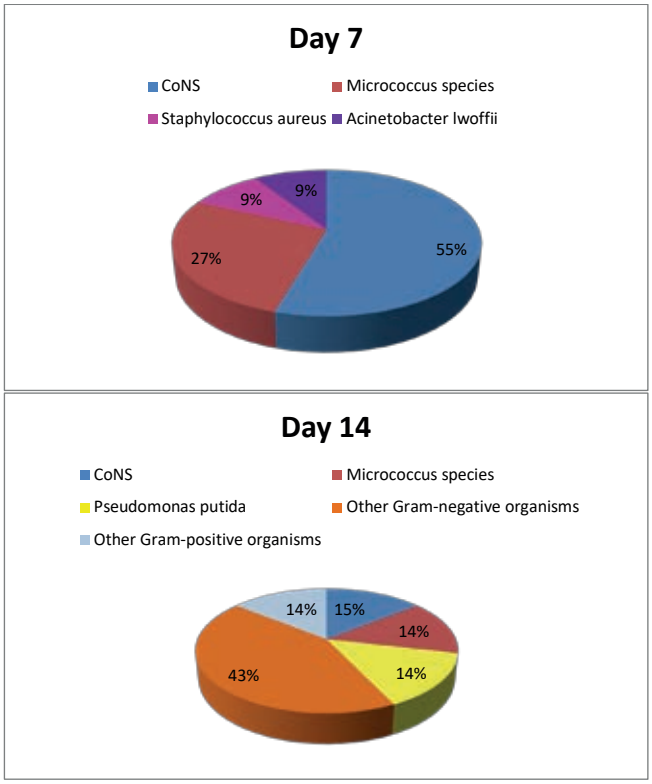
Toys remain a fixture of neonatal intensive care units despite being proven reservoirs of nosocomial microbes.[1] A survey of 13 neonatal units in the UK[2] identified variation in procurement and cleaning procedures and testing for fomites. Washing toys is proven to reduce the bacterial load of potential pathogens.[3] However there remains variation between units, regarding who has responsibility for cleaning toys, and what the interval between washes should be.

Toys within neonatal units have recently received a significant boon in press coverage. A movement originating from Aarhus, Denmark has seen knitted octopodes become an increasing fixture in neonatal units, with hospitals worldwide issuing public appeals for their procurement via social media. Despite emotive stories about the benefits of such woollen crustaceans there remains a paucity of published data proving they help regulate infant breathing, or reducing heart rate as is oft claimed anecdotally. Whilst the physiological benefits of toys in the neonatal setting are yet to be corroborated or refuted by robust testing, they are unlikely to disappear from units. Toys are often preferred by parents, they humanise an otherwise intensely clinical environment. Their presence allows parents to provide a touch of the child friendly environment, similar to that enjoyed on maternity and paediatric wards alike.

Figure 1. NICU Toy swabbing audit 2018







In a 13 bed neonatal unit, we tested all toys for colonization and observed for cleaning behaviours. No prompting was given to the parents to procure, remove or clean toys. Parents were free to supply, remove or take any toy for cleaning as they deemed fit, representing no change in established clinical practice. Toys that were removed for cleaning and returned by the parents were recorded.

During testing the operator washed their hands with the 7 step technique and donned sterile gloves before removing the toy, swabbing the entire surface with a moistened sterile swab and replacing the toy. The same procedure was repeated on day 3, day 7 and day 14 of the toy's sojourn in the neonatal unit.

The anonymised swabs were cultured on plates of MacConkey agar and Columbia blood agar. Results were not communicated from the lab until after the study period.

Figure 1 displays the prevalence of those micro-organisms cultured.

The positive culture rate of the toys was 72-82%. The predominant organisms in the first week were Coagulase-negative Staphylococcus (CoNS) and Micrococcus species, (skin commensals). The predominant Gram-negative organism was *Acinetobacter lwoffii* (an environmental organism). Group B Streptococcus was found on one toy, *Escherichia coli* on 2 toys. *Pseudomonas pudita* was cultured from a toy on day 14. *Pseudomonas* has gained notoriety in neonatal circles as recent outbreaks were associated with mortality in this population.[4]

Of the 28 toys enrolled into this study none were removed for cleaning and thereafter returned by the parents during the 3 month study period. A policy which depends on parents washing toys frequently under their own volition e.g. as suggested by octopusforapremie.com, was unsuccessful. After 7 days failure to do so seemingly increases the risk of colonisation by Gram-negative organisms including pseudomonas.

Yours sincerely

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Dr Peter Yew (Consultant Microbiologist),

Dr Ryan Graydon (Senior Biomedical Scientist),

Doris Wilson (Advanced Neonatal Nurse Practitioner),

Claire Boyce (Advanced Neonatal Nurse Practitioner),

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Abstracts

22nd Meeting of the Irish Society of Human Genetics

Friday 20th September 2019 Stranmillis University College, Belfast.

ORAL PRESENTATIONS:

OP01. The Genetic Landscape of Scotland and the Isles.

Edmund Gilbert[1,2], Seamus O'Reilly[3], Michael Merrigan[3], Darren McGettingan[3], Veronique Vitart[4], Peter K Joshi[5], David W Clark[5], Harry Campbell[5], Caroline Hayward[4], Susan M Ring[6,7], Jean Golding[8], Stephanie Goodfellow[9], Pau Navarro[4], Shona M Kerr[4], Carmen Amador[4], Archie Campbell[10], Chris S Haley[4,11], David J Porteous[10], Gianpiero L Cavalleri[1,2*], James F Wilson[4,5*]. *equal contribution

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The genetic structure within southern Britain and Ireland is well described, however large swathes of Scotland in particular have yet to be characterised. In addition, Scotland and Ireland experienced Norse Viking invasions around the turn of the 1st and 2nd millennia. However, the extent to which these movements impacted the genetic landscape of both Scotland and Ireland is poorly understood. Thus we; i) assembled genotype data for 2,554 individuals from across the entire archipelago with geographically-restricted ancestry (including the Isle of Man and Shetland for the first time), ii) compared population structure in Scotland to the rest of Britain and Ireland, iii) modelled the proportion of Norwegian ancestry in northern Britain and Ireland, and iv) compared this modern structure to ancient Gael and Norse DNA. Extensive geographic structuring is revealed in Scotland; from broad scales such as a NE to SW divide in mainland Scotland, to very fine structure in the Northern Isles of Scotland. We document Norwegian ancestry in the north of Scotland, within Orkney and Shetland (reaching its maximum in Shetland) which falls to minimal frequency outside of the north of the country. We find the best proxies of ancient Icelandic Gaels in to be the north-west of Britain and Ireland, specifically the Hebrides and Donegal. Therefore the genetic diversity of these regions will allow better understanding of Viking movements and the founding of Iceland.

OP02. Interrogating and correcting fine-scale genetic structure in large (>36,000 samples) GWAS datasets using scalable haplotype sharing methods

RP Byrne[1], W van Rheenen[2], JH Veldink[2], RL McLaughlin[1]

[1.] Smurfit Institute of Genetics, Trinity College Dublin. [2.] Department of Neurology, Brain Center Rudolf Magnus, University Medical Center Utrecht.

We leveraged a powerful and scalable haplotype painting algorithm, the Positional Burrows Wheeler Transform (pbwtPaint), to explore the co-ancestry of 36,052 individuals of European descent from a recent amyotrophic lateral sclerosis (ALS) genome-wide association study (GWAS). The resulting haplotype sharing matrix revealed both striking broadscale genetic structure between samples from different countries and subtle genetic structure within each country. This approach captured population structure within the dataset at a far higher resolution than standard methods using unlinked single nucleotide polymorphism data, making it an appealing option for correcting subtle confounding in GWAS. We explored this possibility by fitting principal components (PCs) of this haplotype sharing matrix as covariates in a logistic regression model GWAS, and comparing metrics of statistical inflation and confounding against a model using standard independent marker PCs as covariates. We observed that both the λ_{GC} and LD-score regression intercept were significantly closer to 1 when using PCs of the haplotype sharing matrix, signifying lower inflation and confounding from population structure. Notably, the GWAS analysis that was corrected using haplotype sharing PCs as covariates retained the power to detect all major hits from the original meta-analysis of the data, suggesting that it does not suffer from loss of power to detect true associations. We also detect an additional hit at the established ALS locus *TBK1*, which was sub-threshold in the original analysis, but has since been detected in larger ALS GWAS, implying that this method imparts greater power than traditional approaches in some scenarios.

OP03. Investigating the genetics of cognitive resilience in healthy ageing using the UK Biobank (n = 333,737)

Joan Fitzgerald[1], Laura Fahey[1], Laura Whitton[1], Gary Donohoe[1], Derek W Morris[1]

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Background: Age-related cognitive decline results in increased difficulty in performing tasks that require memory or rapid information processing. Cognitive resilience is the ability to withstand the negative effects of stress on cognitive functioning. The polygenetic contribution to cognitive resilience requires large data sets for analysis. In addition, longitudinal data is needed to identify individual differences in cognitive performance over time. The UK Biobank cohort of over 500,000 participants over the age of 40 offers the potential to advance research on the genetics and biology of cognitive resilience.

Methods: We created a longitudinal cognitive resilience phenotype by combining the phenotypic cognitive parameter of current reaction time with a proxy phenotype of education years (EY). We used this resilience phenotype, in genome-wide association studies (GWAS) to identify genes and gene sets that influence the biological pathways involved in resilience. To remove the influence of the EY on the analysis we compared genetic data on participants that displayed resilience to those that showed expected cognitive decline.

Results: GWAS outputs analysis showed 273 significantly enriched genes for participants that demonstrated resilience. Genotype–tissue expression was significant in brain tissue, particularly in the anterior cingulate cortex, frontal cortex, and hippocampus. Biological Pathway analysis includes synapse, post synaptic density and neuron guidance.

Conclusion: This analysis shows an association between cognitive resilience and enrichment of neuronal activity. Confirmatory examination of these findings in datasets with strong longitudinal cognitive data, such and the Health and Retirement Study, is on-going.

OP04. Genome-wide DNA methylation analysis for type 1 diabetes

LJ Smyth, C Wooster, J Kilner, F Kee, I Young, B McGuinness, AP Maxwell, GJ McKay, AJ McKnight with the

GENIE consortium and NICOLA Collaborative Group

Genetic Epidemiology Research Group, Centre for Public Health, Queen's University Belfast

Introduction: Type 1 diabetes (T1D) is a polygenic disease characterised by autoimmune inflammatory destruction of the pancreas and subsequent hyperglycaemia. Several GWAS have identified loci associated with T1D risk, but recent evidence suggests that epigenetic changes in DNA methylation may have a causal role in T1D.

Methods: To identify potential methylation-based biomarkers of T1D, blood-derived DNA from 250 individuals with ≥15 years duration of T1D was compared to 391 controls with no evidence of diabetes. All individuals were from the British Isles. DNA was bisulphite treated using the EZ DNA Methylation Kit (Zymo). The Infinium HD Methylation Assay MethylationEPIC BeadChips (Illumina) were used to determine the methylation status of >850,000 CpG sites, gene bodies and promoters.

Results: MethylationEPIC data was analysed using GenomeStudio v2011 and Partek Genomics Suite v7.0. Comparing T1D with controls identified 1,706 CpG sites with significantly different ($p<10^{-8}$) levels of methylation (≥±2 fold change). Genes including *HLA-DRB1*, *HLA-DQA1* and *PLEKHA1* have been previously linked to T1D and contained ≥2 differently methylated CpG sites ($p<10^{-8}$). High concordance (R^2=0.994) between duplicate samples (n=7) was observed. The cellular metabolic process pathway was the top-ranked pathway ($p=1.8x10^{-10}$) with the strongest enrichment score.

Discussion: This study suggests that epigenetic factors play a role in T1D and has affirmed previously reported loci. Use of the MethylationEPIC array has provided the opportunity to report on previously unexplored regions of the methylome. Blood-derived methylation signatures may have utility as minimally invasive biomarkers for T1D.

OP05. Development of OPA1 Gene Therapy for Dominant Optic Atrophy

DM Maloney[1], N Chadderton[1], S Millington-Ward[1], GJ Farrar[1]

[1]School of Genetics and Microbiology, Trinity College Dublin

Dominant Optic Atrophy (DOA) is an inherited blinding disease that primarily targets the retinal ganglion cells (RGC) and largely involves disrupted mitochondrial bioenergetics leading to cellular dysfunction. DOA has an estimated prevalence of between 1in 10,000 to 1 in 30,000, making it one of the most common optic neuropathies. Around 90% of DOA cases are caused by mutations in the OPA1 gene. OPA1 is a dynamin-related GTPase that plays a crucial role in the maintenance of the mitochondrial network of the cell, with OPA1 mutations causing characteristic fragmentation of the mitochondrial network. Due to alternate splicing there are several distinct OPA1 isoforms that show unique expression patterns in different tissues.

Here, OPA1 isoforms 1 and 7 are identified as being predominantly expressed in the human retina by interrogating publicly available RNA-seq data. The potential of OPA1 isoform 1 and 7 for use in gene therapy approaches was then investigated using codon-optimised versions of both OPA1 isoforms. This was achieved by ectopically expressing each isoform in OPA1-null mouse embryonic fibroblast (MEF) cells. Of note, cells expressing either of these OPA1 isoforms showed significant improvement in a range of different mitochondrial biomarkers. Rescued cells showed restoration of a wild-type tubular mitochondrial network, along with a significant increase in the rate of mitochondrial fusion. Rescued cells also showed significantly increased metabolic activity in Seahorse XFe96 assays when compared to OPA1-null MEF cells, showing restoration to wild-type MEF cell levels. These data represent an important step forward in the development of OPA1 based gene therapies for DOA.

OP06. Who needs rare disease services in Ireland? Constructing a list of high-prevalence rare diseases for Ireland to inform service needs.

DM Lambert[1], S Nguengang-Wakap[2], A Olry[2], A Rath[2], D Murphy[1], SA Lynch[1], EP Treacy[1]

[1]National Rare Diseases Office, Dublin, [2]INSERM, US14-Orphanet, Paris, France

Introduction: Rare diseases (RDs) are a public health priority but their scarcity and diversity leads to a lack of knowledge and expertise. Accurate epidemiological information about RDs is necessary to inform public policy, but without an Irish rare disease registry, there is a dearth of primary data.

Methods: Collaborative work with Orphanet Coordination derived a global point prevalence of RDs from the 'Orphanet Epidemiological File' (www.orphadata.org) by selecting RDs described by 'point prevalence' from predefined geographic regions, and summing point prevalences. In the National Rare

Disease Office, expert opinion and disease-specific publications were used to adapt a 'high prevalence' list for Ireland.

Results: Globally, 'point prevalence' describes 5,304 RDs (85.9%). The minimum cumulative point prevalence of RDs is 3.5-5.9% of the population. While globally 84.5% RDs analysed (n=3585) had a point prevalence of <1/1,000,000; greater than 95% of the population burden of RDs was attributable to 390 diseases with a prevalence >1/100,000. To construct a comparable Irish 'high-prevalence' list, 191 RDs with known prevalence >1/100,000 across all countries were drawn from the global list. A further 147 diseases with possible prevalence >1/100,000 in Ireland due to ethnic, environmental or founder-effect are currently under consideration for inclusion.

Conclusion: 3.5%-5.9% is the first evidence-based estimate of the global population prevalence of RDs. Creation of an Irish list of high-prevalence RDs permits development of care pathways and systems that address the needs of the majority of Irish people with RDs. Implementation of RD codification in eHealth Ireland will provide more accurate data.

OP07. Birth incidence and survival in an 11 year cohort of liveborn babies with a fatal foetal abnormality in the Republic of Ireland

E Gunne[1], DM Lambert[2], C McGarvey[3], K Hamilton[3], EP Treacy[2], SA Lynch[1,2]

[1.] Children's University Hospital, Temple Street, Dublin; [2.] National Rare Disease Office, Mater Misericordiae University Hospital, Dublin; [3.] National Paediatric Mortality Register, Dublin.

The Health (Regulation of Termination of Pregnancy) Act legalized termination of pregnancy (TOP) in Ireland from January 2019, allowing TOP past 12 weeks of pregnancy for *'a condition affecting the foetus that is likely to lead to the death of the foetus either before, or within 28 days of, birth'*, as defined in the Clinical Guidance Pathway by the Institute of Obstetrics and Gynaecology (2019). Accurate information about survival can aid decision-making regarding TOP in couples with an antenatal diagnosis of fatal foetal anomaly.

Retrospective analysis of anonymised death records (2006-2016), from the National Paediatric Mortality Registry from the Central Statistics Office was undertaken. During this time TOP was unobtainable as it was contrary to the Irish Constitution, allowing natural history data to be sought. Rare disease diagnoses and survival times were assigned from narrative records, and compared to national annual birth rates.

Survival curves constructed for diagnoses of anencephaly, trisomy 13, trisomy 18 and bilateral renal agenesis showed that 88.5%, 35.0%, 38.1% and 89.1% respectively were deceased by 24 hours. Survival time range and median were calculated for severe skeletal dysplasias, hydranencephaly and triploidy whose occurrences were rare, with all deaths occurring in the neonatal period. Birth incidences ranged from 1 in 5,300 to 1 in 388,000.

Potentially fatal fetal anomalies were not included as their variable prognosis is better informed by case-by-case antenatal ultrasound rather than diagnostic label. This analysis did not capture the rate of intrauterine death associated with these conditions, and was confounded by TOPs performed outside the jurisdiction.

OP08. The Molecular Basis of Acute Porphyria and familial Porphyria Cutanea Tarda in the Republic of Ireland – an update

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Introduction: The acute hepatic porphyrias, including acute intermittent porphyria (AIP), variegate porphyria (VP) and hereditary coproporphyria (HP) along with familial Porphyria Cutanea Tarda (fPCT) are autosomal dominantly inherited disorders affecting key enzymes in the haem biosynthetic pathway. Clinically these disorders may manifest as photosensitive skin lesions (VP, HP and PCT) and/or acute neuropathic episodes (AIP, VP and HP). All demonstrate variable penetrance and expressivity. Thus, while biochemical investigations, including blood, urine and faecal porphyrin analysis, are critical for the diagnosis of active porphyric disease, these investigations may not be sensitive enough to identify presymptomatic variant carriers. Hence molecular genetic analysis has become an important component in kindred follow-up for identifying porphyria susceptibility.

Methods: The Biochemistry Department, St James's Hospital, Dublin, has established a molecular diagnostic service based on direct nucleotide sequencing to facilitate diagnosis of genetic susceptibility to AIP, VP, HCP and PCT respectively.

Results: To date over 30 different genetic variants linked with a porphyria phenotype have been identified in different kindreds including non-Irish. The spectrum of variants includes missense, nonsense, splice-site and small insertions and deletions e.g. *HMBS* (R26C, R26H, IVS4+1G>A), *PPOX* (IVS4-1G>A, Q435X, W427X, A150D, Q375X) and *CPO* (R332Q, R332W, c.1291-1292 ins TG). In addition, novel variants have been identified in collaboration with Cardiff Porphyria Centre.

Conclusion: This unique insight into the molecular basis of porphyrias in the ROI indicates that acute porphyrias and fPCT are genetically heterogeneous. Furthermore, the variant scanning assay in St James's Hospital has identified pathogenic variants in >93% of confirmed porphyria kindreds

OP09. European Reference Networks: potential for rare disease research and patient care in Ireland

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Between 5,000 and 8,000 rare diseases impact roughly 30 million people in the EU, and up to 300,000 in Ireland. Diagnosis and treatment of rare diseases is extremely difficult due to low prevalences, scattered patient populations and scarcity of national expertise. Collaboration across countries is essential. European Reference Networks (ERNs) concentrate resources through the centralisation of knowledge and experience of clinicians and researchers across Europe. They comprise virtual networks involving healthcare providers who collaborate via a dedicated IT platform. A fundamental principle of this initiative is that the knowledge and experience travel, not the patient.

Centres of Expertise (CoE) are the physical structures that connect patients to the ERNs. Each CoE is specialised in a particular disease or group of diseases, with the purpose of delivering timely diagnosis and appropriate treatments. With such a vast number of rare diseases and CoEs in Europe, the immediate challenge is mapping out the appropriate care pathway for each patient on

a national basis. Orphanet Ireland has identified 72 Irish CoEs, connected to 22 of the 24 existing ERNs. We have attempted to determine the appropriate Irish CoE and ERN for the 345 most prevalent rare diseases (affecting more than 1 in 100,000). Of these, we successfully assigned 331 to ERNs (3 of which are ambiguous as they affect more than one organ or system), and 248 to CoEs within Ireland. The elaboration of Irish care pathways in collaboration with the CoEs and ERNs is predicted to enhance diagnosis, clinical research and treatment access.

OP10. Mitochondrial Disease Mimics

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A diagnosis of primary mitochondrial disease was traditionally arrived at on the basis of clinical and biochemical features including abnormal respiratory chain analysis on muscle biopsy and/or identification of other "mitochondrial disease markers". With the increased availability of genetic testing, in particular massive parallel sequencing, alternative primary diagnoses which result in secondary mitochondrial dysfunction are being identified

We present a cohort of six cases who previously had a diagnosis of mitochondrial disease. Alternative primary diagnoses have recently been identified which includes Andersen-Tawil syndrome (gene: KCNJ2), COL4A1-related brain small-vessel disease (gene: COL4A1), cardio facio cutaneous syndrome (gene: BRAF), autosomal recessive spinal cerebellar ataxia-10 (gene: ANO10), facio scapula humeral muscular dystrophy (gene: DUX4) and IGSF1 deficiency syndrome (gene: IGSF1).

Conclusion: The reported cohort highlights the important point that many genetic conditions may mimic mitochondrial disease and, although the phenotype and biochemical tests may indicate mitochondrial disease, we suggest that genetic confirmation is required to secure a diagnosis. Establishment of an accurate diagnosis is important, not just prognosis and planning of management and treatments regimes, but also for appropriate genetic counselling and the identification of other at-risk family members for possible cascade analysis. The link between many of these primary diagnoses and secondary mitochondrial dysfunction is poorly understood but reporting such cases will allow these pathways to be elucidated and understood.

POSTER PRESENTATIONS:

P01. Early retinal remodelling in a mouse model of juvenile retinal degeneration

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Mutations in TULP1 are causative of inherited retinal degenerations (IRD). The retina of Tulp1-/- mice is characterized by rapid loss of photoreceptors while much less is known about the changes in the inner retina. Using histology analysis we investigated early remodelling events in Tulp1-/- retinas at postnatal days (p) 5, 8 and 14 (n=3-5). Apart from wt controls, we used Rho-/-, Rds-/- retinas as disease controls. Qualitative and quantitative morphological analysis on microscope images from these samples was performed. In agreement with previous work, we detected minor alterations in thickness of the retinal layers in IRD mice between p5-14. However, using various retinal markers we identified significant cellular and subcellular alterations. In the outer plexiform layer, the photoreceptor synapses were compromised, while the horizontal cell processes invaded the photoreceptor layer in IRD mouse retinas. In the inner nuclear layer, expression of a number of markers, such as PAX6, CTBP2, MAP2 was different between IRD mouse and wt retinas. Additionally, the morphology of Muller glia cells was also altered. Apart from the large number of TUNEL+ cells in the outer nuclear layer in IRD mouse retinas TUNEL+ cells were also detected in the inner nuclear layer in Tulp-/- but not in the other retinas at p14. Our data suggest compromised photoreceptor synaptic development/function in IRD mouse retinas. Delayed development of a number of cellular markers in the inner retina suggests that degeneration in Tulp1-/- retinas is different from that of Rho-/- and Rds-/-.

P02. Detection of putatively pathogenic rare, inherited CNVs from family whole genome sequencing data

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We seek to identify rare copy number variations (CNVs) which may be contributing to disease risk in families with a high load of psychiatric illness. Calling CNVs accurately from short read sequencing data is complex; to date no single CNV caller is capable of detecting all classes (deletions, insertions, translocations, etc.) or sizes of CNVs with high specificity and sensitivity. However, studies have shown that CNV detection can be improved by looking at consensus calls across multiple algorithms. We propose that incorporating family data can also give better control for false positive rates across callers.

Based on this hypothesis we have developed a novel ensemble approach that combines two classes of CNV caller: paired-end/split read methods (Manta and LUMPY) and read depth methods (ERDS and CNVnator), as well as Mendelian inheritance patterns, to improve precision and recall of CNV detection from family data. This pipeline incorporates a rigorous filtering strategy aimed at identifying rare, pathogenic, segregating CNVs within each pedigree. We have used validated CNVs from the gold-standard CEPH 1463 pedigree to assess the performance of our ensemble approach and to compare it against each of the individual component tools.

P03. Improving the State of Polygenic Prediction: Are Neural Networks Applicable to Genetic Data?

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Deep Learning using Artificial Neural Networks (ANNs) has

been gaining traction due to its widespread success in generating accurate prediction models from complex input data such as audio and image information. It is of current interest to explore whether this technique can be applied to handle genetic data as input. It remains an open question as to whether the sheer size and sparsity of information represented within genotype matrices may be amenable to the complex transformations performed by ANNs.

Polygenic prediction has also been seeing improvements recently, however, the explained variance for all traits remains stubbornly lower than the theoretical maximum as represented by its estimated heritability (h^2). This discrepancy may partially be due to the strictly linear methods employed by conventional GWAS and Polygenic Risk Score (PRS) calculation. As it is well established that complex non-linear interactions are ubiquitous in determining the outcome of biological processes, it is reasonable to suspect that some of the variation of a trait is as a result of these epistatic interactions that are not well modelled by the methods currently employed in genetic prediction.

This project aims to investigate the potential of deep learning's known ability to handle and exploit non-linear information in improving on current genetic prediction methods. Both real and simulated genotype and phenotype data are used to determine the feasibility and accuracy of this method using PRS as a benchmark. This may not only be useful from a clinical perspective but could also give insight into a trait's genetic architecture.

P04. The role of common genetic variation in presumed monogenic forms of epilepsy

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Background: The developmental and epileptic encephalopathies (DEEs) are a group of severe epilepsies which co-present with intellectual disability, and occur in cases without a family history of epilepsy. Their severe phenotype means that DEEs are thought to be primarily monogenic, caused by highly damaging rare mutations. Currently, analysis of exome sequence data can identify a causative mutation in around 40% of DEEs. Little is known about the genetic architecture of the remaining DEEs which screen-negative after genomic analysis. Here, we used a method known as polygenic risk scoring (PRS) to test whether the burden of common genetic variation is relevant to the development of the DEEs.

Methods: Exome and GWAS data on DEE cases (n=745), and population controls (n=75,000) were obtained from the DDD cohort and Ukbiobank, respectively. Damaging mutations in known epilepsy genes were bioinformatically inferred. PRS were calculated using the most recent ILAE GWAS of epilepsy and compared between i) DEE cases and the general population, and ii) DEE cases with and without damaging mutations.

Results: DEE cases with and without inferred damaging mutations were found to have elevated PRS for epilepsy. We did not detect a significant difference in PRS between DEE cases with and without damaging mutations.

Discussion: This research provides the first evidence that common genetic variation contributes to the development of the DEEs. Our results suggest common genetic variation contributes to DEE status irrespective of the presence of a highly damaging rare genetic variant. Further work in additional cohorts is required to extend these results.

P05. Investigating the role of microRNAs in the hypoxic response in prostate cancer

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Hypoxia is a well-established driver of aggressive behaviour in prostate cancer (PCa). However, the reasons for this are not completely characterised and the role of microRNAs (miRNAs) in the hypoxic response remains unclear. In this study, we investigated the expression and functional role of miRNAs in response to hypoxia in prostate cancer.

Three models of PCa hypoxia were utilised (i) *in vitro* culture at 0.1% oxygen (ii) 3D spheroid culture and (iii) an *in vivo* tumour xenograft experiment. miRNA expression was measured by RT-qPCR. miRNA functionality was assessed by RT-qPCR, Western blots and bioassays. Bioinformatics analysis of prostate cancer clinical data in The Cancer Genome Atlas (TCGA) repository was also performed.

The miRNAs miR-210 and miR-21 were upregulated by hypoxia in our various models. The subsequent effect on their respective networks of target genes and cell behaviour was investigated. miR-210 and miR-21 expression is positively associated with markers of hypoxia and tumour aggressiveness in clinical samples, suggesting they may have value as novel biomarkers in this disease. Random forest analysis of TCGA data revealed that addition of miR-21 and miR-210 levels to Gleason score could predict treatment response with >90% accuracy.

We provide evidence that miRNAs play a role in the progression of PCa through hypoxia-related mechanisms. In particular, miR-210 and miR-21 appear to contribute to the hypoxic response involved in PCa progression. We propose that miRNA profiling of these and other miRNAs has great value for improving diagnostic, prognostic, and potentially therapeutic approaches for this disease.

P06. The ancient population genetics of Portugal

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The field of ancient population genetics has advanced rapidly since the development of high-throughput next-generation sequencing (NGS) and the discovery that the petrous part of the temporal bone is a rich reservoir for aDNA, allowing the generation of whole genome sequences for ancient individuals. Portugal occupies a unique position in Europe; located on the edge of mainland Europe and facing both the Atlantic and the Mediterranean, it was connected to two major maritime, trade and migration routes as well as experiencing influx from central Europe throughout its prehistory. However, many open questions remain about demographic and selection processes acting on populations at key transition points in European prehistory, such as the early Bronze Age migrations from the Pontic Steppe, the potential source for the R1b Y-chromosome haplogroup which now dominates in European populations. In this study we present whole genome sequences from ancient Portuguese

individuals (0.1-2.9X), covering a period of over 3000 years as well as a wide geographic region. We observe changes in both mitochondrial and Y-chromosome haplogroup frequencies over time, reflecting changing demographic processes acting on Iberian populations. We use principal component analysis (PCA), outgroup *f*-3 statistics, Patterson's D-statistic and ADMIXTURE analysis to investigate questions such as hunter gatherer admixture in the Neolithic and Steppe introgression in the subsequent Bronze Age.

P07. The Epilepsiome Project: revising the Human Phenotype Ontology for epilepsy and seizures

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Rationale: The phenotypic features in a person with epilepsy are often complex with regards to seizure presentations, which is acknowledged by the most recent revision of the seizure classification by the International League Against Epilepsy (ILAE). We provide updated seizure-related human phenotype ontology (HPO) terms to facilitate a deep phenotypic interpretation of heretofore unexplained genetic epilepsies.

Methods: The Epilepsiome project is a Task Force of the Genetics Commission of the ILAE and represent the link to the gene curation efforts within the ClinGen Epilepsy Clinical Domain Working Group (CDWG). Within the efforts to align terminology used in the diagnostic space, the Epilepsiome Project revised HPO terms for epileptic seizures. The updated classification was built through an online portal and consensus was achieved through biweekly conference calls.

Results: Focal, generalised and neonatal HPO seizure terminologies were constructed according to the most recent ILAE classification and aligned with the existing HPO structure. This ontology allows capture of clinical information at various levels of detail and aims to preserve the onset, awareness and motor/non-motor nature of each seizure type, using multiple parentages. We integrated other frequently observed seizures currently not included in the ILAE, which required a separate branch within the ontology due to biological peculiarity of their age of onset, their clinical significance or genetic architecture.

Conclusions: Improvements in HPO terms for epileptic seizures will enable a more versatile seizure ontology leading to deep phenotyping of people with epilepsy to improve associations with genomic data in both a research and diagnostic setting.

P08. Modulation of a prodegenerative pathway as a potential therapy for retinal degeneration.

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Approximately 300 million people suffer from some form of blindness, from monogenic inherited retinal degenerations to complex diseases such as AMD. Due to the vast heterogeneity of genetic forms of blindness, it is challenging to develop gene-specific therapies for each disease. Fortunately, many of these conditions display mechanistic commonalities, with key pathways being implicated in many diseases. By targeting these, in principle we can develop therapies that may be applicable to a wider group of patients. One such pathway involves the degeneration of neurons in response to injury or stress. Pro-degenerative proteins can promote degradation of the axons of damaged neurons, leading to eventual cell death. A knockout mouse model has been used to assess whether the absence of one such gene and encoded product may be neuroprotective against rotenone-induced insult to the retina. Optokinetic response (OKR) measurements suggest that the lack of the encoded product is functionally beneficial, with knockout mice performing significantly better than wild-type mice following rotenone treatment (0.241±0.052 c/d and 0.08973±0.03750 c/d respectively; $p<0.0001$). These data will be complemented by histological and MRI studies to explore the extent of the beneficial effects that may be provided by this approach. Importantly, the preliminary data thus far from this mouse work suggest the potential benefit of modulating this cellular pathway to ameliorate retinal pathologies. Further studies are underway to explore the extent of the therapeutic value of this strategy to provide benefit in the context of retinal degenerations.

P09. Identifying the Genetic Candidates of Previously Unresolved Inherited Retinopathies in Ireland.

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Purpose: *Target5000* aims to genetically characterise approximately 5000 people in Ireland with an inherited retinal degeneration (IRD). Thus far, over 1,000 IRD patients have been sequenced for variants in 260 IRD genes. One arm of the project focuses on improving detection of candidate variants by whole genome sequencing (WGS), by analysing non-coding mutations and performing functional analysis.

Approach: IRD patients are clinically diagnosed by *Target5000* ophthalmologists. When informed consent is given, the *Target5000* study employs target capture next generation sequencing (NGS), with a positive candidate detection rate of 68%. To improve detection rates, whole-gene or WGS was employed on a case-dependent basis to identify pathogenic intronic variants not previously captured.

Results: One common form of IRD is ABCA4-associated Stargardt disease (STGD1), often caused by deep-intronic variants. Thus far, 36 'unresolved' STGD1 and cone-rod dystrophy cases have undergone targeted ABCA4 whole-gene sequencing, positively identifying a candidate in ~50% of cases. A variant in intron 30 resulting in a pseudoexon inclusion was particularly frequent and found in 5/16 (likely) solved cases. Furthermore, 40 patient samples have undergone WGS.

Conclusions: An objective of *Target5000* is to provide actionable outcomes empowering patients with genetic diagnoses and potentially future access to clinical trials or approved treatments, where appropriate. The results presented highlight the significant value of a target capture NGS strategy as a preliminary diagnostic measure, with remaining elusive cases undergoing more extensive genetic analysis. This methodology improves variant detection rates and progresses the goal of fully elucidating the genetic architecture of IRDs in Ireland.

P10. Genes regulated by BCL11B during T-cell development are enriched for de novo mutations found in schizophrenia patients.

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Schizophrenia (SCZ) is a common but severely debilitating adult-onset mental illness. Abnormal neurodevelopment contributes to SCZ risk, but evidence also supports a role for immune dysfunction in SCZ. *BCL11B* is associated with SCZ in GWAS and is a transcription factor involved in regulating the differentiation/development of cells in both the brain and the immune system. Here, we use functional genomics analysis of *BCL11B* to investigate the contribution of neuronal and immune processes to SCZ pathophysiology. We generated three gene-sets that contain the targets of BCL11B in (i) brain striatal cells(n=220 genes), (ii) Thy3 developing T-cells (n=74 genes) and (iii) Thy4 developing T-cells(n=560 genes). For each gene-set, the BCL11B targets were identified using an integrated analysis of differential gene expression data and ChIP-seq binding data. We tested each gene-set for enrichment of genes associated with SCZ using MAGMA and GWAS data. Enrichment of SCZ de novo mutations was tested with denovolyzeR using data from exome sequencing of SCZ trios (n=1,024). MAGMA analysis did not identify evidence of enrichment of SCZ genes in our gene-sets. Analysis of de novo mutations did identify that the Thy4 gene-set was enriched for genes containing protein altering mutations (p=0.0007). When this gene-set was divided up into genes that were either up- or down-regulated upon *BCLL1B* knockout, the enrichment signal was coming from the up-regulated genes (p=0.0002). Pathway analysis of these up-regulated genes identified 'Interferon alpha/beta signalling' and 'Cytokine signalling in immune system' as biological pathways that are enriched for these genes. These analyses, leveraging a GWAS-identified SCZ risk gene and functional genomics datasets, indicate that de novo mutations in immune pathways contribute to SCZ risk.

P11. The biochemical characterisation of a novel missense variant in Fumarase Hydratase identified in an Irish patient with breast cancer

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Fumarase hydratase (FH) catalyses the reversible conversion of fumarate to L-malate during the Krebs cycle. FH has also been identified as a tumour suppressor and contributes to the DNA damage response. Monoallelic variants give rise to the rare tumour predisposition syndrome hereditary leiomyomatosis and renal cell cancer (HLRCC). Variants in *FH* have recently been implicated in tumours of the CNS, bladder, and breast. We identified a novel p.Gly58Ser variant of FH in a breast cancer patient through a targeted resequencing study of an Irish cohort of patients with breast cancer (n=91) and healthy controls (n=77). The variant is predicted to be damaging/pathogenic *in silico* by four independent missense prediction algorithms. Inspection of 3D structures shows that Gly58 is located near the active site and could disrupt a secondary structural element. To test the effect of the mutation directly, we recombinantly expressed and purified wild type and Gly58Ser mutant human FH as well as a mutant Ala308Thr which is known to disrupt activity. We then compared their enzymatic properties with respect to tetramerisation, pH dependence, substrate affinity and activity. Our results show that the Gly58Ser variant significantly impairs enzymatic function of FH. This study illustrates how screening of an Irish patient cohort can reveal novel mutants amenable to detailed structure-function analysis that can be directly tested for biochemical effects.

P12. A randomized controlled trial of folic acid intervention in pregnancy highlights a putative methylation-regulated control element at *ZFP57*

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Maternal blood folate concentrations during pregnancy have been previously linked with DNA methylation patterns, but this has been done predominantly through observational studies. We showed recently in an epigenetic analysis of the first randomized controlled trial (RCT) of folic acid supplementation specifically in the second and third trimesters (the EpiFASSTT trial) that methylation at some imprinted genes was altered in cord blood samples in response to treatment. Here, we report on epigenome-wide screening using the Illumina EPIC array (~850,000 sites) in these same samples ($n=86$). The top-ranked differentially methylated promoter region (DMR) showed a gain in methylation with folic acid (FA) and was located upstream of the imprint regulator *ZFP57*. Differences in methylation in cord blood between placebo and folic acid treatment groups at this DMR were verified using pyrosequencing.

The DMR also gains methylation in maternal blood in response to FA supplementation. We also found evidence of differential methylation at this region in an independent RCT cohort, the AFAST trial. By altering methylation at this region in two model systems in vitro, we further demonstrated that it was associated with *ZFP57* transcription levels. These results strengthen the link between folic acid supplementation during later pregnancy and epigenetic changes and identify a novel mechanism for regulation of *ZFP57*.

P13. AAV-oph*Ndi1*: a potential therapy for Leber Hereditary Optic Neuropathy (LHON).

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LHON is a debilitating mitochondrially inherited eye disorder characterised by rapid, painless loss of central vision in one eye, typically followed by loss of vision in the second eye within months. It is caused by mutations in five of the mitochondrially encoded subunits of Complex I. LHON affects approximately 1 in 30,000 individuals, predominantly males. Currently, gene therapy for the ND4 mutation is showing great promise in clinical trials. However, there is growing evidence that mitochondrial dysfunction may be involved in a wide range of neurodegenerative disorders and the transkingdom approach proposed here may also be applicable to these. The therapy under development uses a nuclear yeast gene, NADH-quinone oxidoreductase (*Ndi1*), that encodes a single subunit complex I equivalent and as such is mutation independent.

We have previously shown the potential of AAV2/2-*Ndi1* to protect retinal ganglion cells (RGCs), the cells primarily affected in LHON, in a rotenone-induced murine model of LHON. Subsequently, we have optimised *Ndi1* codon usage using *in silico* analyses to enhance expression in mammalian cells and to potentially reduce immunogenicity, creating oph*Ndi1*. Here we demonstrate that oph*Ndi1* functions more efficiently than *Ndi1*. When evaluated in the LHON mouse model, intravitreal injection of AAV2/2-oph*Ndi1* significantly reduced RGC death and led to a preservation of retinal function as assessed by optokinetics (OKR). This benefit was attained using significantly less AAV2/2-oph*Ndi1* than AAV2/2-*Ndi*.

oph*Ndi1* holds great therapeutic promise for this debilitating mitochondrial disorder and could be applicable to other conditions where mitochondrial dysfunction may play a significant role.

P14. Investigating DHFR2's growing pool of RNA isoforms

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The complex folate one-carbon metabolism (FOCM) interlinks with homocysteine metabolism with the help of vitamin B2, B6 and B12 to maintain normal cell functions: purines and thymidylate synthesis, glycine and other amino acids synthesis, methylation reactions.

DHFR is the only FOCM enzyme capable of reducing dietary folic acid to Dihydrofolate, and further reduce it to Tetrahydrofolate, the actual methyl-group donor. For a long time, DHFR was thought to be the only reductase of its family to have an active role in FOCM, until a second one was discovered: DHFR2.

DHFR2 is a retrogene, derived from a DHFR RNA copied back into the genome. It has two main isoforms, both harbouring the whole ORF in a single exon. These isoforms could translate into functional proteins even though the endogenous form of the enzyme has not been detected so far. Additional isoforms have been predicted, with some containing the entire DHFR2 ORF and others possibly having regulatory functions.

We performed several PCR assays on cDNA aiming to detect all possible isoforms in different cell lines. Other than confirming the two main transcripts presence, distinct new variants were detected in different cell types. They differ slightly from the predicted isoforms, especially at the 5' and 3' ends. In one case, a new exon has been identified, establishing a brand new transcript. Ultimately, as a result of the differential expression of each transcript due to tissue type and differentiation status, a targeted full-length sequencing approach is the logical next step.

P15. CRISPR/Cas knock-out cell lines to give new insight on DHFR2 function and its interplay with DHFR

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All organisms possess a version of DHFR, from bacteria to humans, but just primates, *H. sapiens* included, present a second active Dihydrofolate Reductase. DHFR has a key role within Folate One-Carbon metabolism, as it reduces Dihydrofolate into Tetrahydrofolate, a methyl group shuttle involved in glycine, purines and thymidylate biosynthesis. Accordingly, its function is essential for DNA synthesis, making DHFR a crucial regulator in cell proliferation and death.

DHFR2 (Dihydrofolate Reductase 2) is a retrogene derived from the reverse transcription of DHFR RNA back into the genome (3q11.2). The recent discovery of DHFR2 being active has opened up to a whole new set of questions, relative to DHFR/DHFR2 function and localisation, their interlinks and subcompartmentalization.

DHFR2 protein has not been detected so far, and its similarity with DHFR (92% homologous), makes it a huge challenge to identify endogenous levels of its protein. To solve this issue, we have engineered two HepG2 cell populations by CRISPR/Cas creating both a DHFR and DHFR2 knock-out lines. The DHFR-negative line will definitively allow the sole DHFR2 isolation and identification. It will also make clear if DHFR2 is able to compensate for the lack of DHFR, replacing its cytosolic function. Instead, the DHFR2-negative line will give us information about the importance of DHFR2 as part of the folate metabolism and its relevance in cell proliferation.

P16. Retinoic Acid Receptor Specificity in Glioma Growth Suppression

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Primary brain tumours have an incidence of 8/100,000/year in Ireland. 80% of these tumours are adult diffuse infiltrating gliomas, and the majority are high grade, causing death within two years. Obstacles to treatment include impossibility of complete surgical resection, outward convection pressures, first-pass metabolism, the blood brain barrier, and the existence of cancer stem cells, reigniting malignant growth following treatment.

Retinoic acid and its synthetic analogues, the retinoids, are potent, lipophilic differentiation agents capable of crossing the blood brain barrier. They have recently been considered as potential adjuvant therapy to trigger the terminal differentiation of glioma cells. Retinoids act via a family of nuclear retinoic acid receptors (RARs) that stimulate the expression of target genes. Three genes exist for RARs (*RARA*, *RARB*, *RARG*). Each gene encodes multiple functional isoforms differing in the N-terminus active protein domain. Most studies examining their expression in tumours have focused on the common regions, not differentiating between the various isoforms. Previous studies highlighted tumour suppressive functions for some RARB isoform (RARB2) while others (RARB1) were shown to stimulate proliferation. Considering the potential therapeutic benefit of retinoids and the mixed functions of RAR isoforms, we wish to determine the role of specific isoforms in controlling glioma growth. To date, our results show that expression of specific isoforms is associated with growth suppression while others are associated with increased proliferative rates. We propose that differential manipulation of RAR isoforms may be key in targeting tumour suppression

P17. Detecting pathogenic repeat expansions from genome sequence data

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Repeat expansions are an important class of genetic variation in neurological diseases and may represent a convergent aetiological molecular mechanism. However, the identification of novel repeat expansions using conventional sequencing methods is a challenge due to their typical lengths relative to short sequence reads and difficulty in producing accurate and unique alignments for repetitive sequence. However, this latter property can be harnessed when using paired-end short read sequencing data to infer the possible locations of repeat expansions and other structural variation.

Here we present REscan, a fast and lightweight command line utility that infers the possible locations of repeat expansions from paired-end short read sequencing data by reporting the proportion of reads orientated towards a locus that do not have an adequately mapped mate. A high number for this statistic relative to a population of data indicates the location of a possible repeat expansion for experimental follow-up. We validate this approach using whole-genome sequence data for 259 cases of amyotrophic lateral sclerosis, of which 25 are positive for a large hexanucleotide repeat expansion in C9orf72, and show that REscan has good discriminative accuracy in identifying repeat expansions from paired-end sequence data. Application genome-wide may infer the locations of other repeat expansions and accelerate the discovery of novel disease-relevant genetic variation.

P18. Genetic risk factors in mitochondrial DNA associated with diabetic kidney disease – GWAS discovery and meta-analysis.

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Diabetic kidney disease (DKD) affects ~40% of persons with diabetes and is the leading cause of chronic kidney disease and end-stage renal disease (ESRD) globally. Mitochondrial dysfunction is implicated in the pathophysiology of DKD. Previous research reported SNPs in nuclear genes, which influence mitochondrial function, are significantly associated with DKD. Furthermore, these genetic and functional data prompted further investigation of SNPs affecting mitochondrial function for association with DKD.

Initial analyses were performed using DNA samples from the All Ireland / Warren 3 Genetics of Kidneys in Diabetes UK Collection (UK-ROI) which comprised 1,804 white individuals with T1D, diagnosed before 31 years of age, whose parents and grandparents were born in the British Isles. Genotyping was performed using HumanOmni1-Quad array (n=1,051,295 SNPs directly typed), with data imputed to the Haplotype Reference Consortium for SNPs in mitochondrial DNA (mtDNA, n=225 total SNPs) and 2,526 nuclear-encoded mitochondria genes (NEMGs) (n=2,880,249 total SNPs).

PLINK was used to investigate association with DKD, ESRD and estimated glomerular filtration rate (eGFR) in the UK-ROI with follow-up in up to 19,406 individuals from up to 17 independent collections. The SNP that showed most evidence for association with decreased eGFR after adjusting for covariates was MitoG11915A (P =0.0003) which is a synonymous variant found in the mitochondrial gene *MT-ND4*. In NEMGs there were 8 SNPs in 4 genes associated with DKD related phenotypes.

In conclusion, mtDNA variants and SNPs in NEMGs are associated with DKD in T1D. Further research is needed to explore the functional impact of these variants.

P19. Exploration of a tissue specific promoter for retinal ganglion cells

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Cell-specific promoters restricting gene expression to retinal ganglion cells (RGCs) and optic nerve may be advantageous when designing gene therapies for disorders such as Leber Hereditary Optic Neuropathy and glaucoma. To identify potential candidates within the ~4.7kb packaging constraint of AAV we analysed the upstream region of genes, 2.5kb from transcriptional start sites, which were believed to be both highly expressed and enriched in the RGCs. Sequence conservation across mammals was used as a proxy for putative promoter function. The lead promoter element was from neurofilament heavy (NEFH), in which we identified two highly conserved regions (F and A). These were used in differential configurations to drive EGFP expression from AAV2 vectors (AAV2-A-EGFP, AAV2-FA-EGFP and AAV2-FspacerA-EGFP). Promoter-driven expression profiles in murine retina were compared to expression from a 2.5kb upstream human NEFH (AAV2-2.5NEFH-EGFP) and a 2.2kb upstream murine Nefh promoter (AAV2-2.2Nefh-EGFP), following both intravitreal and subretinal injection. RNA and histological data (in retinal cryosections and wholemounts) are presented and immunohistochemistry was performed on EGFP and using RGC and amacrine cell-specific antibodies.

Our results demonstrate that AAV-2.5NEFH-EGFP, AAV-2.2Nefh-EGFP and interestingly AAV-A-EGFP represent novel promoters that mediate robust and highly preferential gene expression in RGCs and optic nerve, with additional expression seen in some amacrine cells. Notably conserved element A is only ~300bp and as such represents a versatile promoter for driving expression in RGCs and optic nerve from AAV, where cargo capacity is restricted.

P20. The Contribution of Second-hits in CNV Carriers to Putative Psychiatric Traits

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Background: Copy Number Variants (CNVs) are large genomic deletions/duplications of >1kb, spanning regions that can encompass one or many genes. Though a common form of structural variation, pathogenic CNVs, of population freq. <1%, represent significant risk loci for Neuropsychiatric Disorders (NPDs). NPD-CNVs are associated with phenotypic pleiotropy. Recent reports indicate that the concomitant inheritance of polygenic 'second-hit' variants may underlie this behavioural and neurological pleiotropy. Here we define second-hits as independent single-nucleotide polymorphisms (SNPs) in brain-expressed genes significantly associated with NPDs.

Methods and Results: Using the UK Biobank cohort (n=500,000), we will test whether there is an enrichment of second-hits in brain expressed genes in NPD-CNV carriers vs non-NPD-CNV carriers. We will generate polygenic risk scores (PRS) for autism, schizophrenia, cognition, mood disorders, cross disorder and epilepsy. We will compare the concordance of an individual's PRS to their respective psychiatric profiles and compare NPD-CNV to non-NPD-CNV carrier's results. Psychiatric profiles will be based on self-reported psychiatric illness/symptoms, cognitive scores, educational attainment, health outcomes and other available proxies for psychiatric symptoms in the UK Biobank. Sex differences will also be investigated. Results of these tests will be reported.

Discussion: This study tests the hypothesis that second-hit variants contribute to the phenotypic pleiotropy in CNV carriers. Our research will ultimately improve our understanding of NPD-associated CNVs for researchers, clinicians and genetic counsellors.

P21. Opposite expression patterns of Spry3 and p75NTR in cerebellar vermis suggest a male-specific mechanism of autism pathogenesis.

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Autism is a genetically complex neurobehavioral disorder with a population prevalence of more than 1%. Cerebellar abnormalities, including Purkinje cell deficits in the vermis, are consistently reported and rodent models of cerebellar dysfunction exhibit features analogous to human autism. We previously analysed the regulation and expression of the pseudo autosomal region 2 gene SPRY3, which is adjacent to X chromosome-linked TMLHE, a known autism susceptibility gene. SPRY3 is a regulator of branching morphogenesis and is strongly expressed in Purkinje cells. We previously showed that mouse Spry3 is not expressed in cerebellar vermis lobules VI-VII and X, regions which exhibit significant Purkinje cell loss or abnormalities in autism. However, these lobules have relatively high expression of p75NTR, which encodes a neurotrophin receptor implicated in autism. We propose a mechanism whereby inappropriate SPRY3 expression in these lobules could interact with TrkB and p75NTR signalling pathways resulting in Purkinje cell pathology. We report preliminary characterisation of X and Y chromosome-linked regulatory sequences upstream of SPRY3, which are polymorphic in the general population. We suggest that an OREG-annotated region on chromosome Yq12 ~60 kb from SPRY3 acts as a silencer of Y-linked SPRY3 expression. Deletion of a β-satellite repeat, or alterations in chromatin structure in this region due to trans-acting factors, could affect the proposed silencing function, leading to reactivation and inappropriate expression of Y-linked SPRY3. This proposed male-specific mechanism could contribute to the male bias in autism prevalence.

P22. A genomic exploration of population structure in the Ladakhi, a high-altitude Himalayan population

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The Ladakhi people dwell in the Jammu and Kashmir regions of India, between the Karakoram and Himalayan mountain ranges, at ≥3400 meters altitude. The Ladakhi share similar linguistic, cultural and religious practices with Tibetans. However, relative to Tibetans, the Ladakhi are very poorly studied at the level of population structure and genetic selection. In this context, we set out to conduct a genomic survey of population structure in representative samples of the Ladakhi people.

Methods: We genotyped 310 Ladakhi DNA samples using the Illumina Global Screening Array gene chip. We merged the Ladakhi with data from 800 individuals representing different reference language groups including; Sino-Tibetan (Tibetans, Sherpa, Han), Indo-European (Indo-Aryan, Hazara), Austroasiatic (Munda) and Burusho (a linguistic isolate in Jammu-Kashmir). We performed ADMIXTURE, principal component analysis (PCA), fineSTRUCTURE and ChromoPainter analysis on the combined autosomal data.

Results: In PCA plots, the Ladakhi population cluster together with Sherpa and Tibetans, forming a distinct Himalayan group, different from other mainland populations of South and East Asia. ADMIXTURE analysis at k=4 suggests ancestry proportions in the Ladakhi to be approximately 50% Highlander (Tibetan/Sherpa) and 50% Indo-European. These results suggest contemporary Ladakhi people are the admixed of Tibetans and Indo-Europeans.

Conclusions: Our results suggests a considerable component of the Ladakhi genome descends from ancestral highlander populations residing on the Tibetan plateau for the last 35,000 years, with subsequent admixture with neighbouring Indo-European populations.

P23. Towards estimating the incidence of rare diseases in a paediatric population, born in Ireland in the year 2000.

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Background: The EU recognises rare disease (RD) as life threatening with delays in establishing a diagnosis and treatment. The Irish National Plan for RDs (2014) recommended epidemiological studies of RD prevalence to improve both cost efficiencies and care of patients with RD's.

Objective: To derive the incidence of paediatric RD and the number of paediatric RD mortality cases through analysis of records held at two major tertiary paediatric hospitals, for children born in the year 2000.

Methods: Cases were identified using electronic/manual records from: the National Paediatric Mortality Registry office; Clinical, Cytogenetics and Molecular genetics database; Radiology and the Hospital In-Patient Enquiry system (HIPE). In addition a detailed analysis of national death registration information for RDs from 2006-2016 was undertaken along with a 2year study (2015-2016) of inpatient RD deaths.

Results: There were 54,789 livebirths in 2000. Genetics records identified 801 cases of RDs Ongoing HIPE searches identified 1381 cases. Mortality data revealed that of all deaths on the Register (2006-2016), (n=4044) aged 0-14, 58.56% (n=2368) had a RD diagnosis with age distribution; Neonates, 56% (1140/2050), Post-neonates, 58% (450/778), Children aged 1-14 years, 64% (778/1216). Of the total (n=234) inpatient deaths with a RD from 2015-2016, 52.6% (n=123) were cared for at the two major centres.

Conclusion: This study to-date has identified > 2,200 RD patients presenting by age 17 giving a minimum incidence of 4% for paediatric RDs. We expect the final figure to be higher when we complete analysis of all the HIPE and sub-specialty data from these major centres.

P24. Next generation diagnostics in Irish polycystic kidney disease patients

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Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited renal disease. ADPKD is primarily caused by variants in *PKD1* and *PKD2*. Sequencing of *PKD1* is difficult due to multiple pseudogenes. There is unexplained variance in the age-of-onset of PKD, even within families.

Aim: 1) Establish a targeted NGS panel to improve molecular diagnosis of PKD and 2) characterize large 'super-families' for the study of new ADPKD genes and genetic modifiers.

Methods: NGS was performed using a custom Roche SeqCap targeted panel (273 genes) and Illumina NextSeq. Bioinformatics was performed using an in-house GATK pipeline. Pathogenicity was assigned using American College of Medical Genetics and Genomics guidelines and Mayo Clinic PKD in-house methods. Gap-filling Sanger sequencing was utilized in unsolved cases.

Results: 172 PKD patients were sequenced with average coverage 189X. A molecular diagnosis meeting pathogenicity criteria was obtained in 82% (141/172) of patients following gap-filling Sanger of *PKD1* and *PKD2* (n=41). 46 of the PKD-causing variants we detected were novel. We identified 13 rare, diagnostic PKD variants shared across multiple affected individuals recorded clinically as having no known familial relationship. Second-degree relatedness was confirmed *via* clinical follow-up. These families form the basis for the assembly of PKD 'super-families'.

Conclusions: NGS is suitable for sequencing of PKD genes including *PKD1*, although some gap filling by Sanger is required for complete coverage. We have identified 13 potential ADPKD 'super-families' using genomic data for further study. These results are improving diagnostics of ADPKD in the Irish renal clinic.

P25. A Large Deletion on Chromosome X Causes Choroideremia by Whole Gene Deletion of CHM in Irish Patients.

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Purpose: *Target5000* is a genetic study to detect and characterise variants associated with inherited retinal degenerations (IRD). Choroideremia is an X-Linked recessive chorioretinal degenerative condition with progressive atrophy of several key cells of the retina and the surrounding blood retinal barrier. Here we describe a novel deletion in the CHM gene found in two Irish pedigrees. This 500kb deletion represents the largest yet detected IRD-associated deletion in Ireland.

Approach: As part of the Irish IRD registry, *Target5000*, patients with inherited retinal degenerative conditions are recruited. Target capture sequencing was employed to investigate variation in 254 IRD-associated genes. Upon detection of the deletion in CHM, PCR analysis was used to elucidate the full extent of the deletion.

Results: Two members of a large X-linked Retinitis Pigmentosa pedigree clinically presented with choroideremia and tested negative for the segregating RPGR variant found in other affected members of this pedigree. Both males were sequenced and found to possess large deletions spanning the CHM gene, totalling 500kb.

This deletion has also been detected in a second Irish pedigree since its discovery. Two additional males and two carrier females from this second pedigree were all found to be severely affected with progressive choroideremia.

Conclusions: Typically, female carriers of CHM mutations show mild stationary signs with no symptoms, while males are severely affected. In this instance, females were more severely affected than expected with advanced signs of degeneration and progressive visual decline. This is possibly due to random X-inactivation and the severity of CHM gene deletion.

P26. Epilepsy alone cohort and routine genetic testing – is it needed?

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Only a small proportion of epilepsy is secondary to syndromic conditions and/or mutations in a single gene. The cost of array comparative genomic hybridization (CGH) is ~£300, and the cost of epilepsy gene panel testing ranges from £525-£1,300. Both investigations risk identifying benign copy number variants or variants of unknown significance. We aimed to identify patients who have had an array CGH and/or gene panel test requested for epilepsy, in the absence of an additional phenotype ("epilepsy only"), and to determine the diagnostic yield of these investigations.

Array CGH requests and gene panel tests for epilepsy were reviewed between January 2013 and June 2018. We excluded those patients

with learning difficulties, global developmental delay, dysmorphic features and congenital abnormalities. Requests were extracted from a departmental database, which includes a clinical summary provided by the clinician. We reviewed the medical records for further clinical information relevant to phenotype. Diagnostic yield included all copy number variants identified on array CGH and pathogenic/ likely pathogenic variants detected on gene panel tests.

We identified 40 array CGH requests for patients with "epilepsy only" phenotype. Only one of these yielded a copy number variant, and the clinical significance of this variant was uncertain. We identified 15 gene panel requests for patients with "epilepsy only". Again, only one of these requests identified a likely pathogenic variant in *SCNA1*, a gene associated with Dravet Syndrome. Based on the low diagnostic yield we would not recommend routine array CGH or gene panel testing in individuals with "epilepsy only".

P27. To screen or not to screen; Three cases of *RET* duplication.

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RET is a proto-oncogene which encodes a receptor tyrosine kinase. Loss of function mutations in *RET* are associated with Hirschsprung disease, while gain of functions mutations cause Multiple Endocrine Neoplasia Type 2 (MEN2). Patients with MEN2 have an increased risk of medullary thyroid cancer and phaeochromocytoma. Screening recommendations for patients with MEN2 include annual calcitonin from 6 months and annual metanephrine from 8 years.

We report three unrelated patients with duplications at 10q11.21 which include *RET*. Patient A is 7 years old and has a history of autism and dysmorphic features. Parental studies are pending. Patient B is 2 years old and has a history of developmental regression and autism. The duplication was inherited from her unaffected mother. Patient C is 51 years old and has a diagnosis of neurofibromatosis type 1; Her array also identified a deletion at 17q11.2 which includes *NF1*. None of the patients have a personal or family history of *RET* associated cancers or Hirschsprung disease.

While intragenic duplications, which create an additional cysteine residue, have been identified in patients with MEN2, whole gene duplications of *RET* have not been reported. Therefore it is difficult to determine whether these patients are at risk of *RET* associated disease and whether any screening is required. It is possible that we will see increased reporting of duplications involving oncogenes, such as *RET,* following their inclusion in the ACMG recommendations for reporting of secondary findings. This will present a challenge for clinicians to provide accurate disease risk estimates and screening recommendations.

P28. The Northern Ireland Cohort of Neurofibromatosis type 2 patients & clinical correlation of their Genetic Severity Score

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Neurofibromatosis type 2 is a rare, autosomal dominant, cancer predisposition syndrome caused by mutations in the NF2 gene on chromosome 22. Birth incidence is around 1 in 33,000. Patients typically present in the second decade of life with hearing loss due to the characteristic tumour of acoustic neuroma, which is often bilateral. Other intracranial tumours, such as meningioma, schwannomas or ependymomas, can also occur. Treatment is generally surgical, but this carries many risks, including acquired hearing loss, facial nerve palsy or significant loss of function. The average life expectancy is around 45 years of age. There are many important predictors of severity, e.g. age of onset of symptoms, which can provide useful prognostic information. Genotype-phenotype correlations are well recognised and, in 2017, a revised Genetic Severity Score [1] was devised for NF2. All patients with NF2 in Northern Ireland are followed up at the Regional NF2 clinic in Belfast and we estimate that we have almost complete ascertainment. We have measured the Genetic Severity Score for each patient and assessed its correlation with clinical symptoms. We hope to continue this work by calculating the Score for newly-diagnosed patients, so that it can guide management, aid future research and give patients some prognostic information. [1]. Halliday D et al, Genetic Severity Score predicts clinical phenotype in NF2. *J Med Genet*. 2017;**54(10):**657-664.

P29. The Collar Bone is connected to the Pancreas: a Cytogenetic Explanation

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A male infant was born at 28 weeks after spontaneous rupture of membranes, weighing 700g (0.4^{th} – 2^{nd} percentile), and transferred to the neonatal unit. There had been antenatal concerns over soft markers with short femurs and an absent nasal bone, and amniocentesis was carried out. At birth he was noted to be dysmorphic, with a broad open fontanelle, and required ventilation. Chest X ray showed absent clavicles, a relatively small thorax, and small scapulae. After birth, it transpired that the baby's father and paternal grandmother had absent clavicles, short stature and poor dentition. A diagnosis of autosomal dominant cleidocranial dysostosis was made.

The infant's course was complicated by sepsis. Despite adequate treatment of sepsis he failed to wean from insulin and was subsequently diagnosed with neonatal diabetes. Neonatal diabetes is a rare disorder with a number of different genetic causes.

Microarray and G banding analysis produced a unifying explanation and mechanism for these two apparently unconnected phenotypes.

On microarray the baby had a 143kb deletion within chromosome 6p21.1 that included part of the *RUNX2* gene, which is mutated in cleidocranial dysostosis. He also had a 12.8 Mb duplication of chromosome 6q23.2-24.2, containing a large number of genes that included *PLAGL1* and *HYMAI*. Paternally derived duplications of 6q24, involving those genes, are associated with transient neonatal diabetes mellitus, and one would therefore infer that the 6q duplication is paternally derived, and that the baby's neonatal diabetes is likely to be transient.

The baby also had an unrelated 251kb deletion within 2p16.3 involving the *NRXN1* gene. Such deletions are associated with a variable degree of developmental disorders in children and adults. G band analysis pre and postnatally showed that there was an unbalanced insertion of the duplicated 6q chromosome material into 6p21.1, presumably at the site of the *RUNX2* deletion.

One would therefore expect that the baby's father with cleidocranial dysostosis carries an insertion of 6q23.2-24.2 into 6p21.1, causing his, and likely the baby's grandmother's cleidocranial dysostosis. Parental microarray and G band analysis is under way.

This rare combination of chromosome 6 rearrangement and distinct clinical disorders has not previously been reported in the literature.

P30. The Significance of Genetic screening in PKU adult cohort & the introduction of Sapropterin dihydrochloride

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Introduction: The largest cohort of patients at The National Centre for Adult Inherited Metabolic Disorders (NCIMD) have Phenylketonuria (PKU). The NCIMD manages patients transitioned from Paediatric services upon reaching adulthood. Improved treatments have extended life expectancy and increased quality of life for patients with PKU; however diet and supplements remained the only means of treatment for life until the recent introduction of Sapropterin dihydrochloride.

Aim: To analyse the genotype of the PKU cohort in attendance at The NCIMD with a focus on responsiveness to Sapropterin dihydrochloride.

Method: The data are collated from when the Adult unit was first established in 2013 until the end of May 2019. Exclusion criteria include patients over the age of 53 and patients who have two negatively indicated genotypes for the use of Sapropterin dihydrochloride. Genotypes are recorded in a secured database on-site and descriptive analyses were performed.

Results: The total number of patients examined is 282; 104 were male (36.8%) and 178 were female (63.1%). The total samples processed and available for analysis were 148 (male= 46, 31%; female= 102, 68.9%). The frequency of Saptopterin dihydrochloride responsiveness in both alleles was observed (responsive= 15, 10%; unresponsive= 48, 48.33%; uncertain= 85, 57%). The most common alleles recorded were R408W (41.1%), F39L (13.8%), 165T (11.2%), and L249F (3.8%).

Conclusion: Due to the uncertainty surrounding Sapropterin dihydrochloride responsiveness for various common mutations in the Irish PKU cohort, there is a need for greater genetic and metabolic collaboration. Analysis and treatment may be impacted by time elapsed from sending samples to receiving results.

P31. *POT1*: An emerging oncological phenotype

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Patients with mutations in protection of telomeres 1 (*POT1*) gene are an emerging phenotype and to date 21 families, involving 69 confirmed POT1 gene mutation carriers have been reported in literature. Somatic mutations in *POT1* are also reported in chronic lymphocytic leukaemia, cutaneous T-cell lymphoma and lung tumours. As there are so few reported cases of patients with *POT1* mutations it is difficult for clinicians to counsel patients as to which cancers are more likely to occur in mutation carriers, and what screening, if any, is indicated.

In this four- generation pedigree we describe the oncological burden of three individuals with a known mutation in *POT1* and three first degree affected, deceased relatives who are presumed to be gene carriers. Cancers present in this family reflect some cancers which have previously been described in patients with *POT1* mutations, including melanoma, sarcoma, oligodendroglioma and lymphoma. However, our pedigree also includes disease phenotypes not previously described in the *POT1* cohort, including atypical pancreatic cancer, desmoid tumour, ovarian cystadenofibroma, lipomas and other dermatology cancers.

At present dermatology follow-up is recommended in confirmed *POT1* gene mutation carriers described in this pedigree as evidence suggests an increased lifetime risk of melanoma however, additional screening recommendations are very difficult currently with few *POT1* families ascertained. Our family extends current knowledge on phenotype in *POT1* families reported in literature with the hope that, in the future, it will be possible to offer patients more targeted screening and more accurate disease risk estimates.

P32. Schwannomatosis – the Northern Ireland Cohort

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Schwannomatosis is a rare, autosomal dominant, cancer predisposition syndrome that can lead to schwannomas, which mainly occur in the spinal and peripheral nerves. As acoustic neuromas can occur, the condition can be mistaken for Neurofibromatosis type 2 (NF2). It is, however, important to differentiate between these 2 disorders, as the prognosis is generally poorer for NF2; the average life expectancy in NF2 is around 45 years of age, whereas in schwannomatosis, it is around 75 years. This prognostic information in useful in guiding clinical management and is also helpful for patients. Most schwannomatosis patients will have mutations in the LZTR1 and SMARCB1 genes. In Northern Ireland, our schwannomatosis patients are followed up at the Regional NF2 clinic in Belfast and we estimate that we have almost complete ascertainment. Here we present the findings of genetic analysis of this cohort and summarise their clinical symptoms.

P33. Dying to see you?

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Introduction: The Department of Clinical Genetics at CHI provides services for individuals affected by or at risk of a genetic condition in the Republic of Ireland. There are currently 3,283 referrals waiting to be seen, of whom 930 are waiting longer that the HSE standard of 18 months.

A negative consequence of a long waiting list is that patients die whilst waiting. Resulting harm includes: 1) no diagnosis 2) no genetic testing, no DNA stored, 3) family unaware of a hereditary disorder, denied screening, 4) relatives having unnecessary screening as no predictive test for family, 5) future pregnancy options limited if paediatric proband undiagnosed. As of 13/06/2019, we have recorded 33 deaths on our waiting list. We began to systematically collect data on deaths since March 2018. This study concentrates on these cases; n=15/33.

Aims: To identify the consequences to the relatives of these 15 referrals.

Results: Nine were adult cancer genetic referrals, 5/9 diagnostic, 3/9 predictive, and a further case had NF2. Only 1/9 had DNA stored. Two adult patients had a cardiac family history (Marfan syndrome, cardiomyopathy) respectively. Neither had DNA stored. Four paediatric patients had multiple malformations secondary to a chromosomal or genetic syndrome. In 3/4 a diagnosis had already been reached. The fourth case, who died unexpectedly of unrelated causes, had no DNA stored.

Summary: 11/15 patients who died did not have DNA stored, precluding diagnosis and risk calculation for their relatives. As

each extended 3 generation Irish family has ~64 relatives, lack of diagnosis has far reaching consequences.

P34. Interventions to improve psychosocial well-being in female *BRCA*-mutation carriers following risk-reducing surgery: A Cochrane Systematic Review.

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Background: Women who carry a pathogenic variant in either a BRCA1 or BRCA2 gene have a high lifetime risk of developing breast and tubo-ovarian cancer. To manage this risk, women may choose to undergo risk-reducing surgery to remove breast tissue, ovaries and fallopian tubes. Surgery should increase survival, but can impact women's lives adversely at a psychological and psychosexual level. Interventions to facilitate psychological adjustment and improve quality of life post risk-reducing surgery are needed.

Aim of Review: To examine psychosocial interventions in female BRCA carriers who have undergone risk-reducing surgery and to evaluate the effectiveness of such interventions on psychological adjustment and quality of life.

Methods: We searched the Cochrane Central Register of Controlled trials (CENTRAL) in the Cochrane Library, MEDLINE via Ovid, Embase via Ovid, CINAHL, PsycINFO, Web of Science and Scopus up to April 2019.

Results: We identified two studies; one randomised controlled trial and one nonrandomised study.

Conclusions: The effect of psychosocial interventions on quality of life and emotional well-being in female BRCA carriers who undergo risk-reducing surgery is uncertain given limited high quality evidence. Next Generation Sequencing, along with targeted cancer treatments, increasing knowledge around the biology of cancers and the results of the 100K Genome Project will open up genetic testing to many more women. For as long as surgical interventions remain the dominant risk-reducing option for management of women with a deleterious BRCA gene, health professionals have a responsibility to ensure there is provision to holistically manage the outcomes of such surgery.

P35. An Irish male with bilateral Fibular Aplasia Tibial Campomelia and Oligosyndactyly (FATCO) syndrome

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Introduction: FATCO (Fibular Aplasia, Tibial Campomelia and Oligosyndactyly) syndrome is a rare descriptive diagnosis first defined by Courtens *et al*. in 2005, who recognised a comparable pattern of malformations with his own case and 4 others described in the literature. Aetiology remains unknown, however defects involved in *SHH* (Sonic hedgehog) gene expression have been proposed.

Case Description: We report on a term male infant born with severe malformations. On examination, there was absence of the left radius and ulna, bilateral anterior angulation of lower limbs with skin dimpling overlying. Both ankle joints were dysplastic and there was oligosyndactly of both feet. Right upper limb was normal. X-rays of the limbs revealed dysplastic tibiae, absence of both fibulae, a right foot containing 3 ossified metatarsals with 2 formed digits, and a left foot with a single ossified metatarsal and two soft tissue digits with small bony elements. The infant had no other associated anomalies, and is developmentally appropriate at 1 year. Management included Symes amputation, prosthetics and following genetic referral FATCO syndrome was suggested as the best fitting diagnosis. Whole genome sequencing of the infants blood is currently being performed.

Discussion: This is an important case to report as there are very few descriptions in the literature, In keeping with the majority of reports, this case appears to be sporadic and development is normal. Our case is male, keeping with preponderance. Treatment aims at optimising functionality of limbs and stabilisations of joints.

P36. Natural history of a fibrous cephalic plaque and sustained eight decade follow-up in an 80 year old with tuberous sclerosis complex type 2.

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Introduction: Fibrous cephalic plaques (FCP) are a characteristic manifestation of tuberous sclerosis complex (TSC) and occur in one third of cases. Their natural history and long term course is unknown, as is the outcome of long term follow-up of TSC cases in old age.

Phenotype and methods: We describe an 80 year old with TSC due to a c.2784dupC TSC2 mutation, who was diagnosed in infancy with an FCP and was regularly followed up at the TSC clinic over 8 decades with regular epilepsy treatment and renal monitoring.

Results: Regular clinical photography and clinical records document the plaque at different ages. The FCP naturally resolved at 74 years. Facial angiofibromas also faded with time in the last decade. His epilepsy and renal abnormalities remained under control with careful surveillance and monitoring.

Discussion: Natural aging in the eighth decade causes progressive laxity of collagen and leads to natural resolution of FCPs. This novel finding with a unique 80 year follow up yields valuable insights into the aging changes within FCPs and facial angiofibromas as the pathways linking facial angiofibromas and FCP's through the TGF-β1 pathway are now being elucidated.

Conclusion: We present a clinical odyssey showing the natural progression and history of FCPs in TSC and comment on the mechanistic pathways allowing potential interventions in this disfiguring condition. TSC cases can be successfully managed and complications – particularly in the brain and kidney, can be avoided over an entire lifetime. This is encouraging for long term prospects for patients with TSC.

P37. Genotype/phenotype landscape of adult Fabry disease in Republic of Ireland

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Introduction: Fabry disease is an X-linked inherited disorder due to deficient activity of the enzyme alpha-galactosidase A and progressive lysosomal deposition of globotriaosylceramide in cells.

Aim: To report the genotype/phenotype landscape of the adult Fabry disease cohort attending The National Centre for Adult Inherited Metabolic Disorders (NCIMD).

Method: All Fabry patients (N=70) attending NCIMD until end of May 2019 were included in this analysis. Genotypes and phenotypes were recorded by chart review. Descriptive analyses were performed.

Result: 26 (37.1%) were male (median age 43 [32:54]) and 44 (62.9%) were female (median age 46 [25:61]). The *AGAL* pathogenic variants were missense (52, 74.3%), deletion (9, 12.9%), nonsense (8, 11.4%) and duplication (1, 1.4%). Most missense variants occurred in exon 2 (25%), exon 3 (19.2%), exon 5 (23.1%) and exon 6 (21.2%). 21.2% of missense variants were N215S. 28 patients were on enzyme therapy and 2 were on oral chaperone therapy. The incidence of cardiac (M=18/26; F=18/44; p=0.021), renal (M=14/26; F=18/44; p=0.304), neurological (M=17/26; F=20/44; p=0.107) and hearing (M=14/26; F=19/44; p=0.399) involvement were observed. Within N215S cohort, 2 had hypertrophic cardiomyopathy and 5 with a degree of left ventricular hypertrophy.

Conclusion: Pathogenic variants were observed across the *AGAL* gene in the cohort. Incidence of cardiac involvement in both genders is similar. Females had more frequently observed renal, neurological and hearing involvement. N215S *AGAL* variant is the most common variant which is associated with a predominant cardiac phenotype, thus collaboration between clinical geneticists and cardiovascular physicians are important when establishing diagnosis and management.

P38. 'Long shadow of metabolic entropathies: a Tale of Two Extreme Case'

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Inherited genetic disorders of energy utilisation ('entropy') from glucose can have clinical consequences with extreme variability of phenotype. This primarily depends on the location of enzyme defect along the metabolic pathway, i.e. upstream glycolysis or downstream oxidative phosphorylation, thus causing a catabolic bottleneck. Herein, we compare and contrast two extreme clinical cases: one of pyruvate dehydrogenase (PDH) deficiency and another of cytochrome c oxidase (COX) or respiratory chain complex IV deficiency. Through molecular genetic analysis, the first case was confirmed as a homozygous, missense mutation-driven defect in the E2 subunit of PDH which governs entry of glycolytic end product into the citric acid cycle; conversely, the second case demonstrated reduced activity of cytochrome *c* oxidase (COX), the penultimate enzyme complex in the mitochondrial electron transport chain. PDH deficiency is a rare autosomal recessive condition characterised by a constellation of severe neurological symptoms including intellectual disability, seizures and metabolic stroke. On the contrary, complex IV deficiency leads to a phenotype of predominantly generalised myopathy. We coin these syndromes at opposite ends of the bioenergetic pathway 'metabolic enteropathies'. As such, they exemplify two diagnostic baskets that should be high on the differential diagnoses of suspected inherited metabolic disorders (IMDs) of neuromuscular presentation.

P39. Genetic Characterisation of two Copy Number Variants (CNVs) in the *LDLR* Gene causing Familial Hypercholesterolaemia

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Familial hypercholesterolemia (FH) is an autosomal dominant disorder due primarily to mutations in *LDLR, APOB* and *PCSK9*, which causes marked increases in LDL cholesterol levels and predisposes to premature CVD. It has an estimated prevalence of 1 in 250 suggesting approximately 23,000 FH sufferers in the Republic of Ireland. The most cost-effective strategy for identifying FH is genetic cascade screening in kindreds with an identified proband. To date our service has genetically diagnosed 30 disease-associated variants in *LDLR* and *APOB*, including four CNVs in *LDLR* detected using MLPA. The elucidation of mutations which are associated with FH can facilitate a better understanding of the pathology of the disorder, as well as improving genetic diagnostic methods for variant detection. This study reports the characterisation of two CNVs.

A novel exon 6 deletion was identified using a short-range PCR strategy followed by direct sequencing. This variant was then used to validate a long-range PCR assay which subsequently facilitated the identification of an aberrant PCR product caused by a second *LDLR* deletion in exon 15-18.

Over 10% of FH-causing mutations are attributed to complex rearrangements due to the high degree of *Alu* elements within *LDLR i*ntronic sequences. While MLPA is effective at identifying CNVs it is an expensive method to use for cascade screening within large family groups. This project identified the breakpoints in a novel LDLR exon 6 deletion and an aberrant PCR product caused by a deletion of exon 15-18, and both findings will facilitate future cost-effective cascade testing of family members within the respective kindreds.

P40. Characterisation of the pathogenic basis of an early-onset familial mucocutaneous ulcerative condition in Irish families

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Bechet's disease (BD) is a heterogeneous multifactorial auto-inflammatory condition characterised by recurrent episodes of oral and genital ulceration, uveitis and skin lesions, with less frequent involvement of the gastrointestinal tract, large blood vessels and central nervous system. Recent studies reported monogenic mucocutaneous ulcerative syndromes with similarities to BD in a number of un-related families caused by mutations in NF-κB pathway genes; RELA, a transcription factor of the NF-κB family, and TNFAIP3, a negative regulator of NF-κB activity and inflammatory cytokine production. The NF-κB pathway is a 'master-regulator' of

immune and inflammatory signalling, with the ability to control the expression of genes associated with inflammation, apoptosis and proliferation. Five multi-case Irish families have been identified with a similar illness, primarily involving childhood-onset chronic oral and genital ulcers. Using whole exome sequencing (WES), this study aims to identify the potential disease-causing mutations, and to elucidate their biological effects.

In the largest, a three generation family, WES revealed segregation of a mutation in RELA with the condition. The mutation involves a cytosine deletion causing a His487ThrfsTer7 frameshift resulting in a truncated protein, which is expressed at similar levels as the wild-type in PBMCs. Crucially the mutation interrupts the two C-terminal RELA transactivating domains. Genotyping of this variant in other families revealed the presence of the wild-type allele only, suggesting genetic heterogeneity. Current genetic analysis of the remaining families is expected to reveal novel disease-causing mutations. These discoveries will contribute to our understanding of the disease mechanism and the inflammatory pathway, leading to personalised treatment for patients resulting in earlier disease control.

P41. Hurdles to genetic research in Ireland; GDPR and Health Research Regulation in practice.

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The General Data Protection Regulation (GDPR) aims to protect EU citizens from privacy and data breaches. The Department of Health in Ireland issued further legislation designated the Health Research Regulation (HRR) pertaining to data processing for the purposes of health research.

We were awarded an international peer-reviewed grant to conduct a translational study on clinical genetics patients. The aims of the project are three-fold: 1. To review cardiac genetic patients and update their variant pathogenicity status using the 2015 ACMG guidelines. 2. To collate phenotypic and penetrance data on these patients over time. 3. To offer extended panel testing to 30 families who were gene-negative on the original four-gene panel.

Due to HRR, the requirement for "explicit consent" to perform a large-scale retrospective genetic test review was highlighted by an ethics committee, despite previous patient consent to genetic testing having been obtained. On consultation with the local Data Protection Officer (DPO), we were advised that explicit consent was not required for parts 1 and 2 of the study (defining them as clinical audit and usual practice, respectively). For part 3, we require explicit consent from participants, issuing our own patient information leaflets/consent forms and arranging consultation with a genetic counsellor prior to enrolling in the study.

Ambiguity over the implementation of the new guidelines was evident throughout the process. This is contributing to stasis in audit and research as all stakeholders are learning how best to interpret the guidelines.

We would encourage researchers to engage with stakeholders to ensure compliance with GDPR.

P42. Diagnostic Yield for genetic testing for Hypertrophic Cardiomyopathy in the Irish Population

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Background: Hypertrophic cardiomyopathy (HCM) is the most common inherited cardiovascular disease with a worldwide prevalence of 1:500. Genetic etiology is suspected in up to 50% of HCM patients. To gain insight into the diagnostic yield and mutation spectrum of HCM, a retrospective review was performed for 114 consecutive cases with a clinical suspicion of HCM who underwent multigene panel testing at our laboratory between 2014 and 2019.

Method: Data was manually extracted from laboratory reports with respect to indication for testing, number of genes on panel, variants identified and classification at the time of testing.

Results: A total of 114 patients with a diagnosis of HCM had samples submitted for diagnostic testing using a multigene panel of between 16 and 20 genes, depending on the year of testing. 56 patients had no genetic variant identified, 33 patients had a pathogenic or likely pathogenic variant identified and 25 had a variant of uncertain significance identified. One 11 year old patient had a normal result from an 18 gene panel for HCM, but was later diagnosed with Friedrich ataxia. One adult female patient had a normal result from a 19 gene panel but was later diagnosed with Fabry disease.

Conclusion: Clinically actionable 'Pathogenic' or 'Likely pathogenic' variants were identified in 29% of patients with a Clinical diagnosis of Hypertrophic Cardiomyopathy with VUS being identified in 22%. The most common 2 genes in which clinically actionable variants were found were MYH7 (47%) and MYBPC3 (31%).

P43. A 3-year review of Huntington's disease referrals to the Department of Clinical Genetics, CHI at Crumlin.

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Huntington's disease (HD) is an inherited progressive neurodegenerative condition. In the Republic of Ireland genetic testing for HD is available via two routes. Symptomatic individuals can access testing via a Neurologist. Asymptomatic individuals with a known family history of HD can seek testing via a genetic counselling multi-step process.

Aim: The aim of the audit was to review the activity of the HD specialty clinic.

Methods: Retrospective chart, laboratory and clinical database review for HD referrals received for 2016, 2017 and 2018 was carried out. Parameters examined included: number of referrals, age profile, motivation for testing, results.

Results: Over this 3 year period 93 referrals were received. 80 referrals were for predictive testing and 13 for genetic counselling post testing through neurology. The youngest person was 18 years of age at time of referral. More females requested a referral for predictive testing than males, 48 (60%) and 32 (40%) respectfully. The most common motivation given for predictive testing was with regard to family planning and concerns for children and to

help them plan for the future. Of the 30 tests carried out to date, 52% were mutation positive and 42% were mutation negative. The average age of those who proceeded with testing was 37yrs.

Conclusion: These findings reflect data published from the UK with regard to age of presentation and female to male bias. The most common motivation for testing was family planning unlike the UK where the most common reason provided was to reduce uncertainty.

P44. Survival Modelling Incorporating Genetic Profile: application to a TCGA dataset

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This work is on analysing methods for high-dimensional survival data and applications of them to a TCGA dataset from The Cancer Genome Atlas on ovarian carcinoma. The dataset clinically annotated as "HGS-OvCa" includes both clinical and genomic gene expression profile of patients which was measured with the motivation of increasing the successful treatment strategies in 2011.

Ovarian cancer is one of the leading causes of death in women in recent years with most deaths for patients with advanced-stage, high-grade serous ovarian cancer (HGS-OvCa) as reported in some papers. The standard treatment is aggressive surgery followed by platinum taxane chemotherapy. After therapy, platinum resistant cancer recurs in approximately 25% of patients within six months, and the overall five-year survival probability is 31%.

The Cancer Genome Atlas provided researchers a possibility to study comprehensively genomic and epigenomic abnormalities on clinically annotated HGS-OvCa samples. In this study the mRNA expression, microRNA expression, promoter methylation and DNA copy number in 489 high-grade serous ovarian adenocarcinomas and the DNA sequences of exons from coding genes in 316 of these tumours are measured. In Cancer Genome Atlas projects gene expressions of the samples are measured multiple times on different microarray platforms. We have used the complete-data unified gene expression (a weighted average of the platforms) profile of patients and their associated clinical data, which consists of 269 patients gene profiles with 11864 employed genes, to build a predictive model for patients' survival and interpret how effective the treatment is for the patients in high-risk and low-risk prognosis groups.

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