



Bachelor of Medical Science (Honours) Abstracts

The Global Health Classroom: Experiences and learning outcomes of collaborative global health learning between New Zealand and Samoan medical students in a virtual classroom

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Background: Global Health Classroom (GHCR) is a virtual collaborative global health learning model being developed and delivered at the Otago Medical School, New Zealand (OMS) in partnership with Patan Academy of Health Sciences, Nepal (PAHS) and School of Medicine, National University of Samoa, Samoa (NUS).

Aims: To explore the learning and experiences of New Zealand and Samoan medical students in the GHCR and ascertain the key elements contributing to their learning and experience.

Methods: A mixed-method study approach using a post-GHCR questionnaire and semi-structured interviews. A triangulation approach informed the synthesis of the data.

Results: Of the participants, 85% (74/87) responded to the post-GHCR questionnaire. Nineteen semi-structured interviews were conducted: 13 OMS students and six NUS students. Students reported gaining knowledge about patient care, healthcare systems and the culture and determinants of health, with regards to their partner country. There was evidence that attitudes such as cultural understanding and respect were promoted among students by their GHCR experiences. Majority (64%) of students reported increased interest in learning about global health after their GHCR experience. Reported outcomes in the GHCR align favourably with the recommended global health learning concepts in the literature.

Discussion: Key elements that promoted learning in the GHCR were: use of clinical cases and global health themed guiding questions, teachers as facilitators not deliverers of content, promotion of students as self-directed learners, peer learning, social interactions, and video-

conferencing. Students in the GHCR found that learning with their international peers in a virtual classroom made learning about global health "more real and tangible" and "much more accessible than learning on a purely theoretical basis."

Conclusions: The findings in this study suggest that GHCR presents a promising global health learning model with core values of partnership, collaboration and reciprocity between medical students and institutions. Medical schools in different countries can partner together to deliver global health learning for their students by integrating the GHCR into their curriculum. GHCR continues to be delivered at the OMS, with plans to extend partnership to other overseas medical schools.

An appraisal of depression, anxiety and stress among Pacific youth at a New Zealand university

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Introduction: University students and Pacific youth may both have a high prevalence of mental health challenges. This research aimed to identify the prevalence and correlates of depression, anxiety and stress in Pacific youth aged 16 – 24 who attend university and their unique experiences of mental health.

Materials and methods: This research used mixed methods design. After conducting a literature review, an anonymous online survey was distributed. The survey included the short-form Depression, Anxiety and Stress Scale (DASS-21), demographic information, the Pacific Identity and Wellbeing Scale (PIWBS) and health services interaction. Three focus groups were also undertaken with eight participants, using the Pacific methodology Talanoa. Focus groups were analysed using grounded theory and Te Vaka Atafaga, a Tokelauan assessment model for mental health.

Results: There were 112 valid survey responses. The prevalence of mild to very severe depression, anxiety and stress among sampled Pacific youth at university were 68.8%, 66.1% and 57.2%. The PIWBS factors of perceived familial wellbeing, perceived societal wellbeing, Pacific connectedness and belonging and cultural efficacy were negatively correlated with DASS-21. Focus groups emphasised the impact of family, social support, sense of purpose, personal expectations, environmental factors and the importance of accessing help.

Conclusion: A mixed methods approach has allowed us to demonstrate Pacific youth at university have a high prevalence of mental health challenges and that better support is needed. More research is required on the topic of mental illness in Pacific youth. Recommendations from

this research may help to inform Pacific youth mental health initiatives.

A novel nutrient recycling device for gastrointestinal fistulas and stoma: design and feasibility

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Introduction: Enterocutaneous fistulae and high-output enterostomies often require intensive medical support including fluid replacement and parenteral nutrition. Refeeding stoma output has been recognised as beneficial, however clinical implementation has been limited due to the lack of an efficient and palatable method. This work aimed to develop and test a novel refeeding pump device.

Materials & Methods: The refeeding pump comprised a compact impeller connected to a commercial feeding tube inserted into the distal intestinal limb. The pump is activated across the stoma appliance via magnetic coupling to an electrically-operated motor. Nutritional, medical, psychological and human-use factors were evaluated in a feasibility trial. Patients were asked to use the device at least daily over a minimum three-week period. Data encompassed interviews, diaries, bloods, nutrition and admission statistics. The device was iteratively improved throughout the trial.

Results: The novel device was successfully validated on benchtop tests then trialled in 7 patients. Indications for inclusion included remediation for high output stoma, weaning from TPN and gut rehabilitation before re-establishment of bowel continuity. A range of chyme viscosities were successfully recycled following iterative device improvements. Preliminary data illustrate a variety of benefit from refeeding using the device including reduced stoma losses (>65%), improved renal and liver function, electrolyte levels and quality of life.

Conclusions: A novel nutrient recycling device was developed and shown to be feasible in clinical practice. The device has potential benefits in enhancing nutrition, improving surgical outcomes and reducing costs of care for these complex patients. Further validation is in progress.

Studies in the mechanisms and therapy of post-operative ileus

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Introduction: Post-operative ileus (POI) is the most frequent complication following abdominal surgery. POI has a large economic impact and poses a significant clinical burden. Autonomic imbalance and electrolyte derangements are commonly associated with POI however, clear pathophysiology and therapies are limited.

Objectives: To i) introduce non-invasive electrocolonography ("ECoLG") to investigate acute colonic dysmotility ii) conduct a systematic review on existing therapeutic methods for POI; iii) investigate the relationship of electrolytes and their role in POI pathophysiology.

Methods: ECoLG techniques were developed, used in pre- and post-operative surgical patients and validated against high-resolution (HR) manometry. A systematic review was conducted to critically appraise the use of electrical stimulation to alleviate POI. A joint clinical and

theoretical study was undertaken to evaluate the relationships between postoperative electrolyte concentrations and POI occurrence.

Results: ECoLG feasibility studies showed proof-of-concept and patient tolerance. These data were correlated with simultaneous HR manometry in three patients with approximately eight hours of data. The systematic review showed electrical stimulation appears to be a promising technique to improve post-operative GI recovery. Sodium and chloride trend downwards post-operatively. Cell models with a 10% reduction in extracellular NaCl demonstrated a 27% reduction in frequency of electrophysiological activity in interstitial cells of Cajal and smooth muscle cells.

Conclusion: ECoLG is introduced and validated as a tool for non-invasively assessing colonic motility. Electrolyte correction and electrical stimulation offer useful directions for novel therapeutic interventions for POI. Future studies should apply ECoLG in other settings and investigate non-invasive electrical stimulation for post-operative GI recovery.

Vision for the future: bioengineering transition zone stem cells into corneal endothelial sheets for transplantation

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Introduction: Corneal endothelial disease represents a significant healthcare burden in New Zealand. Corneal transplantation using limited donor tissue is the only available treatment. The recent discovery of putative corneal endothelial stem cells in the 'transition zone' of the cornea holds exciting potential for in vitro cell regeneration and subsequent therapeutic application. Our lab group has successfully isolated and expanded these transition zone cells in vitro and shown that cells can spontaneously differentiate into corneal endothelium by 24 weeks. The aim of this project was to optimise the cell culture protocol to accelerate this differentiation process into functional endothelium.

Materials and Methods: Transition zone (TZ) cells were isolated from human donor corneal rims and expanded in vitro. Different culture media were systematically trialed to optimise the cell differentiation protocol. Examination of the morphological cell features under light microscopy, immunohistochemistry, western blot and flow cytometry were used to assess differentiation into mature endothelial cells.

Results: TZ cells spontaneously differentiated into corneal endothelium by 24 weeks, with cells developing a characteristic polygonal shape and expressing functional endothelial cell markers. Addition of 'ROCK inhibitor' significantly increased the rate of cell proliferation and shows promise in accelerating cell differentiation.

Conclusion: Transition zone cells have the capacity to differentiate into functional endothelial cells and ROCK inhibitor may enhance this process. With further research, bioengineering this ethical source of stem cells may help to overcome the challenges associated with a limited donor tissue supply and provide timely treatment for patients with endothelial disease.

Exploring perceptions of nutrition education in Year 3 medical students at the University of Auckland

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Background: Globally, the rates of nutrition related diseases is on the rise. This has led to a call for doctors to provide nutrition care to patients. However, medical students are reported to be inadequately prepared to provide nutrition care. This study aims to investigate students' perceptions of the nutrition education they receive at medical school and to identify the gaps in knowledge to help inform students' specific needs.

Method: Thirty-five year three University of Auckland Medical students took part in six semi structured focus groups at the Grafton campus. Each focus group was audio recorded and transcribed verbatim. The constant comparative method was used to analyse data.

Results: Four inter-related themes emerged from students' responses. In "Doctors' role in providing nutrition care," students opined that patient centred barriers meant general practitioners were the most accessible and sources of nutrition advice. In "Medical nutrition education," students expressed that the nutrition education they had received was inadequate. In "Nutrition in a wider context," students recognised that nutrition behaviours existed in a larger context. Lastly, in "Recommendations to improve nutrition education," students expressed that there needed to be more time and resources allocated to nutrition care (i.e. more lectures, tutorials, resources for self-directed learning).

Conclusion: Students felt it important that doctors play a role in providing nutrition care. However, most students felt ill prepared to provide nutrition care. A more comprehensive incorporation of nutrition science in the medical curriculum is needed to improve the nutrition education of medical students.

Fixing the whare: whānau experiences and wider health benefits of a healthy home initiative

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Introduction: Limited qualitative evaluations of healthy home initiatives exist in the literature and even fewer look past physical health benefits to wider health outcomes. A qualitative evaluation of Manawa Ora, a healthy home initiative in Whangarei, was conducted to ascertain whānau experiences of a healthy home initiative looking particularly at the wider health benefits.

Materials and Methods: Participants of the Manawa Ora programme were recruited by staff members trained in the Manawa Ora process. Participant experiences were ascertained through qualitative semi-structured interviews and analysed using Charmaz's grounded theory method.

Results: Three main themes emerged from the semi-structured interviews. "Overcoming the system" describes the successful aspects of the Manawa Ora programme and the barriers participants face when dealing with organizations. "Not defined by illness" pertains to improved health, both physical and mental health, following the programme. It also describes the way participants have redirected their focus from their home and health towards other things. Finally, "From a simple space to a place with meaning" highlights the way the Manawa Ora programme improved the home environment and took a simple 'space' and created a 'place' that holds meaning.

Conclusion: Healthy home initiatives can improve physical health as well as wider health outcomes. The Manawa Ora programme has broken down barriers; barriers to accessing health services, barriers to achieving good health and broken down the perceived idea that health exists in isolation and isn't impacted upon by the environment.

Prioritizing long-term outcomes for babies born preterm: The HIP survey

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Introduction: Preterm babies are at risk of both cognitive impairment and health complications in later life. Perinatal interventions may improve cognitive outcomes, but at the risk of worsening longterm health. Our aim was to determine what people believe are the most important long-term outcomes for babies born preterm.

Materials and Methods: An online survey was distributed among: clinicians taking care of preterm babies, parents of preterm babies and adult controls. Six variables were examined: education (finish secondary school), longevity (live to at least 70 years of age), wealth (enough money to pay for rent and food), normal weight, health (no significant chronic illness), and intelligence, using a hierarchy ladder, Likert scale and a hypothetical scenario. Data are n(%) and mean(SD).

Results: Between July and September 2018, 110 participants completed the survey (35 controls, 36 clinicians, 39 parents. Health was the most frequently top ranked variable on the hierarchy ladder (76/110(69.1%)). Clinicians were most likely to choose health as the most important outcome (clinicians 26/36(72.2%), controls 24/35(68.8%) and parents 26/39(66.7%), p=0.03). The most frequently chosen outcome for the scenario was the option of normal body weight, longest life span and lowest wealth (36/110(32.7%)). On the Likert scale (1-5, 5 being most important), education had the highest mean score overall (mean(SD), 4.34(0.83)). However, parents and controls scored health as the most important variable (mean(SD), parents 4.49(0.72), controls 4.29(0.71)).

Conclusions: Health was perceived as the most important long-term outcome for preterm babies. Future research should prioritise health outcomes for babies born preterm.

A fully automated segmentation algorithm for the volumetric analysis of perihematomal oedema in patients with spontaneous intracerebral haemorrhage

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Introduction: Secondary injury is a significant contributor to morbidity and mortality in patients with spontaneous intracerebral haemorrhage (ICH). Perihematomal oedema is a radiologic marker of secondary injury in ICH patients. The aim of this study was to develop a fully-automated image segmentation algorithm for the volumetric analysis of perihematomal oedema.

Methods: From consecutive ICH patients that were enrolled in the Intracerebral Hemorrhage Outcomes Project between 2009-2017, a random sample of 500 CT scans was manually segmented by two independent users and split into training (4/5) and validation (1/5) sets. A fully convolutional neural network (CNN) architecture was constructed and its performance was tested using Dice similarity co-efficient and area under the receiver operator curve (AUROC) analyses. The time to

perform segmentation, at each instance, was recorded for both manual and automated methods.

Results: The training and validation sets comprised 4,915 and 1,229 volumetric slices, respectively. After a training time of 33,3340s, the CNN achieved an overall Dice ratio of 0.935 ± 0.041 , sensitivity of $93 \pm 5\%$, specificity of $91 \pm 5\%$ and AUROC of 0.895 ± 0.026 . The mean time to perform segmentation was significantly lower for the automated (0.19 ± 0.01 s vs. 900 ± 60 s; $p=0.001$) upon comparison to the manual method.

Conclusions: CNN can accurately predict oedema in patients with spontaneous ICH at a significantly faster rate than manual segmentation. The application of this tool may permit the systematic investigation of periaematoma oedema in large, multi-center cohorts and provide reliable criteria for assessing the efficacy of novel treatments in ICH patients. External validation of the network is warranted.

Understanding the clinical utility of streptococcal serology for the diagnosis of group A streptococcus infections

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Introduction: Immune sequelae of Group A Streptococcus (GAS) infections such as rheumatic fever and post-streptococcal glomerulonephritis utilise serological tests to aid diagnosis. Current tests measure antibody titres to two GAS antigens, streptolysin O (anti-SLO; ASO) and deoxyribonuclease B (anti-DNase B; ADB), but have limited predictive value in diagnosing GAS sequelae in endemic settings due to high background titres. SpnA is a cell-wall anchored, conserved GAS antigen that has recently shown potential as an additional serological marker for GAS infection. The aim of this study was to characterise the immunokinetics and specificity of anti-SpnA compared with ASO and ADB in bacteraemia patients to further inform clinical utility.

Materials and Methods: Adult bacteraemia patients infected with GAS ($n=10$) or non-GAS Gram positive bacteria ($n=15$) were recruited from Auckland City Hospital and Middlemore Hospital between March-September 2018 following informed consent (HDEC 17/STH/233). Serial serum or plasma samples were obtained over the disease course and the ASO, ADB and anti-SpnA titres were determined using an in-house multiplex bead-based immunoassay.

Results: All of the patients with GAS bacteraemia for whom two or more samples were obtained 7-days apart showed increased titres to 2 of the 3 antigens. Of the patients infected with non-GAS Gram positive bacteria, only those infected with the closely related Group C/G streptococcus showed elevated titres to the GAS derived antigens.

Conclusions: This study provides additional evidence on the value of anti-SpnA as an adjunct to current streptococcal serology and novel data with respect to GAS cross-reactive antibodies generated following non-GAS bacteraemia.

Bariatric surgery in New Zealand: a retrospective analysis of prevalence, post-operative medication changes and cardiovascular risk prediction

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Introduction: Rising obesity rates are contributing to a significant healthcare burden in New Zealand. Bariatric surgery is an effective intervention for facilitating substantial weight loss. We aimed to analyse the annual volume and location of bariatric surgery in New Zealand and outcomes such as mortality, CVD events and alterations in medication utilisation by type of surgery.

Methods: Clinical data from New Zealand national hospital discharge codes for bariatric procedures were recorded for all patients from 1 January 2004 to 31 December 2017. Pharmaceutical data was limited to CVD medications dispensed within 6 months of the index surgery and at 1 and 5 years afterwards. The study dataset included demographic information, hospitalisations and deaths. The statistical software RStudio was used for data analysis.

Provisional results: A total of 9114 patients received their first bariatric procedure within this study period. Bariatric surgery increased from 34 and 4 procedures (in 2004) to 470 and 614 (in 2015) in public and private sectors, respectively. Gastric bypass (GB, $n=3986$) and sleeve gastrectomy/gastric reduction (SG, $n=8599$) were the most frequently coded procedures. The majority of publicly funded procedures have been completed by the Auckland region District Health Boards. GB and SG procedures have similar efficacy by medication reduction and equally low CVD morbidity and mortality.

Conclusion: Bariatric surgery is increasing in frequency in New Zealand, with similar outcomes between the two most commonly performed types of surgery SG and GB.

Acute Pancreatitis and Cx43 – the Effect of Lymphatic Drainage

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Introduction: Multiple organ dysfunction syndrome (MODS) is the main cause of death due to acute pancreatitis (AP). During the course of AP, it is proposed that the intestine is damaged and releases toxic substances into its lymphatic fluid, which then negatively influence other organs, contributing to MODS. The mechanism for the organ toxicity is unknown but lymphatic drainage (LD) is reported to reduce critical illness severity. Pathological opening of Connexin 43 (Cx43) hemichannels participates in inflammatory pathways by activating the NLRP3 inflammasome complex, and may thus contribute to organ dysfunction. It is unknown if LD alters connexin expression or inflammasome activity.

Aim: To investigate if altered Cx43 expression is present in AP and altered by LD.

Methods: Nineteen male SD rats were randomised to four groups: Sham±LD and AP±LD. Subjects were anaesthetised, ventilated and supplied with maintenance fluid. AP was induced by taurocholic acid infusion into the pancreatic duct and in the LD groups lymph was drained from the mesenteric duct. Changes were analysed in physiology, biochemistry and organ oedema, as well as Cx43 and NLRP3 expression in the gut, kidney and heart by immunohistochemistry.

Results: The AP model was established and showed organ dysfunction and biochemical derangement. Cx43 staining was detected in all three organs studied and increased in the gut mucosa of AP animals. LD significantly improved pathological lung oedema, while its effect on Cx43 and NLRP3 expression is still unclear.

Conclusion: LD improved pathological AP lung oedema. Gut Cx43 was successfully detected and was altered by AP.

Novel transanal tubes for the prevention of anastomotic leak

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Introduction: Anastomotic leaks are the most important complication of colorectal surgery. Transanal tubes (TAT) have been proposed as a method to decompress the bowel and prevent leaks. However, results have been conflicting, most devices are not purpose-built, and data is lacking on the effect on anastomotic pressures.

Materials and Methods: A systematic review was conducted, critically appraising TAT use, design features and relationship to leak outcomes. 3D-CAD modelling and simulation was performed to achieve an optimised novel purpose-built TAT design. Fibre-optic manometry sensors were incorporated into a further TAT design to enable evaluation of absolute and manometric endoluminal pressures. Pre-clinical feasibility studies were also performed of a novel negative-pressure TAT bypass device in a porcine model.

Results: Systematic review demonstrated inconsistency in the use, design and outcomes of current TATs. Best-performing designs were employed as a design foundation. Further improvements were achieved by expanding drainage points with finite-element analysis employed to determine structural integrity. For the pressure measuring TAT device, a 15cm high-resolution sensor array was incorporated and validated. The negative-pressure bypass device was found to be a feasible alternative to stomas, but it caused anastomotic damage during insertion.

Conclusion: TATs may play a role in decreasing anastomotic leak and the need for stomas. A novel optimised TAT was created and is ready for feasibility testing, along with an adapted version for pressure monitoring. Design modifications and additional preclinical trials are necessary before the negative-pressure device is ready for human trials.

Alterations in glutamate receptor and transporter expression in the hippocampus in Alzheimer's disease

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Background: Alzheimer's Disease (AD) is the leading type of dementia. Currently the mechanism of AD is unknown. The glutamatergic system is extensively implicated in its pathophysiology but there is a lack of knowledge regarding the expression of glutamate receptors and transporters in AD. This study aimed to characterise expression of specific glutamate receptors and transporters in a mouse model of AD

and postmortem human brain tissue using immunohistochemistry and confocal microscopy.

Materials and Methods: AD and control post-mortem human brain tissue sections were obtained from the Neurological Foundation of New Zealand Human Brain Bank. For mouse work, C57Bl6 mice were bilaterally stereotactically injected with beta-amyloid, euthanised and tissue sections retrieved 30-days post-injection. Freefloating immunohistochemistry was used to quantify the density of specific glutamate receptor subunits and transporters in specific cell layers of hippocampal subregions.

Results: We report significant ($P < 0.05$) decreases in density of glutamate receptor subunits GluA1 and the vesicular glutamate transporter VGLUT1 in the CA1 region of the hippocampus, specifically the striatum and radiatum, in the AD mice compared to controls. Glutamate receptor subunits GluA2, GluN1 and transporter VGLUT2 showed no changes in expression in AD mice. Quantification of GluN2A expression in human postmortem hippocampus revealed a significant ($P < 0.05$) increase in expression in AD compared to control in the CA1 region, whilst glutamate transporter EAAT2 showed no significant differences between control and AD.

Conclusions: These findings indicate that expression of glutamatergic receptors and transporters show brain region specific changes in AD, suggesting altered activation mechanisms during neuropathology.

Relationship between recurrence of acute pancreatitis and pancreas size

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Introduction: Progression to chronic pancreatitis (CP) from first attack of acute pancreatitis (AP) via recurrent attacks is common. The absence of pathognomonic imaging findings in early CP makes risk stratification for transition difficult. Pancreas size (assessed by total pancreas volume (TPV) and pancreas diameters) is reduced in advanced CP but has not been investigated after AP. The aim of this study was to investigate pancreas size in individuals after clinical resolution of AP and their associations with number of AP attacks.

Materials and Methods: Individuals with a history of AP and healthy individuals were recruited. Those with a history of AP were grouped based on the number of attacks (1, 2 and ≥ 3 attacks). All participants underwent magnetic resonance imaging, from which 2 blinded raters measured TPV and pancreas diameters (across head, body and tail) independently. Generalised additive models adjusting for age, sex, body mass index and glycated haemoglobin were used.

Results: A total of 123 individuals were studied. Total pancreas volume and tail diameter were significantly reduced in both unadjusted [TPV ($p = 0.036$), tail diameter ($p = 0.009$)] and adjusted [TPV ($p = 0.026$), tail diameter ($p = 0.034$)] models in individuals with ≥ 3 attacks compared to healthy individuals, but not in individuals with 1 or 2 attacks. Head and body diameters did not differ significantly.

Conclusion: Reduced TPV and tail diameter in individuals after ≥ 3 attacks of AP may be one of the earliest morphological changes after AP. Individuals with ≥ 3 attacks of AP might represent a high risk population for transition to CP.

The architecture of the infant gluteal musculature

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Introduction: Gluteus maximus (Gmax), medius (Gmed) and minimus (Gmin) together form a large and functionally important muscle group. Synergising to stabilise the hip, individually they extend (Gmax) and abduct (Gmed and Gmin) the hip. Intramuscular architecture is an indicator of muscle function and how the architecture of the infant gluteal muscles differs to the adult has not been studied. The objective was to quantify the architecture and function of the infant gluteal muscles.

Materials and Methods: One infant (6 months-old), formalin embalmed specimen was used. After exposing the gluteal muscles, fibre bundles, tendons and aponeuroses were volumetrically dissected, digitised, (Microscribe G2X) and modelled in 3D (Autodesk®Maya®). Architectural parameters were quantified; physiological cross-sectional area (PCSA), pennation angle, fibre bundle length and muscle volume (MV).

Results: Infant Gmax had one distal aponeurosis and three partitions. Gmed had one aponeurosis anteriorly while Gmin had two (anterior and distal); Gmed and Gmin both had four partitions. Architectural parameters differed between intramuscular partitions as well as between whole muscles, e.g. the ratio of MVs was approximately 9:2:1 (Gmax:Gmed:Gmin) however the ratio of PCSAs was approximately 4:2:1.

Conclusion: Each infant gluteal muscle had unique morphology and architecture which was distinctly different to the adult as described in literature. Architectural data suggest the infant muscles have different functional capabilities to the adult's. This is the only 3D volumetric study of the infant gluteal muscles and may provide insight regarding normal muscle development and developmental pathologies during childhood.

A three-dimensional study of infant gastrocnemius and soleus architecture

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Introduction: Gastrocnemius and soleus are important muscles in gait and maintenance of posture. However, their architectural development is unknown. Developmental knowledge may improve understanding of disorders that impair development of muscle architecture (e.g. cerebral palsy). Therefore, the aim was to determine the 3D spatial relationships of the fibre bundles (FBs), aponeuroses and tendons of an infant gastrocnemius and soleus and quantify their architectural parameters.

Materials and methods: Gastrocnemius and soleus from the right leg of one 6-month-old, formalin embalmed specimen, were serially dissected and digitised (Microscribe®G2X) in situ. 3D models were created (Autodesk® Maya®) and the architectural parameters, fibre bundle length, pennation angle (PA) and physiological cross-sectional area computed.

Results: The medial (MG) and lateral (LG) heads of infant gastrocnemius had mean PAs of 17.1° and 10.4°. Infant soleus had marginal, posterior and anterior partitions, with mean PAs of 13.4°, 16.4° and 23.6°, respectively. Distal attachment of the anterior partition was to the medial aspect of a tendon joining the calcaneal tendon (CT) distally.

Conclusion: Significant architectural differences were evident when compared to the adult. Mean PA of MG and LG are approximately 2.4x and 1.5x greater in the infant. For soleus, mean PA of the marginal partition is approximately 2.5x greater in the adult. Additionally, distal attachment of adult anterior partition is to the medial and lateral sides of a septum joining the CT. As the first volumetric study on infant gastrocnemius and

soleus architecture, further work is needed to elucidate architectural development from infant to adult.

In pursuit of precision: Validating determinants of sensitivity and resistance to the drug trastuzumab emtansine for HER2-positive breast cancer

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Introduction: Trastuzumab emtansine (Kadcyla®/T-DM1) is an antibody-drug conjugate consisting of the Herceptin® antibody linked to a potentially cytotoxic drug. T-DM1 shows significant efficacy in HER2-positive breast cancer patients, extending survival with lower toxicity. However, approximately 60% of patients show intrinsic resistance to T-DM1 and acquired resistance develops in all cases. Greater understanding of the mechanisms of sensitivity and resistance could identify predictive biomarkers, with the possibility of improved response rates in precisely selected patients.

Materials and methods: i. Methodology for high-throughput production of clonogenic CRISPR-Cas9 knockout breast cancer cell lines was explored. ii. 14 top gene hits identified in genome-scale screens for T-DM1 were investigated in public databases for their expression, copy number and influence on clinical outcome in breast cancer patients. iii. Eight drugs targeting pathways identified in genomewide screens were tested for their effect in combination with T-DM1.

Results: i. A method for high-throughput generation of clonogenic CRISPR-Cas9 knockouts was developed and implemented. 42 lentiviral vectors containing Cas9 and sgRNAs targeting 14 genes were produced and transduced into the MDA-MB-361 breast cancer cell line. ii. Gene hits had varied expression and copy number in breast cancer patients, with SLC46A3 expression, SLC46A1 amplification and TCL1A expression associated with differences in survival outcome. iii. RTA-408, GSK26992A and MK-1775 are antagonistic and Volasertib and KU-55933 display moderate synergism, in combination with T-DM1.

Conclusions: Clonogenic CRISPR-Cas9 knockout breast cancer cell lines can be generated in a high-throughput manner. The 14 genes must be further validated for their influence on T-DM1 efficacy.