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## GLI ACTIVATED NESTED MALIGNANT EPITHELIOID CELL TUMOUR

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Soft tissue neoplasms displaying a nested epithelioid morphology and abnormalities of the GLI-1 locus are emerging as a distinctive new tumour type. In 2018, a series of 6 such tumours was published, showing frequent S100 positivity and a tendency for aggressive clinical behaviour. Recently, a case series was published describing a related group of tumours showing morphologic overlap with the earlier examples and harbouring GLI-1 amplification as an alternative pathway of GLI-1 activation. We report a 9-year-old female who presented with a 5-year history of a slowly growing lesion on the left great toe. Microscopy revealed a dermally-based tumour with a multinodular growth pattern, arranged in tight nests separated by thin fibrovascular septa. The tumour cells had uniform ovoid nuclei with granular chromatin and inconspicuous nucleoli. Necrosis was absent, but mitoses were frequent. There was strong positivity for BCL2, Glut A, and CD56. S100 was seen in isolated cells. FISH for GLI-1 and DDIT3 showed amplification of both loci. We propose the term 'GLI-activated nested malignant epithelioid cell tumour' to describe this entity. This case also highlights the utility of FISH for DDIT, which lies in close proximity to GLI on chromosome 7, as a surrogate marker for GLI-1 amplification.

## MUTATIONAL ANALYSIS OF UNDIFFERENTIATED MELANOMA

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In recent years, the use of checkpoint inhibitors and targeted molecular therapy has dramatically improved survival in metastatic melanoma. Accurate and prompt diagnosis is essential to initiate appropriate management. Dedifferentiated tumours, i.e., those that have lost some or all morphologic and immunohistochemical features of melanoma, pose a major challenge to this endeavour. In these instances, identification of a melanoma-related mutation can be a useful ancillary investigation. The aims of this study were to describe the histological, immunochemical, and molecular features of undifferentiated melanomas. A search of our institutional database (2012–2019) identified 23 cases of undifferentiated malignant tumours that underwent subsequent mutational analysis. Of these, 15 tumours were found to harbour a melanoma-related mutation including BRAF V600E (3/15), BRAF V600K (3/15), and NRAS Q61R (5/15) among others. On the basis of the molecular findings, a diagnosis of melanoma was favoured. Sites of disease included lymph nodes (5/15), skin or subcutis (5/15), lung (2/15), small bowel (1/15), mediastinum (1/15), and epidural space (1/15). A prior history of melanoma was documented in 10 cases. This study illustrates the value of mutation testing in establishing a diagnosis in cases of undifferentiated malignancy, particularly when melanoma metastases are clinically suspected.

## GENOMIC ALTERATIONS IN METASTATIC BASAL CELL CARCINOMA

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Basal cell carcinoma (BCC) is the single commonest human malignancy. Histologically, BCC is classified into one of several subtypes based on the growth pattern, a feature that correlates with risk of aggressive behaviour. Metastasis is exceptionally rare and portends a poor prognosis. Although the genome of BCC has been fully characterised, little is known about genomic events associated with metastatic potential. We sought to identify clinicopathologic and molecular features associated with an increased risk of metastasis in BCC. Cases were identified from a search of our institutional database. The pathology of each primary tumour and corresponding metastasis was reviewed, followed by DNA extraction and whole-exome sequencing. The detected molecular alterations were compared between the primary tumour and the corresponding metastasis. The findings were compared to publicly available genomic data. 9 patients were identified, with matched primary tumour tissue available in 7 cases. 6 cases originated in the head and neck. Sites of metastasis were local lymph nodes (7/9) and lung (2/9). Most primary tumours were at least partially infiltrative (4/7) or morphoeic (2/7). Results of genomic analyses will be presented and will provide insights into molecular events that may serve as biomarkers for the rare complication of metastasis in BCC.

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## ASSESSMENT OF THE PROGNOSTIC ROLE OF REGRESSION IN PRIMARY CUTANEOUS MELANOMA

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Regression in melanoma is an immunological phenomenon that results in partial or complete disappearance of the tumour. The associations between regression, sentinel lymph node (SLN) status and prognosis, and its implications for treatment, have been questioned for many years. Currently Breslow thickness, tumour mitotic rate, and ulceration are the most important characteristics of primary melanomas for predicting SLN status, which in turn is the most powerful predictor of melanoma survival and is critical for determining appropriate therapy and clinical trial eligibility. It has been suggested recently that regression status may help refine patient selection for SLN biopsy. With this in mind, we are investigating the association of regression in primary melanoma with SLN status and survival by analysing prospectively collected data from the Melanoma Institute Australia database. Results will be presented. As far as we are aware, this will be the largest study of its kind undertaken to date.

## FOLLICULAR LYMPHOMA (WHO GRADE 2) OF THE PAROTID GLAND

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Lymphomas arising in salivary glands are rare accounting for less than 5% of lymphomas overall and constitute 1.7–5% of all salivary gland neoplasms. The parotid gland is the most commonly involved salivary gland (70%). Among lymphomas originating from salivary glands, the ratio of follicular lymphoma is very low. This is a case of a 73-year-old female patient who presented with a parotid mass with a past history of breast cancer. The patient underwent parotidectomy. Macroscopically, there was a well circumscribed white to red nodule up to 18 mm. Microscopically, the salivary gland contained a large lymphoid nodule with well developed architecture, which consisted of variably sized nodules of atypical lymphoid cells. There were 7 centroblasts per 10 high-power field. Immunohistochemistry was performed. The atypical lymphoid cells were positive for CD20, PAX5, BCL2 and CD10 and they were negative for CD5, CD23 and CD3. Features were consistent with follicular lymphoma, WHO grade 2 with Ki-67 proliferative index of 55%. Follicular lymphoma has an unpredictable, prolonged clinical course with indolent behaviour. There is tendency to transform to a higher grade lymphoma. Although various treatment modalities are used to treat follicular lymphoma, none of them is curative. This necessitates prolonged follow up.

## CASE REPORT AND LITERATURE REVIEW OF BURULI ULCER (BU): AN EMERGING DISEASE IN AUSTRALIA CAUSED BY MYCOBACTERIAL ULCERANS SKIN INFECTION

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A skin biopsy was received from a 68-year-old female who presented with a non-healing ulcer on the buttock.
Microscopically, ulcerated skin was seen with underlying necrotic tissue and patchy active chronic inflammation. Ziehl–Neelsen and Wade–Fite stains demonstrated abundant acid-fast bacilli in and around the ulcer site, consistent with BU.
BU is an indolent skin infection caused by *Mycobacterial ulcerans*. People of any age can get infected, and symptoms may occur from 4 weeks to 10 months after exposure. The method of transmission is unclear. Three clinical stages described are: pre-ulcerative, ulcerative and healed disease. PCR or microbiology confirmation is usually necessary for treatment. The first line treatment for early lesions is a combination of antibiotics while surgery is reserved for refractory cases.
The disease exists in 31 countries worldwide, mostly in West and Central Africa. There has been a steady increase in BU notifications since 2015 in Australia. Most cases were encountered in parts of Victoria and Queensland, with a few sporadic cases in Northern Territory, Western Australia and New South Wales. Awareness among pathologists is important to perform special histochemical stains for *Mycobacteria* in persisting ulcers, nodules, papules, oedema or cellulitis, especially on exposed parts of the body.

## MUCINOUS ADENOCARCINOMA OF PROSTATE (MAOP), A RARE VARIANT OF PROSTATE ADENOCARCINOMA: A CASE REPORT AND LITERATURE REVIEW

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A prostatectomy specimen was received from a 72-year-old male with a previous needle core biopsy diagnosis of prostatic adenocarcinoma, Gleason score 3+4=7.
Microscopic examination of the prostatectomy specimen demonstrated single and fused neoplastic glands floating in copious amounts of extracellular mucin representing >50% of the tumour volume. There was a minor component of non-mucinous conventional adenocarcinoma in the background. Immunhistochemistry NKX 3.1 and PSA showed positive staining of tumour cells. Clinical, radiological or serological evidence of carcinoma of another site was not revealed. A diagnosis of MAOP, Gleason score 4+3 =7 (WHO/ISUP Grade Group 3) with a tertiary component of Gleason pattern 5 comprising <1% of total tumour volume was made.

MAOP is a rare variant, comprising 0.38–0.43% of prostatic carcinoma. It is characterised by tumour cells floating in >25% of extracellular mucin excluding any intraluminal mucin. The diagnosis should only be made in resection specimens, and following exclusion of secondary deposits of extra-prostatic origin of mucinous adenocarcinoma by clinical-radiological correlation and with confirmatory immunohistochemistry. Grading and scoring for MAOP should be performed according to the growth pattern similar to conventional adenocarcinoma. The prognosis appears to be similar to non-mucinous prostatic adenocarcinoma.

## ADENOMA MALIGNUM AND OVARIAN SEX CORD TUMOUR WITH ANNULAR TUBULES IN A PATIENT WITH PEUTZ–JEGHERS: A CASE REPORT

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Peutz–Jeghers polyposis syndrome is characterised by pigmented melanotic lesions, hamartomatous gastrointestinal polyps and increased risk of multiple cancers, including those of the female genital tract. The genetic defect is autosomal dominant, affecting the STK11 gene, which normally functions as a tumour suppressor. We report the case of a 48-year-old female who presented with dysfunctional uterine bleeding who was found to have a cervical mass, which on resection was diagnosed as minimal deviation adenocarcinoma (adenoma malignum). In addition, there was extensive local involvement and ovarian metastases, with associated concurrent ovarian sex cord tumour with annular tubules.

## AN UNUSUAL CAUSE OF A MULTIFOCAL BONE LESION: EPSTEIN–BARR VIRUS-ASSOCIATED SMOOTH MUSCLE TUMOUR (EBV-SMT) INVOLVING BONE

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Epstein–Barr virus-associated smooth muscle tumours (EBV-SMTs) are rare neoplasms of uncertain biological potential, which occur in the setting of immunodeficiency of a variety of causes, including HIV infection and post-transplant immunosuppression. The association between SMTs and immunosuppression was first described by Pritzker *et al.* in 1970. They have a male predominance and occur at unusual sites in adults. The CNS is the most common site in the setting of HIV while post transplantation cases are more likely to occur in liver, lungs and GIT. Other sites have also been reported including bone.
We report a case of an EBV-SMT presenting as multifocal, lucent lesions of proximal tibia, proximal fibula and distal femur in a 45-year-old female patient with previous lung transplantation. A biopsy of the tibial lesion showed a smooth muscle tumour with positive staining for EBER (EBV ISH) supporting a diagnosis of EBV-SMT.
EBV-SMTs of bone are rare and to our knowledge this is the first example of multifocal EBV-SMT confined to bone.

## STUMP APPENDICITIS – A RARE CASE REPORT

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Acute appendicitis is perhaps the commonest cause of acute abdomen and the most common operation performed worldwide is appendicectomy. Stump appendicitis is interval re-inflammation of remnant appendix due to incomplete removal of the appendix. Stump appendicitis is rare, only 61 cases were reported in the literature between 1945 and 2005,[1] however, it is under recognised and has been estimated to occur in 1:50,000 appendicectomy patients.[2]
We present the case of a 66-year-old woman with a history of appendicitis with acute perforation treated with appendicectomy who represented 3 years later with the symptoms of an acute abdomen. She did not improve with conservative management and a limited right hemicolectomy was performed. Gross examination showed extensive purulent exudates around the caecum and H&E stained sections from the appendiceal stump revealed transmural inflammation with a neutrophilic abscess extending into the remnant mesoappendix with overlying fibrinous serositis.
Although appendicitis is usually dismissed as a cause of an acute abdomen where there is a history of appendicectomy, it is important to be aware of stump inflammation in patients who may re-present years after their original surgery.[3]

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## MUCINOUS TUBULAR AND SPINDLE CELL CARCINOMA OF KIDNEY: A CASE REPORT OF A MUCIN AND STROMA POOR TUMOUR CAUSING DIAGNOSTIC DIFFICULTY

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Mucinous tubular and spindle cell carcinoma (MTSCC) is a rare and unusual variant of renal cell carcinoma (RCC). We report an unusual tumour in an 81-year-old male with an incidental finding of a tumour in the lower pole of the left kidney. The core biopsy showed a renal cell carcinoma with mostly tubular morphology and an immunophenotype indistinguishable from papillary renal cell carcinoma. The partial nephrectomy showed a tumour

comprising predominantly tubular structures with focal abortive papillae, psammomatous calcifications and scattered small aggregates of foam cells. Only focal areas showed myxoid change and spindle cells, but this made the diagnosis of a mucinous tubular and spindle cell carcinoma more straightforward. This case highlights the importance of recognising a mucin/stroma poor variant of MTSCC of the kidney and how the entity can cause diagnostic confusion with papillary renal cell carcinoma as there is morphologic and immunophenotypic overlap, particularly on core biopsy.

## DUODENAL POLYP WITH MIXED FEATURES – A CASE REPORT

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Epithelial polyps are a common finding in the colorectum. They are less common in small bowel in the absence of any polyposis syndromes. These polyps are conventionally divided into adenomatous polyps and serrated polyps, with the latter further subdivided into hyperplastic polyps, traditional serrated adenomas and sessile serrated polyps. Polyps with mixed features displaying more than one type of morphology have been described but are less common. Tubular adenomas are common in the colorectum with a lifetime prevalence of 30–50% in industrialised countries.[1] Mixed adenoma-serrated polyps comprise only <1% of all colorectal polyps,[1] with few duodenal variant case reports identified in the literature. We present a case of a mixed polyp in the duodenum without any known history of polyposis syndrome.

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## PRIMARY NEUROENDOCRINE TUMOUR OF THE GALLBLADDER – A CASE REPORT

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Neuroendocrine tumours can develop in many organs, and while are extremely rare in the gallbladder and extrahepatic bile ducts, have been reported, and as such are an entity recognised by the World Health Organization. Histologically they resemble neuroendocrine tumours of other organs, and are graded in a similar fashion, based on mitotic rate and Ki-67 proliferative index. There is currently no formal staging system and are recommended to be staged like other gallbladder carcinomas. While prognostic data is limited, it is felt that tumours measuring >20 mm are at an increased risk of malignant behaviour. We present a case of a 64-year-old female who underwent a routine laparoscopic cholecystectomy for recurrent biliary colic. Gross dissection revealed an 8 mm pink polyp, which was shown to be a low-grade neuroendocrine tumour histologically. In context of no prior or concurrent primary neuroendocrine lesions and with negative imaging, the case was thought to be a primary neuroendocrine tumour of the gallbladder and staged according to other gallbladder carcinomas.

## TWO CASES OF ANTI-MDA5 ASSOCIATED INTERSTITIAL LUNG DISEASE IN TASMANIA

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Clinically amyopathic dermatomyositis (CADM) is an uncommon subtype of dermatomyositis. CADM is characterised by cutaneous features of classic dermatomyositis without features of myopathy.[1] CADM associated with anti-MDA5 antibody is more likely to be associated with interstitial lung disease and show a more aggressive clinical course.[2,3] We present two cases of anti-MDA5 associated interstitial lung disease. Two male patients, aged 34 and 52, presented with progressive respiratory symptoms. Both were noted to have cutaneous manifestations consistent with dermatomyositis, but neither showed features of myopathy. Anti-MDA5 antibody was positive in both cases. Lung biopsy revealed changes of a non-specific interstitial pneumonia and superimposed organising pneumonia in one case, and changes of an organising pneumonia in the other. A diagnosis of CADM with associated interstitial lung disease was made in both instances.

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## EXTRAPULMONARY LYMPHANGIOLEIOMYOMATOSIS OF THE UTERUS AND PELVIC LYMPH NODES: A CASE REPORT

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Extrapulmonary lymphangioleiomyomatosis (LAM) is a rare neoplasm of spindle cells with a myoid appearance and a unique immunophenotype exhibiting melanocytic, myoid and oestrogen receptor expression. This neoplasm is part of the perivascular epithelioid cell tumour family (PEComa) and can be associated with pulmonary LAM and more uncommonly with tuberous sclerosis complex. It arises as a mass in the mediastinum, retroperitoneum, uterine wall and/or retroperitoneal lymph nodes and is composed of bland myoid spindle cells closely associated with abnormal lymphatic vessels.

We present an incidental case of LAM in uterine corpus and pelvic nodes resected during a hysterocystectomy for an urothelial carcinoma of bladder in a 72-year-old woman with no known pulmonary LAM or tuberous sclerosis complex. This case supports the current hypothesis that the uterus may be the primary site of LAM.[1]

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## VERRUCIFORM XANTHOMA BEHAVING BADLY

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Verruciform xanthoma is an uncommon, asymptotic, mucocutanous lesion which occurs predominantly in the oral mucosa of patients in their 5th to 7th decades. Other extraoral sites include skin of the anogenital area. It presents as a well circumscribed, rough, granular or pebbly plaque and can mimic a squamous cell carcinoma macroscopically. Recurrence is extremely rare. Histologically, verruciform xanthoma is characterised by a papillary epithelium with acanthosis and parakerathosis invaginating between the epidermal projection, as well as elongated rete ridges which sometimes coalesce at their base. Within the connective tissue papillae there is a collection of large xanthoma cells.
Forty-four cases of verruciform xanthoma have been reported in our laboratory over a 10 year period representing <0.001% of the dermatological cases. Although 38 of 44 (86%) of the lesions occurred in the common sites (oral and anogenital), six cases were present at atypical sites including ear, wrist, thumb and leg. We are presenting these atypical cases of verruciform xanthoma to highlight the importance of considering this diagnosis when reporting a lesion mimicking a SCC in locations where verruciform xanthomas are not usually present.

## OESTROGEN RECEPTOR EXPRESSION IN A RARE CASE OF LEIOMYOMA OF DEEP SOFT TISSUE – A CASE REPORT

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Uterine leiomyoma is a common smooth muscle neoplasm. Gynaecologic type leiomyoma of deep soft tissue, on the other hand, is rare and commonly occurs in the retroperitoneum or abdominal cavity of young to middle aged women. We report a 42-year-old female who initially had hysterectomy performed for uterine leiomyoma at another institution but was also noted to have a 30 cm retroperitoneal mass. She was then referred to our institution where resection of the mass revealed a well-circumscribed tumour with histology features of a leiomyoma, supported by the expression of smooth muscle markers with immunohistochemical staining. Additionally, the lesional cells were both oestrogen-receptor and progesterone-receptor positive, a typical feature of this lesion which suggests derivation from hormonally sensitive smooth muscle cells in this extrauterine location. Awareness of this benign entity is important to avoid a misdiagnosis of leiomyosarcoma so that unnecessary additional treatment can be avoided.

## HISTOPATHOLOGY OF THE PLACENTA IN CONGENITAL SYPHILIS

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Syphilis, a disease with a long and controversial past, has recently shown a resurgence in many countries. Cases of congenital syphilis are now being reported in New Zealand, having previously been very rare prior to 2012. Congenital syphilis may lead to perinatal death or long term morbidity. The traditional histological triad seen in placentas consists of enlarged hypercellular villi, proliferative villous vasculature, and villitis. Necrotising funisitis, with a 'baberpole' appearance at macroscopy, is another common finding. *Treponema pallidum* immunohistochemistry may assist in the diagnosis. The previous rarity of the disease means that many pathologists may not be very familiar with the histopathological features. We present two recent cases of congenital syphilis, with placental histology, as a reminder. Recognition of congenital syphilis is important in aiding diagnosis, leading to appropriate follow up and treatment for both mother and infant.

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## ROSETTE-FORMING GLIONEURONAL TUMOUR IN A PATIENT WITH NEUROFIBROMATOSIS TYPE 1 – A CASE REPORT

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Rosette-forming glioneuronal tumour (RGNT) is a rare primary CNS neoplasm originally described arising in the fourth ventricle, and displaying a distinctive biphasic appearance of neurocytic and astrocytic components. Patients with neurofibromatosis type 1 (NF1) can have a variety of CNS manifestations, including neoplastic, and RGNT has been described in four cases to date. This case study reports a patient with NF1 who underwent resection of a left cerebellar lesion. Histology showed a lesion dominated by synaptophysin positive, neurocytic cells in a myxoid background, forming perivascular pseudorosettes and true rosettes surrounding a central eosinophilic fibrillary core. A second component of Olig2+, oligodendroglial-like cells was also noted in a nondescript glial background. Due to its readily recognisable appearance, a diagnosis of RGNT was made. This is now a fifth case report of RGNT, an already rare tumour, in a patient with NF1 and raises the interesting possibility of a potential association between the two.

## SOLID PAPILLARY CARCINOMA OF THE BREAST WITH REVERSE POLARITY – A CASE REPORT OF A RARE ENTITY WITH A NOVEL IDH2 MUTATION

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Solid papillary carcinoma with reverse polarity (SPCRP) is a rare breast carcinoma bearing resemblance to the tall cell variant of papillary thyroid carcinoma (PTC). These tumours have been

found to harbour mutations in the isocitrate dehydrogenase 2 (IDH2) gene. The patient presented with an impalpable 8 mm right breast lesion, detected on staging CT scan for known endometrial carcinoma. The lesion was well defined and hypoechoic on ultrasound, and occult on mammogram. Core biopsy demonstrated a papillary neoplasm with focal atypical features. Excisional biopsy revealed a circumscribed papillary neoplasm composed of cuboidal to tall columnar cells with abundant granular eosinophilic cytoplasm. Nuclei were notably aligned away from the basal aspect of the cells and exhibited PTC-like nuclear features including grooves and intranuclear pseudo-inclusions. The cells diffusely expressed cytoplasmic CK5/6 and there was very focal nuclear positivity for ER. Calretinin was patchy and cytoplasmic. No intact myoepithelial layer was demonstrated. A diagnosis of SPCRP was made and ancillary molecular testing revealed a novel IDH2 variant c520G>A, p.(Ala174Thr). SPCRP is a rare tumour with a favourable prognosis, which exhibits distinctive histological and immunophenotypical features that are readily recognisable to pathologists.

## UTERINE INFLAMMATORY MYOFIBROBLASTIC TUMOUR: A CASE REPORT

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Inflammatory myofibroblastic tumour (IMT) is a mesenchymal neoplasm with intermediate biological potential, which may be under-recognised in the uterus.[1–3]

Morphological and immunophenotypic overlap exists between uterine IMT and some other uterine mesenchymal neoplasms, including smooth muscle tumours.[2] Morphological features suggestive of IMT may be subtle or focal and include myxoid change, tapered nuclei, and a lymphoplasmacytic infiltrate.[1]

Chromosomal rearrangements involving the *anaplastic lymphoma kinase (ALK)* gene appear to be frequent in uterine IMT,[1–3] and absent in other uterine mesenchymal neoplasms.[2] Therefore, ALK immunohistochemistry (IHC) and *ALK* florescent *in situ* hybridisation (FISH) appear to be useful tools to confirm the diagnosis of uterine IMT.[3]

Although most uterine IMTs follow a benign clinical course, local recurrence and metastases have been observed in a small subset.[1] Correct diagnosis is important to ensure accurate prognosis and optimal management, which may include a tyrosine kinase inhibitor.

We present a case of uterine IMT with morphology and IHC suggestive of a leiomyosarcoma with myxoid change. ALK IHC was positive and an *ALK* rearrangement was demonstrated with FISH, confirming the diagnosis of uterine IMT.

This case illustrates the importance of a low threshold for ALK testing in uterine mesenchymal tumours with morphological features suggestive of IMT.

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## LOCALISED PULMONARY CRYSTAL-STORING HISTIOCYTOSIS WITH UNDERLYING EXTRANODAL MARGINAL ZONE LYMPHOMA: A CASE REPORT

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Crystal-storing histiocytosis (CSH) is a rare entity, composed of a proliferation of non-neoplastic histiocytes with an accumulation of intracytoplasmic crystalline material. It is often associated with an underlying lymphoproliferative disorder, most often those that express monoclonal immunoglobulins, such as multiple myeloma and lymphoplasmacytic lymphoma. Here we report a case of localised pulmonary CSH in an asymptomatic 54-year-old man, found to have an incidental solid lesion in the right lung on computed tomography (CT). The lesion was composed of sheets of CD68 positive histiocytes that contained refractile eosinophilic crystalline inclusions, scattered lymphoid follicles of CD20 positive B lymphocytes, and occasional plasma cells. PCR for immunoglobulin heavy chain gene rearrangement confirmed the presence of a monoclonal population of B cells. These findings were supportive of a diagnosis of CSH with an underlying B cell/ plasma cell lymphoproliferative disorder, which was favoured to be an extranodal marginal zone lymphoma after clinical and radiological workup. Recognition of this rare entity is important as it may obscure an underlying lymphoproliferative disorder. A diagnosis of CSH should prompt careful exclusion of neoplasia, including clinical workup for systemic disease. In this case report we also discuss clinical features and diagnostic pitfalls.

## WHOLE EXOME SEQUENCING (WES) ENHANCES THE DIAGNOSTIC RATE OF PERINATAL AUTOPSY: A PROSPECTIVE CLINICAL UTILITY TRIAL WITH IMPLICATIONS FOR PRENATAL DIAGNOSIS

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Genomic classification is rapidly becoming a routine and integral part of diagnosis in pathology. Perinatal pathology is following this trend. The aims of this study were to determine the utility of WES in perinatal autopsy for congenital anomalies and to model the outcome of WES as a prenatal test. A total of 131 probands with congenital anomalies who underwent post mortem examination were referred by pathologists to the study. 82 probands were considered suitable for sequencing. The parents of 5 declined enrolment and 10 could not be consented. 67 probands were enrolled. Autopsy identified specific diagnoses in 11 cases (17%). WES identified specific diagnoses ('pathogenic' or 'likely pathogenic' variants) in 23 cases – a diagnostic rate of 35%. The combined diagnostic rate of autopsy and sequencing was 38%. A geneticist blinded to the autopsy findings reviewed the probands' antenatal imaging reports and recommended a gene list to model the clinical utility of prenatal WES. The use of antenatal sequencing in this cohort would have identified a specific diagnosis in 18 of the 23 cases with positive sequencing findings. In conclusion, WES doubles the diagnostic rate of autopsy for congenital anomalies and our data supports the prenatal use of genomic sequencing.

## PRACTICE FOR SPEED AND PROFICIENCY IN CYTOLOGY EXAMS USING THE NEW RCPA DIGITAL CYTOLOGY eCASES AND SECTRA

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**Aim:** Create and share a digital a slide workshop using Sectra slides.
**Background:** The RCPA Cytopathology exam is planned to transition to digital slides viewed on the Sectra platform. Screening and reaching a diagnosis using digital cytology is slower than glass slides.[1] Proficiency and speed comes with practice.[2] There are currently >200 cases of digital cytology in the RCPA eCases library, many with z-axis focus and digital annotations. Registrars and supervisors need to know how to efficiently navigate and share digital practice slide sets.
**Methods:** A metaphor of door, library and window help us navigate the data architecture. Enter the cytology slide library through the DOOR of the RCPA website. The cytology slides are found in the eCases LIBRARY, a digital repository of virtual slides linked to case data and diagnosis. View and share the slides via the Sectra WINDOW. The methods are demonstrated in 6 online videos.[3]
**Result:** Follow these steps to make and share a Sectra digital slide set. There is also an online example test set (https://digipathed.wordpress.com/2020/01/07/sectra-practice-test-sets/) and an answer set (https://digipathed.wordpress.com/2020/01/07/sectra-practice-test-set-with-answers/).
**Conclusion:** Teaching and learning with digital slide sets is an opportunity to practice digital proficiency, which is a 21st century skill for all of us.
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## WHY DOES MY BRAIN HURT? PATHOLOGIST PERFORMANCE AND PATTERN RECOGNITION

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**Aim:** To test whether indicators of pattern recognition moderate performance of new tasks.
**Background:** You, or your colleagues may have participated in this research, where we recruited Anatomical Pathologists and Registrars at the 2019 RCPA Update meeting, and online, to complete an online series of tasks.
**Methods:** We recruited 54 participants, who completed a series of 5 online tasks.[1] To measure 'brain strain', 27 participants wore an infrared head band measuring pre-frontal cortex blood flow.[2]
**Result:** Higher pattern recognition was associated with greater accuracy on diagnostic tasks, and diagnosis of uncommon entities. Those participants with lower pattern recognition were less likely to select unlisted diagnoses for example, 'none of the above' in multiple choice questions. High pattern recognition was associated with higher cerebral blood flow.
**Conclusion:** The results validated our online task tool.[1] The finding that those participants with lower pattern recognition skills were more likely to select an incorrect diagnosis from a list of answers indicates susceptibility to confirmation, and availability biases.[3] Those participants with higher pattern recognition were less prone these cognitive errors. The finding of higher 'brain strain' in those with high pattern recognition suggests that higher levels of accuracy were achieved with greater cognitive effort. Reproducibility and longitudinal studies are planned.
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## ADULT MESENCHYMAL HAMARTOMA OF LIVER: A CASE REPORT AND DISCUSSION OF ASSOCIATED MOLECULAR ABNORMALITIES

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Mesenchymal hamartoma of liver (MHL) is the third most common paediatric liver tumour. It accounts for 8% of all liver

tumours and 18% of benign tumours in the paediatric population, with a male to female ratio of 2:1.[1] Rarely, adult cases have been reported with an age range of between 19 and 69 years of age, with a female predominance. We report a case of MHL in a 45-year-old Filipino female, who presented with symptoms of reflux and headaches for investigation. Cytogenetic analysis was performed and revealed loss of 19q13. This is similar to what had been reported previously in the literature.

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## BENIGN BLUE NAEVI INVOLVING LYMPH NODES: A CASE SERIES WITH ACCOMPANYING MOLECULAR DATA AND LONG TERM FOLLOW-UP CONFIRMS CLINICAL BEHAVIOUR

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**Background:** Blue naevi are common, benign, cutaneous melanocytic neoplasms. Like other naevi, these can occur within lymph nodes, and can mimic metastatic melanoma. Few cases of this rare entity have been reported. We present the largest case series to date, as well as novel molecular data and accompanying clinical and follow-up data.
**Methods:** Cases of capsular blue naevi were identified from the archives of Sydney Hospital and the Royal Prince Alfred Hospital, Sydney. DNA was extracted from suitable cases and underwent sequencing using a custom capture panel and ddPCR for GNA11 Q209L, GNAQ Q209L and GNAQ Q209P. Clinical and follow up data were also analysed.
**Results:** We collected 15 cases with capsular blue naevi between 1981 and 2018. 3 were atypical blue naevi, 3 were cellular blue naevi and 9 were common blue naevi. The patients were between 3 and 72 years of age, and 8 were female. Follow up of two patients (for 10 and 12 years) showed no recurrence. 9 cases were available for molecular testing, with 6/9 cases having a detectable mutation (GNAQ Q209L in 5/9, GNA11 Q209L in 1/9).
**Conclusion:** Both histopathologically and genetically, nodal blue naevi show the same features as their cutaneous counterparts and exhibit clinically benign behaviour.

## ATYPICAL HYERPLASIA OF THE VULVA – A CASE REPORT

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The presence of ectopic mammary tissue in the vulva is rare. During embryonic development, paired ectodermal thickenings produce mammary ridges which extend from the axillae to the medial thigh. Incomplete resorption can lead to ectopic breast tissue.[1] Ectopic breast tissue can be subjected to the same physiological and pathological changes seen in the breast. We report a case of a post-menopausal woman presenting with a vulvar swelling which had been present for one year. Examination showed a 2×2 cm cystic lesion on the right labia minora which was clinically consistent with a benign epithelial inclusion cyst. Histologically the lesion showed ectopic breast tissue with an atypical proliferative process with features consistent with atypical hyperplasia. The lesion involved the surgical resection margin and patient was offered further surgical resection, however opted for regular follow up.

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## 'BALLS TO THE INTESTINAL WALL': AN UNUSUAL CASE OF METASTATIC SEMINOMA

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**Introduction:** Metastatic testicular germ cell tumours arising within the gastrointestinal tract is uncommon, comprising approximately 5% of cases.[1]
**Case description:** We present an unusual case of metastatic seminoma of the small intestine in a 57-year-old man who presented with anaemia, abdominal pain and nocturia. A computed tomographic scan revealed thickening of the small intestinal wall without mesenteric lymphadenopathy. Open small bowel resection was performed and subsequent histology and immunohistochemistry confirmed the diagnosis of two deposits of metastatic seminoma within the small bowel. Subsequent scrotal ultrasonography revealed 3 solid testicular nodules within the left testis, consistent with testicular primary.
**Conclusion:** Metastatic germ cell tumour should be considered in any poorly differentiated tumour arising in a male.

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## WHIPPLE DISEASE: A GREAT MIMICKER

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Whipple disease is a rare systemic infection caused by the bacterium *Tropheryma whipelii,* and often presents a diagnostic

challenge to both clinicians and pathologists. The classic symptoms are those of diarrhoea, malabsorption, and weight loss, reflecting infection of the small intestine. Involvement of the colon is uncommon. A range of systemic symptoms, many non-specific, such as arthralgia, fatigue, weakness, fever and anaemia may also occur. Presentation with systemic symptoms without intestinal manifestation may be far more common than previously appreciated, and the diagnosis may be missed, resulting in a protracted and life threatening course. We report a case of Whipple disease in a 47-year-old man with a prolonged extra-GIT presentation, resulting in misdiagnosis and mistreatment with immunosuppression. The diagnosis was finally reached after he developed mild diarrhoea, prompting colonoscopy and endoscopy. We discuss the biopsy findings in both colonic and duodenal biopsies, and highlight the diagnostic difficulties and recent advances in our understanding of this disease.

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## UNUSUAL SPINDLE CELL LESION IN THE GASTROINTESTINAL TRACT: WHEN ALL ELSE FAILS

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Follicular dendritic cell sarcoma (FDCS) is a rare neoplasm affecting patients of a wide age range, typically in the young to middle-aged adult years. The primary lesion may be nodal or extra-nodal in more than half of cases. We present a case of FDCS in a 31-year-old male with a caecal mass and adjacent lymphadenopathy. Endoscopic biopsy of the caecum showed an atypical spindle cell lesion, formed by plump cells with indistinct cell borders, showing a vaguely nodular and whorled architecture. A scattering of lymphocytes were seen in amongst the neoplastic cells. Multiple entities from various cell lineages were considered in the wider differential diagnosis. Based on the morphologic features, the immunohistochemical work-up included CD21 and CD23 which confirmed the lesion to be FDCS. This case highlights the importance of awareness of this rare entity when considering the broader differential diagnosis of unusual spindle cell neoplasms in the GI tract. When recognised, it has a characteristic morphology and immunophenotype which allows for correct diagnosis.

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## SEEING RED: TWO CASES OF CONGOPHILIC FIBRILLARY GLOMERULONEPHRITIS

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The presence of glomerular fibril deposition poses a diagnostic challenge for the pathologist as it may be seen in multiple disorders, in particular fibrillary glomerulonephritis (FGN) and renal amyloidosis. Traditional teaching dictates that these two entities can be differentiated using Congo red staining, with FGN not demonstrating positivity. However, a number of cases of congophilic FGN have been reported in the literature, suggesting that Congo red positivity can no longer be considered a robust differentiating marker. This case study outlines two separate cases at our institution in which FGN and amyloidosis could not be differentiated using Congo red staining alone. In these cases, other defining characteristics such as the immunoglobulin pattern on immunofluorescence and electron microscopic appearance were necessary to arrive at the final diagnosis. Recent studies have demonstrated that novel immunohistochemical stains such as DNAJB9 can be utilised as an alternative to Congo red staining to aid in differentiating between FGN and amyloidosis.

## PULMONARY ADENOFIBROMA: A RARE INCIDENTAL FINDING MIMICKING MALIGNANCY

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**Introduction:** Pulmonary adenofibroma is a rare soft-tissue tumour, composed of epithelial and stromal components, both of which are histologically benign. The diagnosis is based on histopathological examination.

**Case description:** We present a 60-year-old ex-smoker male patient with a 21 mm nodule in the right lower lobe of his lung, which was an incidental finding in chest CT-scan. He underwent wedge resection of the right lung for frozen section examination, which was reported as low-grade neoplasm, with epithelial and stromal components.

**Pathological findings:** Permanent sections showed a reasonably well-defined neoplasm, characterised by cup-shaped papillary structures, surrounded by collagenised bland spindle-cell stroma. The papillary structures were lined by a layer of simple uniform cuboidal epithelium. No mitotic activity or significant nuclear pleomorphism was seen, neither in epithelial nor in stromal component. The epithelial cells were positive for CK7, EMA and TTF1, and negative for CK20 and CD10, whereas the stromal cells were positive for vimentin and Bcl2, and negative for SMA and CD34. The histological and immunohistochemical findings favoured pulmonary adenofibroma.

**Discussion:** The rarity of this tumour makes it a challenging clinical-radiologic diagnosis. The pathological importance is to distinguish it from other benign lesions, such as hamartoma and

solitary fibrous tumour (SFT), plus malignant tumours. A definitive diagnosis is required to plan appropriate management, while avoiding inappropriate and unnecessary surgical intervention.

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## CASE REPORT: PRIMARY SPLENIC ANGIOSARCOMA – A RARE ENTITY

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Primary splenic angiosarcoma (PSA) is a rare, highly aggressive malignant neoplasm arising from splenic vascular endothelium, most commonly presenting in adults over the age of 50. Incidence is estimated 0.14–0.25 annual cases per million people. Patients present with splenic rupture and acute haemoperitoneum in up to 30% of cases. PSA is associated with a very poor prognosis, median survival is 5 months and historically shows no significant survival benefit with therapy.

We describe a case of a PSA to expand the literature of this rare entity. Given significant variability of histological features, even within a singular case, diagnosis between benign vascular tumours, malignant nonvascular tumours and malignant vascular splenic tumours can be challenging.

An 85-year-old woman presented with spontaneous splenic rupture. Emergent splenectomy was performed and macroscopic review of the spleen confirmed focal capsular rupture and diffuse areas of intraparenchymal haemorrhage. Microscopically, we found a highly vascular lesion featuring anastomosing vascular channels lined by variably atypical cells. The atypical cells showed enlarged nuclei, moderate eosinophilic cytoplasm, inconspicuous nucleoli, with frequent mitotic figures. Lesional growth pattern was inhomogenous, with areas of papillary, solid and spindle cell growth. Immunohistochemistry showed strong positivity for vascular markers CD31, CD34, Factor VIII and ERG. Ki-67 index was 20%.

## KNOW YOUR ANATOMY: CASE REPORT OF A RECTAL GIST PRESENTING AS A PROSTATIC MASS

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Gastrointestinal stromal tumour (GIST) most commonly occurs in the stomach, followed by the small bowel and uncommonly the colorectum. GISTs can be composed of spindled or epithelioid cells, with most cases characterised by a gain of function mutation of the KIT gene. This case study reports a patient presenting with urinary retention due to a prostatic mass which was biopsied. The histology was of a mitotically active spindle cell lesion with necrosis. Positive staining for CD117 and DOG1 confirmed the diagnosis of GIST. Subsequent imaging demonstrated a rectal origin of the tumour.

## A MISSING TOOTH: CASE REPORT OF AN AMELOBLASTIC FIBROSARCOMA OF THE MAXILLA

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Ameloblastic fibrosarcoma is a rare malignant odontogenic tumour with slightly less than 100 published cases in the literature. It is characterised by benign ameloblastic epithelial cells admixed within a malignant mesenchymal component. It occurs more commonly in the mandible and is a locally aggressive tumour with a small potential for distant metastasis. This case study reports a patient with ameloblastic fibrosarcoma of the maxilla, including both the initial diagnostic biopsy and the subsequent surgical resection. In the initial biopsy both the epithelial and mesenchymal components were well represented, however in the surgical resection the malignant mesenchymal component dominated.

## OLIGOSARCOMA, AN UNUSUAL BIPHASIC TUMOUR

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Gliosarcomas are a rare variant of IDH-wildtype glioblastoma, WHO grade IV that exhibit biphasic glial and mesenchymal differentiation. The described glial component is usually astrocytic in nature, however fewer than fifteen cases with an oligodendroglial component, so called 'oligosarcoma', are described in the literature. With the advent of modern molecular phenotyping and classification, only a subset of these tumours have been subjected to investigation by molecular modalities. We describe a case of a 65-year-old man who presented with headaches, right visual impairment and left sided weakness. His past medical history includes a low-grade glioma arising in the right temporal lobe twenty-one years prior. The glioma was diagnosed as a 'well-differentiated astrocytoma' and was treated with surgical resection and radiotherapy. Imaging studies showed a new peripherally enhancing, right temporal lobe lesion causing mass effect and midline shift. Histopathology showed a biphasic tumour exhibiting anaplastic oligodendroglioma admixed with sarcomatous areas. Isocitrate dehydrogenase-1 (IDH1 R132H) immunohistochemistry was strongly positive in the oligodendroglial component and weakly positive in the sarcomatous component. Fluorescent *in situ* hybridisation demonstrated a 1p19q co-deletion in the oligodendroglial component only. Next Generation Sequencing of the sarcomatous component confirmed an IDH1 mutation, TERT promotor mutation and 1p19q co-deletion confirming oligodendrogliomatous derivation.

## PRIMARY CERVICAL MALIGNANT MELANOMA

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Primary malignant melanoma of the uterine cervix is a rare form of mucosal melanoma. It typically has a poor prognosis due to late stage at presentation, aggressive nature and resistance to radiotherapy. Unlike cutaneous malignant melanoma, UV radiation is not an apparent risk factor for tumorigenesis. Furthermore, mucosal melanomas exhibit lower incidences of activating BRAF mutations and higher incidences of KIT mutations compared to their cutaneous counterparts suggestive of divergent aetiologies. We describe a case of a 51 year-old-woman who presented with vaginal bleeding and a cervical mass. Initial biopsy of the cervix and adjacent vaginal mucosa showed an ulcerated malignant tumour with spindled and epithelioid morphology which stained positive for melanoma markers S100, HMB45 and Melan A. The patient underwent a total hysterectomy, bilateral salpingo-oophorectomy and vaginal biopsy sampling where residual malignant melanoma was identified in the cervix with evidence of in-situ melanoma confirming the primary site of origin. Molecular analysis showed no evidence of a BRAF, MEK1, KIT or NRAS mutation. While locoregional control through surgical resection remains the mainstay of treatment, novel advancements in therapies targeting driver oncogenes such as BRAF and KIT, and immune checkpoint inhibitors have shown variable results.

## HISTOPATHOLOGICAL PATTERNS OF IMMUNOTHERAPY TREATMENT EFFECT – A CASE REPORT

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Immune checkpoint inhibitors, such as anti-PDL1 antibodies, have proven to be an effective first line treatment for advanced PDL-1 positive non-small cell lung carcinoma (NSCLC). In comparison to conventional chemotherapy and radiation, the histopathological patterns seen with treatment effect are not well established.
This case study reports a patient with metastatic NSCLC, who had treatment with pembrolizumab, with subsequent metastatic tumour regression. We review the histopathological findings.

## DONOR-DERIVED *STRONGYLOIDES STERCORALIS* INFECTION IN A SIMULTANEOUS KIDNEY-PANCREAS TRANSPLANT RECIPIENT DIAGNOSED ON A BRONCHOALVEOLAR LAVAGE SPECIMEN

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Donor-derived *Strongyloides stercoralis* infection occurs rarely after transplantation and can lead to potentially fatal hyperinfection syndrome.[1,2] We present a case of a 29-year-old man who was in a critical state due to *Strongyloides stercoralis* hyperinfection after receiving simultaneous kidney-pancreas transplant. The diagnosis was established following cytologic examination of a bronchoalveolar lavage (BAL) specimen showing numerous typical larvae of *Strongyloides stercoralis*. This illustrates the importance of a thorough examination of BAL and careful search for *Strongyloides stercoralis* in immunocompromised patients, particularly when the donor has lived in an endemic area.

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## EVALUATING SELF REPORTED STUDENT COMPETENCY IN CLINICALLY INTEGRATED HISTOPATHOLOGY USING A MULTI-STATION BASED AND STUDENT-CENTRED APPROACH IN GRADUATE MEDICAL EDUCATION

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**Aim:** To develop and evaluate a pathology curriculum which has substituted didactic practicals for a multi-station tutorial integrating self-assessment questions, clinical scenarios and pathology.
**Method:** Eighty medical students were asked to review the curriculum using qualitative comments and based on a quantitative Likert scale.
**Results:** We demonstrated that the multi-station approach improved student understanding of anatomy, histology, radiology, macroscopic pathology and clinical practice. There was improvement of student self-reported understanding of the clinical applications of pathology (2.19±0.1 in old curriculum versus 3.25±0.09 in new curriculum, $p<0.05$). In addition, we showed that this new teaching approach integrated well with the problem-based learning and provided students with more autonomy to approach their learning in ways that worked for them (2.13±0.12 old versus 2.67±0.12 new, $p<0.05$). Finally, the students regarded the self-assessment questions being the most useful (3.80±0.05), followed by the presence of student tutors (3.65±0.62).
**Discussion:** Engaging the medical students to study clinically integrated histopathology using a multi-station based and student-centred approach is highly useful for learning of pathology in problem-based learning settings.

## A RARE INCIDENCE OF ONLY PANCREATIC ENDOCRINE TISSUE IN MECKEL'S DIVERTICULUM

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**Background:** A 49-year-old female presented with lower abdominal pain and vomiting. No significant history of any previous illness. CT scan showed acute Meckel's diverticulitis. Small bowel was resected.
**Results:** Microscopic examination showed ulcerated and necrotic Meckel's with focal viable areas and clusters 0.3–0.8 mm in maximum dimension, of bland neuroendocrine cells in the muscularis propria and adjacent adventitial adipose tissue. These nests morphologically resembled islets of Langerhans with developed capillary network and stained with synaptophysin, chromogranin. Insulin stained insulin secreting cells towards the centre of the islets and Glucagon stained glucagon secreting cells located peripherally in the islets confirming similar morphology to pancreatic islets of Langerhans.
**Discussion:** Ectopic endocrine pancreatic tissue is histologically present within 20% of Meckel's diverticula. Only two cases of endocrine only ectopic pancreatic tissue have been reported, in the stomach and Meckel's diverticulum respectively, both occurring in insulin-dependent diabetics.[1] Primary or metastatic neuroendocrine (carcinoid) tumour is the main differential diagnosis. Extensive specimen sampling, examination, immunohistochemistry and awareness of the entity is required for differentiaton.[1] It is usually asymptomatic and diagnosed only during examinations for other diseases.[2] Definitive preoperative diagnosis is challenging.[3] Due to the possible chance of malignant transformation, it should be excised.

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## MALIGNANT SFT WITH NODAL METASTASIS, A CASE REPORT

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Solitary fibrous tumours (SFT) are generally rare neoplasms. These tumours were first described in the pleura and later appeared to involve almost every organ. They affect all ages with no sex predilection. Most of the pleural lesions are discovered incidentally. The majority of these tumours are benign with 13–25% considered malignant.
Microscopically the tumours are cellular and consist of fibroblastic spindle cells in a pattern-less pattern with a variable amount of hemangiopericytoma like vascular spaces and stromal hyalinisation. The lesions are positive for CD34, BCL2, CD99 and STAT6. Malignant SFTs are differentiated from benign SFTs by hypercellularity, pleomorphism, necrosis and mitosis of more than 4/10 HPFs.
In this case report, we present a patient who presented to their GP with back pain and during workup was found to have a right lower lobe lung mass. A lobectomy was performed and the tumour was found to be a malignant pleural based SFT with metastasis to a single peri-hilar lymph node.
Seventeen months later, the patient presented with a secondary metastatic nodule with features similar to the primary lung tumour. At this stage, the patient was considered unamenable to further surgery or curative radiotherapy.

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## RHABDOID TUMOUR OF THE KIDNEY, A RARE AND DEVASTATING DIAGNOSIS OF INFANCY – A CASE OF A 9-MONTH-OLD PRESENTING WITH STAGE IV DISEASE

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Rhaboid tumour of the kidney is a rare tumour of infancy with one of the poorest outcomes of all malignancies. It has an incidence of approximately 1 in 5 million and a mean survival of 5 to 10 months.[1] Typical features of this disease include late stage presentation before the age of 12 months, a kidney tumour with characteristic rhabdoid features on histology, an underlying SMARCB1 or SMARCA4 mutation and a very poor prognosis regardless of treatment modality. We present a very recent and classic case of a very uncommon tumour and discuss the most recent understanding of the driver mutations and associated rhabdoid tumour predisposition syndrome.

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## A NEW HISTOPATHOLOGY SERVICE FOR VANUATU

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The Republic of Vanuatu is a collection of over 80 islands located in the 'Melanesian triangle' of the South Pacific Ocean. They have a population of roughly 300,000 people, scattered over a geographical distance of 1300 km between the furthermost islands. Port Vila, on the island of Efate, is the capital and largest city of Vanuatu. Vila Central Hospital has a newly built laboratory and recently appointed their first full time General Pathologist (Dr Garae Tarinavanue). With a busy practice dominated by haematology and microbiology specimens, currently all histopathology specimens are sent to Australia for reporting. The laboratory now has the trained personnel and equipment to run their own histology service although there remain some space and infrastructure issues. We report on a recent visit by the Pacific Island Program, funded by the Australian Government Department of Foreign Affairs and Trade (DFAT) and supported by the RCPA Pacific Education Outreach Committee (PEOC). What does Vanuatu have, what do they need and how can we help this service develop?

## THE MANY FACES OF UROTHELIAL CARCINOMA; DIVERGENT VILLOGLANDULAR AND SMALL CELL NEUROENDOCRINE DIFFERENTIATION IN A 47-YEAR-OLD MAN

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A great many morphological subtypes of urothelial tumours have been described, including rare and concurrent patterns stemming from a common neoplastic urothelial stem cell. Herein we report a 47-year-old man with minimal medical history presenting with painless haematuria, and on radiological investigation was found to have thickening of the urinary bladder wall, with an associated soft tissue mass. Transurethral resection of the 5 cm solid tumour at the right bladder neck was unable to fully resect the tumour. The histology showed urothelial carcinoma with villoglandular differentiation, with associated muscle invasive small cell neuroendocrine carcinoma. These are two rare divergent differentiations of urothelial carcinoma, and concurrence has been reported only twice. Study of these rare subtypes of urothelial carcinoma, both of which have poor prognoses, would be of great use to both pathologist and clinician, especially in development of a standard treatment protocol

## UNCLASSIFIED SEX CORD / GONADAL STROMAL TESTIS TUMOUR WITH A PURE SPINDLE CELL COMPONENT

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Incompletely differentiated sex cord / gonadal stromal tumours of the testis (SCST) of pure spindle cell morphology are extremely rare with only four reported cases in the literature.[1] We report a case of a 73-year-old man who presented with acute on chronic renal failure and noted to have an enlarged tender left testicle. Ultrasound examination revealed an enlarged testis (40 cc) with diffuse heterogeneity of the testicular parenchyma. A radical orchiectomy procedure was performed. The histological examination revealed a well circumscribed tumour (55 mm in maximum diameter) comprised purely of fascicles of spindle cells with elongated to ovoid nuclei. Immunohistochemical stains demonstrated positive staining for Vimentin, S100, SMA, Inhibin, Calretinin and CD99. EMA, Cam 5.2, AE1&3, Desmin, CD34, Melan-A, HMB-45, Sox10, CD117 and PLAP stains were negative. The overall features were consistent with the diagnosis of unclassified SCSTs of pure spindle cells morphology. Due to the rarity, SCST of spindle cell morphology are under studied. They are of unknown clinical behaviour. However, they should be considered in the differential diagnosis of spindle cell lesions of the testis.

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## INVESTIGATING THE COMMON CLINICAL AND HISTOPATHOLOGICAL FEATURES IN DYSFUNCTIONAL UTERINE BLEEDING

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**Background:** Dysfunctional uterine bleeding (DUB) is a diagnosis of exclusion and accounts for about one-third of all cases of abnormal uterine bleeding. It usually affects the extremes of age groups (menarche and perimenopause). Management is usually conservative.
**Aim:** To check for any associations between clinical features and histological diagnosis to assist clinicians in the effective management of DUB patients.
**Methods:** A questionnaire was used on every DUB patient undergoing endometrial biopsy. Questions interrogated were demographic history, obstetrics and gynaecological history and past medical history. Also their body mass index (BMI) was measured as well. Then checking for associations between histological diagnosis and common clinical presentation using Chi-square – Mantel-Haenszel test.
**Results:** In young adults, those who were obese (10.3%), had diabetes (9.62%), irregular periods and polycystic ovarian syndrome (9.43%) were likely to develop simple endometrial hyperplasia. There was significant association between older women (>35 years of age) and endometrial carcinomas ($p$ value = 0.050). There was also significant association between post-menopausal bleeding and endometrial carcinomas ($p$ value = 0.0328).
**Conclusion**: Therefore, these following criteria should be used for surgical evaluation of DUB patients: (1) younger women who are obese, diabetic, have polycystic ovaries, and irregular periods, (2) middle-aged and post-menopausal women.

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## MALIGNANT PERITONEAL MESOTHELIOMA ASSOCIATED WITH EWSR1 GENE REARRANGEMENT

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**Background:** Peritoneal mesothelioma accounts for less than 3% of mesotheliomas.[1] In patients under the age of 40, the incidence of pleural vs peritoneal disease is equal, without gender disparity; overall 5-year survival is 38%.[2] Usually characterised by complex genetic abnormalities, a subset is associated with EWSR1 (Ewing sarcoma breakpoint region 1) gene

rearrangements. Desmeules *et al.* reported 4 cases of EWSR1/FUS-ATF1 fusion with epithelioid morphology within a younger cohort with no known asbestos exposure.[3]

**Case report:** We present a previously well 19-year-old male with no prior asbestos exposure with EWSR1 gene rearranged peritoneal mesothelioma. CT/PET demonstrated widespread FDG avid peritoneal deposits with supra-diaphragmatic nodal involvement. Cytoreductive surgery and adjuvant hyperthermic intraperitoneal chemotherapy was performed. Histopathological findings demonstrated epithelioid malignant mesothelioma (CK5/6, WT1/calretinin positive, BAP1 positive, ALK negative). There were long, slender microvilli on electron microscopy, and FISH revealed EWSR1 rearrangement.

**Discussion:** EWSR1 fusions are usually associated with sarcoma. Together with other reports, this case demonstrates that EWSR1 rearrangements may occur in young patients with malignancies showing mesothelial differentiation. Usually classified as epithelioid mesothelioma, this group shows several clinicopathological differences to other mesotheliomas.

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## THE ROLE OF PD-L1 IN THE PREDICTION OF TREATMENT RESPONSES TO NEOADJUVANT CHEMOTHERAPY IN BREAST CARCINOMA

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**Aims:** To assess programmed death ligand 1 (PD-L1) expression and its correlation with prediction of response to neoadjuvant chemotherapy (NACT) in invasive breast carcinoma (IBC).

**Introduction:** NACT is being increasingly utilised in IBC management with pathologic complete response (pCR) strongly correlated with excellent disease-free and overall survival. PD-L1 has recently gained attention in breast carcinomas as a potential therapeutic target as well as a prognostic indicator. PD-L1 is expressed in response to inflammation and has been found to be expressed on a number of tumours. The presence of tumour infiltrating lymphocytes has been found to be strongly associated with pathological complete response (pCR) and a relationship between PD-L1 and pCR has been suggested in recent studies.

**Methods:** Pretreatment core biopsies and their matched subsequent surgical excision from 74 consecutive patients with IBC from the PathWest pathology database, Fiona Stanley Hospital, in 2013–2016 were assessed for TILs and PD-L1 expression.

**Results:** Eighteen cases achieved pCR while 56 cases did not. When comparing these groups, there was a greater likelihood of pCR in patients with higher TILs scores ($p$=0.006) and higher PD-L1 scores ($p$=0.018).

**Conclusion:** Our study demonstrates a significant association between PD-L1 expression with pCR in NACT.

## APPLICATION OF MSH3 IMMUNOHISTOCHEMISTRY AND TETRANUCLEOTIDE MICROSATELLITE ANALYSIS TO IDENTIFY ELEVATED MICROSATELLITE ALTERATIONS AT SELECTED TETRANUCLEOTIDE REPEATS (EMAST) IN COLORECTAL TUMOURS

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**Background and aims:** Reduced function of the DNA mismatch repair enzyme MSH3 in tumour cells results in elevated microsatellite alterations at selected tetranucleotide repeats (EMAST). In contrast to microsatellite instability (MSI) caused by MLH1/PMS2/MSH2/MSH6 defects, EMAST in CRCs is a marker of poor prognosis. This study examined the prevalence of EMAST-positive CRCs in a Western Australian population and critically evaluated immunohistochemical and molecular detection methods.

**Methods and results:** MSH3 immunostaining of 250 archival CRCs identified aberrant MSH3 expression (focal or widespread reduction of nuclear MSH3, cytoplasmic MSH3 mis-localisation) in 66% cases. Tetranucleotide MSI (EMAST) was detected in 46% cases, a proportion consistent with limited previous reports. Discordance between MSH3 immunostaining and molecular detection of tetranucleotide MSI resulted from over-detection of abnormal MSH3 immunostaining, which is focal and confounded by common tissue damage (crush, autolysis).

**Summary and conclusions:** Aberrant MSH3 function in CRCs results from elevated inflammatory signalling, a potentially modifiable risk factor that may be targeted to reduce or prevent disease relapse. A combination of MSH3 immunostaining and molecular methods can be used to identify EMAST-positive CRCs, however further antibody development and establishment of consistent tetranucleotide panels will improve the reliability and reproducibility of its detection in routine practice.

## THREE DIFFERENT APPROACHES TO QUANTIFICATION OF KI-67 IMMUNOHISTOCHEMISTRY IN NEUROENDOCRINE TUMOURS OF THE LUNG AND MEDIASTINUM

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Classification of neuroendocrine tumours (NETs) of the lung and mediastinum is largely based on mitotic index. Ki-67 immunohistochemistry has been incorporated into the grading system of gastrointestinal tract and pancreatic NETs. However, the significance of Ki-67 in pulmonary and mediastinal NETs is still a

controversial issue. Our study aims to investigate three different methods of quantifying Ki-67 in both pulmonary and mediastinal NETs. We retrieved 40 cases of pulmonary and mediastinal NETs. Manual counting with a graticule, manual counting on a printed image of the hotspot area and automated digital image analysis (DIA) were used to calculate the Ki-67 proliferative index.

## METASTATIC PLEOMORPHIC DERMAL SARCOMA TO SMALL BOWEL – A CASE REPORT

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Pleomorphic dermal sarcoma (PDS), a dermal based tumour that is related to atypical fibroxanthoma with overlapping morphological and immunohistochemical features but with subcutaneous invasion, necrosis, perineural or vascular invasion. PDS has low malignant potential with risk of local recurrence and metastases. Reported sites of metastases are distant skin, lymph nodes and lung. We report a case of a male aged 65 who presented with gastrointestinal bleeding due to haemorrhage from a small bowel lesion. His medical history included Muir-Torre syndrome, stage IV colon cancer (with liver metastases) and PDS of the lower lip (resected February 2018) with known lung metastases. He underwent a segmental resection of small bowel in June 2019; macroscopically a solitary 39 mm lesion was noted. Histopathology showed a tumour composed of sheets and nests of pleomorphic, mitotically active, epithelioid and spindle cells. Immunohistochemically the malignant cells showed positive for CD10 and negative staining for cytokeratins, CD117 and melanoma markers. The morphology and immunophenotype were the same as his previously diagnosed lip PDS. This is the first reported case of metastatic PDS to small bowel, and highlights the importance of clinical-pathological correlation. Although rare, metastatic sarcoma should be considered in the differential of pleomorphic epithelioid/spindled small bowel neoplasms.

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## AN UNUSUAL CASE OF METASTATIC GASTRIC ADENOCARCINOMA TO THE OVARY WITH YOLK SAC DIFFERENTIATION AND AFP PRODUCTION

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Raised serum AFP in adults is most commonly associated with hepatocellular carcinoma (HCC) or yolk sac tumour (YST). However, studies have reported diseases other than HCC or YST which are associated with high serum AFP levels. We describe a case of metastatic adenocarcinoma to the ovary showing yolk sac differentiation, as a primary presentation of a gastric tumour.

## AUDIT ON THE PERFORMANCE OF MMR PROTEIN IHC STAINING ON BIOPSIES AND RESECTIONS OF COLORECTAL CANCER

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Colorectal cancer may arise from an accumulation of uncontrolled DNA mutations that is a result of damage to or absence of mismatch repair (MMR) genes. These DNA damage repair genes consist primarily of MLH1, PMS2, MSH2 and MSH6. Mismatch repair deficient (MMRD) colorectal cancers may arise from acquired or inherited loss of protein expression; the latter referred to as Lynch syndrome.

Immunohistochemical (IHC) testing for MMR protein expression is part of the standard of care for the work up of colorectal cancer. Identification of absent protein expression prompts referral of the patient to genetic services for further work up.

The aim of our study was to audit the performance of MMR protein IHC staining on biopsies and resections of colorectal cancer, in particular turnaround-time. This is relevant to patient review at multidisciplinary team meetings and timely referral to genetic services when appropriate.

## UTILITY OF KI67 AND P53 IN EARLY DETECTION AND PROGNOSIS ASSESSMENT OF ORAL SQUAMOUS CELL CARCINOMA

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Carcinoma of the oral cavity constitutes 3% of all cancers. The incidence is higher in India because of use of smokeless tobacco (chewing). 90% of oral cavity carcinomas are oral squamous cell carcinoma (OSCC) and mucosa surrounding them more than often shows features of dysplasia of varying degree. It is well established fact that early detection and timely intervention in case of oral cancer reduces the morbidity, mortality and cost of treatment. Hence it is important to explore the use of ancillary techniques for early detection and assessment of prognosis. Molecular proliferation markers Ki-67 and p53 can be used for assessing the potential of malignancy in the tumour tissue and its surrounding dysplastic tissue. In the present study tissue sections from 64 paraffin blocks containing tissue from cases of OSCC and surrounding dysplastic area were immunohistochemically stained for Ki-67 and p53. It was found that for Ki-67 among the tumour area 58 cases were positive and 32 cases showed positivity in dysplastic areas. For p53 the positivity was 23 and 9 for the tumour and dysplastic areas, respectively. Significant $p$ value was obtained to indicate usefulness of utilising these markers for early detection and prognostication.

## AN UNEXPECTED CAUSE OF PREMATURE MENOPAUSE

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**Presenting complaint:** A 42-year-old female presented with 6 weeks of bloody vaginal discharge, as well a history of abrupt early menopause 2 years prior, with no post-menopausal symptoms. Her last known pregnancy was 14 years ago.
**Investigations and results:** The patient had a serum bHCG level of 59,000. An ultrasound scan revealed a 42 mm intrauterine mass with a complex cystic structure, and she underwent a total abdominal hysterectomy for suspected gestational trophoblastic neoplasia. Histology showed a 90 mm mixed choriocarcinoma and placental site trophoblastic tumour (PSTT) arising in the uterus and extending into the proximal cervix. Immunohistochemical stains supported this diagnosis. The tumour underwent quantitative fluorescent PCR analysis (QF-PCR), and was found to be gestational in origin.
**Case discussion:** We will review the clinical, histological and immunohistochemical features of choriocarcinoma and placental site trophoblastic tumour. We will demonstrate how QF-PCR analysis may be used to determine whether a tumour is gestational,[1] and discuss the clinical significance of this finding for this patient.
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## A STUDY OF GATA-3 IN MALIGNANT PLEURAL MESOTHELIOMA

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**Background:** Malignant pleural mesothelioma is an asbestos-associated tumour with high incidence in Australia.[1] Diagnosis and prognostication remain difficult.[2] We investigated the usefulness of GATA-3 and BAP-1 immunohistochemistry for diagnosis and prognostication in pleural mesothelioma.
**Methods:** We scored immunohistochemical labelling for GATA-3 and BAP-1 in 116 malignant pleural mesotheliomas and correlated labelling with clinical parameters, histological subtypes and survival. SPSS version23 statistical software was used for analyses.
**Results:** Median age at diagnosis was 74.5 years (93 males:23 females). GATA-3 was positive in 56/116 (48%) cases (23/62 (37%) epithelioid, 22/32 (69%) sarcomatoid and 11/22 (50%) biphasic). 73% of the biphasic subtype showed either positivity or negativity on both components. There was a trend to better survival in GATA-3 positive cases with epithelioid histology ($p$=0.081) and among women ($p$=0.001). GATA-3 was not an independent prognostic marker on multivariate analysis. BAP-1 loss was seen in 44/106 (42%) and was associated with the epithelioid subtype ($p$<0.001) on Chi square analysis but not independently with survival.
**Conclusion:** Almost half our cohort of malignant pleural mesotheliomas labelled for GATA-3 with highest incidences among sarcomatoid mesotheliomas. Discordance in GATA-3 labelling among the components of the biphasic subtype was unexpected. Neither GATA-3 nor BAP-1 showed clear association with survival.
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## SIMPLE YET RARE: SIMPLE PANCREATIC CYST IN AN ADULT – A CASE REPORT

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Pancreatic cysts (PC) are very common, and with the increased use of cross-sectional imaging the incidence of PC seems to increase too. Simple pancreatic cysts are very rare and most are found in children in the context of other congenital anomalies, such as von Hippel-Lindau disease and polycystic kidney disease. Here, we report a case of a simple pancreatic cyst in a 69-year-old female. A 6 cm cyst in the tail of the pancreas was incidentally discovered on a computerised tomography colonography. Due to the size and morphological pattern on the imaging mimicking a mucinous cystic neoplasm, laparoscopic spleen-preserving distal pancreatectomy was performed. Macroscopically the pancreatic cyst was unilocular, filled with runny clear fluid. No solid component or papillary projection was seen within the cyst lining. Microscopically, the cyst was lined by a single layer of cuboidal epithelium, and there was no ovarian-like stroma. The surrounding pancreatic parenchyma was unremarkable. The immunohistochemical stains for the cyst lining were positive for panCK (strong) and EMA (weak). They were negative for calretinin, inhibin, synaptophysin, CD56, chromogranin, CEA and S100. ABPAS and DABPAS staining did not show mucin or glycogen.
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## DIFFUSE DERMAL ANGIOMATOSIS – A CASE REPORT

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Diffuse dermal angiomatosis (DDA) is usually considered as a variant of reactive angioendotheliomatosis (RAE). Awareness of

this condition is necessary to differentiate it from more aggressive vascular malignancies such as Kaposi's sarcoma and angiosarcoma. We present a case of DDA in a patient with end-stage renal disease (ESRD) on haemodialysis who was clinically diagnosed with calciphylaxis.

DDA presents as painful, livedoid, erythematous plaques commonly occurring in the extremities and occasionally in the breasts. Clinically, it is associated with atherosclerosis, peripheral vascular disease, ESRD on haemodialysis and smoking. Histologically, DDA is characterised by dermal proliferation of benign endothelial cells and vascular channels which are interstitially arranged between collagen bundles. Although the cells generally lack atypia, there can be focal spindled cells with vacuolated cytoplasm. Immunohistochemistry is useful in confirming the endothelial phenotype of the cells, they are positive for CD31, CD34, ERG and typically negative for D-240 (marker of lymphatic endothelium). Though the cutaneous lesions of DDA are clinically indistinguishable from those of RAE, divergent histological features dictate the two to be regarded as separate entities.

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## ERDHEIM CHESTER DISEASE: A TRIO OF INTRIGUING CASES

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Histiocytoses are a group of heterogeneous diseases that comprise Langerhans cell histocytosis (LCH) and non-LCH. Erdheim Chester disease (ECD) is a non-LCH, clonal systemic proliferation of histiocytes resulting in lesions that can manifest in virtually any tissue within the body. Diagnosis is based on the combined clinical features, histology and characteristic radiological findings. We present three cases.

These cases include a 63-year-old woman investigated for bony abnormalities discovered on staging investigations following a diagnosis of breast cancer, a 71-year-old male presenting with diminishing renal function and left ureteric obstruction and a 67-year-old man with fatal multi-systemic ECD involvement, including retroperitoneal fibrosis, dilated cardiomyopathy and bone pain that was diagnosed late in its course. $BRAF^{V600E}$ mutational analysis was performed and a mutation was detected in each of the three cases.

Recent research into such cases has described an association between LCH and ECD and it is suggested that $BRAF^{V600E}$ has an important role in the emergence of both diseases. Like LCH, the majority of ECD patients harbour acquired activating mutations in the MAPK/ERK pathway genes with $BRAF^{V600E}$ and NRAS mutations the most prevalent. These findings open the gateway to the possibility of targeted therapeutic treatment for those with significant clinical disease.

## INCIDENTAL DYSPLASIA IN ROUTINE CHOLECYSTECTOMY SPECIMENS. SHOULD ADDITIONAL SECTIONS BE TAKEN?

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The finding of incidental dysplastic epithelium in the histological analysis of routine cholecystectomy specimens is common. There is no protocol which addresses how this finding should be handled by the pathologist. We present a case of a 68-year-old woman who underwent routine cholecystectomy with no macroscopically described lesion. Routine sections showed low grade gallbladder dysplasia, an additional two blocks showed high grade dysplasia, and upon submission of the entire gallbladder she was found to have T2 invasive adenocarcinoma. After encountering this case we performed a retrospective analysis of all cases of incidental dysplasia found in routine cholecystectomy specimens performed at a tertiary centre from 2011–2019. This analysis revealed an additional case of invasive carcinoma which was identified only in additional sections. These findings suggest that additional sampling of incidental gallbladder dysplasia is warranted.

## INTESTINAL ADENOMYOMA – AN UNUSUAL CAUSE OF INTUSSUSCEPTION IN AN INFANT

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Intestinal adenomyoma is a rare benign tumour which can occur in infancy. We report a case of a 1-year-old boy who presented with neurological symptoms who was found to have intussusception with an anatomic lead point. Histopathology demonstrates a nodule within the submucosa, characterised by variably dilated glands lined by mucin-secreting columnar epithelium which are accompanied by smooth muscle bands within the stroma. Awareness of this benign entity is useful as it may be mistaken for clinically relevant entities such as a hamartomatous polyp or well differentiated adenocarcinoma.

## PAPILLARY THYROID CARCINOMA IN STRUMAL CARCINOID TUMOUR

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Strumal carcinoid tumour is a type of ovarian germ cell tumour characterised by an admixture of thyroid tissue and carcinoid tumour. The finding of papillary thyroid carcinoma (PTC) within strumal carcinoid is rare, with only two described cases in the literature. We present a case of a 37-year-old woman who had removal of a large complex ovarian cyst. Initial histological

sections showed thyroid follicles and carcinoid tumour characterised by a rosette-forming uniform cells which were positive for neuroendocrine markers with a low Ki-67 proliferative index. Additional sections of tumour revealed nodules with classic architectural and nuclear features of PTC admixed with the strumal component. This case highlights the importance of careful examination and adequate sampling of ovarian teratomas for features of PTC especially in cases of struma ovarii or strumal carcinoid.

## METASTATIC PARAGANGLIOMA AS A DIAGNOSIS FOR A CLEAR CELL-LIKE TUMOUR

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A paraganglioma is a potentially malignant neuroendocrine tumour with the cells derived from the embyronal neural crests. They can arise in the sympathetic paravertabral ganglia of the thorax, abdomen and pelvis as well as along the glossopharyngeal and vagal nerves in the neck and base of skull.[1] The specific incidence of paraganglioma is unknown as it is commonly described in conjunction with phaechromocytoma and together there are approximately 500–1600 cases in the United States per year.[1] Paragangliomas at different sites have been reported to have different rates of metastases, ranging from 2% (carotid and middle-ear type) to 16% (glomus vagale).[2] Overall metastatic paragangliomas and phaechromocytomas are rare, with an incidence of less than one per one million and with a long latency of up to 20 years.[2,3] Subsequently metastatic paraganglioma is not commonly encountered in daily practice and can be a mimic of other pathologies. A case demonstrating this is presented and the diagnosis was inevitably made more difficult as the incorrect medical terminology was used.

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## LARGE VESSEL VASCULOPATHY ASSOCIATED WITH LUPUS ANTICOAGULANT: A CASE REPORT

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**Background:** Vasculopathy associated with lupus is a rare form of vascular involvement characterised by non-inflammatory vascular injury resulting in luminal narrowing. Vasculopathy in large vessels is uncommon and should be distinguished from vasculitis.[1]

**Case report:** We report a case of 51-year-old woman with chronic ischemic stricture of the small intestine due to large vessel vasculopathy. She presented with abdominal pain and vomiting and had a history of stroke six months before. CT scan showed focally dilated prominently thickened small intestinal loops. She'd had thrombosis in left external and internal carotid artery, and multiple emboli to liver, spleen, kidney and lung. Lupus anticoagulant and ANA (in speckled pattern) were positive. Histological examination from the strictured site revealed large areas of ulceration, inflammatory granulation tissue forming pseudomembrane and extensive pyloric metaplasia. The vascular changes were peculiar as the large vessels showed widespread intimal thickening with irregularly narrowed lumen. No thrombosis or vasculitis was seen.

**Conclusion:** Large vessel vasculopathy may occur in lupus and could be easily overlooked. It should be considered as a potential cause of ischemia in a patient with lupus when no obvious thrombosis is detected.

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## IgG4 ASSOCIATED AUTOIMMUNE HEPATITIS: A RARE ENTITY

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**Background:** IgG4-related disease is an immune mediated multisystem disorder fibroinflammatory condition. Two types of hepatic involvement in IgG4 related disease have been described: IgG4 hepatopathy and IgG4 related autoimmune disease,[1] which is rare with only few cases reported.

**Case report:** We present a case of 50-year-old lady who presented with a history of malaise and nausea, and had deranged LFTs, raised IgG4 and serum lipase levels, and positive ANA and SMA antibodies. Abdominal CT showed no bile duct abnormality. Liver biopsy showed features of autoimmune hepatitis with grade III activity. Unusually, a significant amount of pericapsular tissue was present which showed fibroinflammatory reaction with infiltration of IgG4 bearing plasma cells. No significant bile duct damage was seen. The patient fulfilled the diagnostic criteria for definite AIH using IAIHG scoring system and responded well with steroid therapy.

**Conclusion:** The diagnostic criteria for IgG4 associated autoimmune hepatitis are not well defined and additional studies are needed to clarify the clinical significance and diagnostic guidelines.[2]

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## LOW GRADE SEROUS CARCINOMA OF THE TESTIS: A CASE REPORT

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Ovarian-type epithelial tumours of the testis represent rare entities.[1] Due to their relative scarcity these tumours hold the

potential for misdiagnosis both clinically and histologically. Here we present a case from our institution of a 27-year-old man with a testicular low grade serous carcinoma, arising from a serous borderline tumour, with a discussion of the histologic, immunohistochemical and molecular findings.[1–3]

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## BENIGN MESOTHELIAL INCLUSIONS IN A MEDIASTINAL LYMPH NODE

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Benign mesothelial proliferations found in lymph nodes present a diagnostic dilemma as they can mimic metastatic disease. There are only a few case reports of mesothelial proliferations in lymph nodes in the literature. We report our findings in a patient who developed heart failure and had an incidental mediastinal lymph node removed at the time of coronary artery by-pass graft and aortic valve replacement. Histologically the proliferations are characterised by epithelioid cells lacking atypia and which demonstrate an immunohistochemical profile characteristic of mesothelium. Incorrect diagnosis can lead to over-treatment and morbidity for the patient.

## ROLE OF NEXT GENERATION SEQUENCING IN PANCREATOBILIARY BRUSHING SPECIMENS – A PILOT STUDY

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**Introduction:** Pancreatobiliary brush cytology has high specificity but low sensitivity. Next generation sequencing (NGS) may improve its sensitivity. This pilot study aimed to evaluate diagnostic performance of NGS in detecting pancreatobiliary malignancy in brush cytology specimens.
**Methods:** NGS analysis was performed retrospectively on 17 pancreatobiliary duct brushing specimens sent to cytology department for routine cytological evaluation, between May 2018 to Dec 2018. NGS panel comprised the following frequently mutated gene-regions: KRAS, TP53, PIK3CA, CTNNB1, ERBB2, FGFR3, ATM, FGFR2, ALK, AKT1, BRAF, NRAS, MAP21K1, SMAD4 and STK11. Performance characteristics for each diagnostic modality were calculated based on clinic-pathological follow-up.
**Results:** Fifteen of 17 cases were analysed by NGS. Two failed due to poor sample quality. NGS revealed genetic mutations in 6 of 8 cases of pancreatobiliary adenocarcinoma. Mutations detected were KRAS, TP53, BRAF, NRAS, ALK, MAP2K1 and SMAD4. On cytology, 5 of 6 NGS positive cases were diagnosed as malignant and one diagnosed as degenerate atypical cells. Both cytology and NGS had one false positive result on the same case which showed STK11 mutation. One case of cholangiocarcinoma was negative on both. Cytology and NGS had sensitivities of 63% and 75%, respectively, and similar specificities of 86%. The combination of NGS and cytology increased the sensitivity to 91% while specificity was not increased.
**Conclusion:** These results suggested that NGS improved the sensitivity of pancreatobiliary duct brushings and provided additional information on genetic mutations which may be used for targetable genomic therapies.

## CYTOLOGY OF RARE MALIGNANT NEOPLASMS IN THE SALIVARY GLAND: MORPHOLOGIC AND HISTOPATHOLOGIC CORRELATES

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**Background:** Mucoepidermoid carcinoma and acinic cell carcinoma are common malignant salivary-gland tumours. Rarer tumours include secretory carcinoma, epithelial-myoepithelial carcinoma and salivary duct carcinoma. Herein, we present five cases illustrating cytomorphology and subsequent histopathological/molecular diagnoses of rarer salivary-gland malignant neoplasms.
**Results:** Cytological smears from five patients 40–75 years old with 1.5–4.2 cm sized tumours were studied. Three cases showed cellular clusters of atypical cells exhibiting enlarged, irregular nuclei and prominent nucleoli diagnosed to favour salivary duct carcinoma on ancillary cytology testing and concurred on subsequent resection specimens. In another case, cytologic smears showed clusters of ductal cells admixed with spindled myoepithelial cells in close association with some acellular matrix. Initial cytologic diagnosis rendered was pleomorphic adenoma; subsequent resection showed epithelial-myoepithelial carcinoma. Fifth case showed cellular yield of epithelioid cells exhibiting mildly enlarged, uniform nuclei, conspicuous nucleoli and ample, finely-vacuolated cytoplasm, with cytologic diagnosis of epithelial neoplasm. Subsequent histopathological examination yielded a diagnosis of secretory carcinoma, confirmed with *ETV6-NTRK3* fusion on molecular analysis.
**Conclusions:** Diagnosing rare malignant salivary-gland neoplasms on cytology is challenging. Although the malignant nature of high-grade malignancies is often correctly made on cytologic examination, low-grade malignancies may appear deceptively benign. Thorough cytologic examination including cell types and matrix/background components is crucial for accurate diagnosis of these neoplasms.

## SOLID PAPILLARY BREAST CARCINOMA WITH REVERSE POLARITY, A CASE REPORT

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Solid papillary carcinoma with reverse polarity is a rare breast cancer of specific morphologic and immunohistochemical profile with favourable prognosis. However, this carcinoma is not yet included in the current WHO classification. The tumour shows histologic features resembling tall cell variant of papillary thyroid carcinoma. We report a case of a 63-year-old lady with an incidental finding of a discrete oval mass on routine breast screening. Clinical and radiological findings are suggestive of a fibroadenoma. Histologically, the tumour shows papillary, follicular and solid structures. The cells are tall and columnar with abundant eosinophilic cytoplasm and apically located nuclei giving the impression of reverse nuclear polarity. Eosinophilic colloid like secretion is present. Nuclear pseudoinclusions and occasional grooves are also observed. Immunohistochemistry stains demonstrate the lack of myoepithelial cells, indicating its invasive nature. The tumour shows positive staining for cytokeratin 5/6, calretinin and luminal staining for EMA. Thyroid marker, TTF1, is negative. Despite the indolent behaviour, the tumour is triple negative (negative ER, PR and HER2). Our findings demonstrate that solid papillary carcinoma with reverse polarity is a unique breast neoplasm that should be distinguished from other papillary carcinomas of the breast.

## DABIGATRAN-INDUCED OESOPHAGITIS DISSECANS SUPERFICIALIS

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Dabigatran is a direct thrombin inhibitor frequently prescribed for prophylaxis of stroke in the setting of atrial fibrillation. The histologic features of dabigatran-induced drug injury have not been described in the literature. We describe herein five patients taking dabigatran, presenting with histologic features of oesophagitis dissecans superficialis.

The patients included three men and two women with a median age of 82 years (range 67–91 years). The clinical indications for taking dabigatran were atrial fibrillation (80%) and deep vein thrombosis (20%). Presenting symptoms included dysphagia (40%), anaemia (40%), nausea and vomiting (40%), and epigastric pain (20%). Endoscopically, epithelial sloughing typical of oesophagitis dissecans was seen in the mid or lower oesophagus in all patients. Histologically the oesophageal biopsies showed necrosis and splitting of the superficial squamous epithelium with preservation of the basal cell layer, characteristic of oesophagitis dissecans superficialis. This is the first report describing histologic features of dabigatran-induced drug injury in the gastrointestinal tract.

## ANTERIOR MEDIASTINAL CHOLESTEROL GRANULOMA – A CASE REPORT

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Cholesterol granuloma is a foreign-body giant cell reaction to cholesterol crystals. It is a well-documented phenomenon that is usually seen in the middle ear and mastoid processes of patients with diseases associated with chronic inflammation such as otitis media and cholesteatoma.[1] There are a few reported cases of anterior mediastinal cholesterol granulomas in the literature.[1] We report a case of an anterior mediastinal cholesterol granuloma in a 62-year-old male, which was found incidentally during a work up for unprovoked bilateral lower limb deep vein thrombosis (DVT). Computed tomography (CT) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed a 26×22 mm intensively FDG avid anterior mediastinal mass. As the mass was not amenable to biopsy, the patient underwent a radical thymectomy and concurrent coronary artery bypass graft for his ischaemic heart disease. Histological analysis of the mass showed a well circumscribed lesion composed predominantly of cholesterol crystals with focal foreign-body giant cell reaction.

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## CASE CATEGORIES FOR CERVICAL BIOPSIES AND EXCISIONS: CONSISTENT TERMINOLOGY TO SUPPORT THE NATIONAL CERVICAL SCREENING PROGRAM (NCSP)

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**Background:** The RCPA Structured Reporting Protocol for Excisions and Colposcopic Biopsies Performed for the Diagnosis and Treatment of Pre-invasive Cervical Neoplasia was developed to provide consistent terminology for histological reporting, allowing for data capture and clear implementation of management guidelines within the NCSP.

**Aims:** To report distribution of cases, assess practical utility and potential issues associated with the use of diagnostic categories for reporting histological cervical specimens.

**Methods:** Reports from consecutive diagnostic cervical biopsies and excision specimens were retrospectively reviewed and categorised for the squamous, glandular, and 'other' components according to the RCPA Structured Reporting Protocol.

**Results:** All cases were able to be retrospectively categorised. In 418 cervical biopsies, squamous component: not identified 7.7%, normal/benign 44.7%, LSIL 17.7%, possible HSIL 1.2%, HSIL 26.1%, and malignant 2.6%; endocervical component: not identified 15.9%, normal/benign 76.3%, possible AIS 0.2%, AIS 0.2%, malignant 1%. 'Other neoplastic lesion' in 6 biopsy cases. In 249 cervical excisions, squamous component: normal/benign 28.9%, LSIL 9.7%, HSIL 58.6%, and malignant 2.4%; endocervical component: not identified 0.4%, normal/benign 92.8%, AIS 4.8%, malignant 0.4%.

**Conclusions:** Use of diagnostic categories in cervical biopsies and excisions is readily achievable for pathologists allowing for clear management pathways for women participating in the NCSP.

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## PARAGANGLIOMA IN AN UNEXPECTED LOCATION – A CASE REPORT

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Paragangliomas are non-epithelial neuroendocrine neoplasms most commonly occurring in the head and neck. When they arise in unexpected locations such as the gallbladder, they can create diagnostic errors. This is a case report of a rare gallbladder paraganglioma in a 78-year-old patient who underwent cholecystectomy for a gallbladder mass. Histopathological examination revealed a well-circumscribed subserosal nodule with no connection to the biliary mucosa. The lesion was composed of nests and trabeculae of polygonal cells with round to oval nuclei with granular chromatin and eosinophilic cytoplasm staining positive for synaptophysin and chromogranin, features which could have led to misdiagnosis of a metastatic neuroendocrine tumour. However, further ancillary studies demonstrated negative CAM 5.2 expression, consistent with paraganglioma. Making this diagnostic distinction has important clinical implications.

## IMMUNOPROFILE OF BREAST CANCER AT PROF. DR. W. Z. JOHANNES KUPANG HOSPITAL, EAST NUSA TENGGARA, INDONESIA

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Breast cancer is the most prevalent malignancy among women in Indonesia. The present study aimed to describe the immunoprofile of breast cancer patients in Prof. Dr. W. Z. Johannes Kupang Hospital and the correlation with metastasis events. In this descriptive retrospective study, we reviewed records of immunohistochemistry results of patients of breast cancer at our hospital in 2018. Data with respect to findings of clinical data, histological and immunohistochemistry features were obtained. Among 22 cases, mean age of presentation was 50.14 (range 29–75 years). Most patients had invasive carcinoma of no special type and with histological grade 2. Immunoprofile showed most subtype was Luminal A (45%), followed by Luminal B, Her-2 and basal-like. We documented metastasis in 18 patients. ER and PR were positively correlated with each other ($r^2$=0.649, $p$=0.001<0.05). There was correlation between Ki-67 expression and metastasis event ($r^2$=0.463, $p$=0.30<0.05). In summary, our findings indicate of Ki-67 expression as one of important prognostic factors in breast cancer.

## MONOMORPHIC EPITHELIOTROPIC INTESTINAL T-CELL LYMPHOMA – A CASE REPORT

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Monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL) is a rare, aggressive T-cell lymphoma derived from intraepithelial lymphocytes without associated coeliac disease. We report an 89-year-old male with hypertension and hyperlipidaemia who presented with generalised abdominal pain of one week duration. There was no prior history of chronic malabsorption. Computed Tomography scan of the abdomen revealed dilatation and irregular wall thickening of the duodenum with surrounding fat stranding. The resected segment of bowel showed a grey, fleshy tumour measuring 6.5 cm in maximum dimension involving the bowel wall and surrounding soft tissue. Microscopy demonstrated sheets of malignant lymphoid cells featuring medium to large, round to slightly irregular nuclei with small nucleoli and scant to abundant pale cytoplasm. There was focal prominent epitheliotropism of the adjacent villous epithelium but preserved villous architecture away from the tumour. The tumour cells expressed CD3, CD56 and TIA-1 as well as patchy, weak aberrant expression of CD20. There was loss of CD5 expression in addition to partial loss of CD4 and CD8. CD30, EBER and PAX5 staining were negative. Monoclonal T-cell receptor beta and gamma rearrangements were detected. The overall clinical presentation as well as tumour morphology and immunoprofile were most consistent with a diagnosis of MEITL.

## DIFFUSE GANGLIONEUROMATOSIS AND PLEXIFORM NEUFROFIBROMATOSIS OF SMALL INTESTINE WITH NO ASSOCIATED PHENOTYPIC FEATURES OF SYSTEMIC SYNDROMES: CASE REPORT AND LITERATURE REVIEW

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Diffuse ganglioneuromatosis and plexiform neurofibromatosis of the gastrointestinal tract are closely associated with multiple endocrine neoplasia type 2B and neurofibromatosis type 1. Isolated cases of intestinal ganglioneuromatous lesions without additional features of a systemic syndrome are very rare. We report a rare case of diffuse ganglioneuromatosis with plexiform neurofibromas limited to the small intestine in a 16-year-old female with an initial preoperative diagnosis of inflammatory bowel disease. The patient had no associated phenotypic features of a systemic syndrome.

## REVIEW OF HER2 IMMUNOHISTOCHEMISTRY AND *IN SITU* HYBRIDISATION CONCORDANCE IN BREAST CANCER

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As per current Royal College of Pathologists of Australasia (RCPA) recommendations for practice from the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) 2018 HER2 testing for breast cancer guidelines, routine HER2 *in situ* hybridisation (ISH) testing of immunohistochemistry (IHC) 0 or 1+ cases is not recommended. In light of the updated guidelines, we performed an audit of up to 4,000 cases from 2011–2019 at our institution with the aim of identifying

discordance between IHC and ISH (single probe silver ISH, SISH; or dual probe fluorescence ISH, FISH). Of the 1,701 HER2 IHC 0 test results retrieved, 99.2% were HER2 SISH negative, 0.8% equivocal, and no SISH positive cases were identified. Of the IHC 0 and SISH equivocal cases, all were subsequently shown to be HER2 negative by further FISH testing. Of the 881 IHC 1+ test results, 96.7% were SISH negative, 3.0% equivocal, and 0.3% were positive. The majority of IHC 1+ cases with equivocal or positive SISH were ultimately shown to be HER2 negative by FISH. The IHC 1+ cases that were subsequently shown to be HER2 amplified by FISH were reviewed and some exhibited either tumour heterogeneity or were in the neoadjuvant setting. Our review supports the current recommendation against reflexive ISH testing of IHC 0 and 1+ cases, and referral for further testing in cases of tumour heterogeneity.

## ANALYSIS OF PTEN EXPRESSION IN PROSTATE CANCER

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Mutations in the tumour suppressor gene PTEN have been identified in a variety of cancers, including thyroid, breast, kidney and endometrial carcinoma. PTEN loss identified by immunohistochemistry (IHC) in prostate cancer has been associated with higher Gleason score, early recurrence, castrate resistance, metastases, and shorter survival. Here we performed PTEN IHC on a tissue microarray (TMA) and analysed 288 prostate adenocarcinoma cases. 20% of cases showed PTEN loss. PTEN negative cases showed a higher Gleason score and Grade group, however among Gleason 7 cases, PTEN loss was not associated with a significant increase in Group 3 verses Group 2. PTEN negativity was associated with adverse tumour features including perineural and lymphovascular invasion, however this was no longer significant when cases were matched by Gleason score. PTEN loss by IHC appears to be a promising biomarker of aggressive prostate carcinoma. However further research is required into the role of PTEN in prostate cancer.

## NESTED VARIANT OF UROTHELIAL CARCINOMA CAN BE CONFUSED WITH BENIGN TUMOURS SUCH AS INVERTED PAPILLOMA

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Nested variant of urothelial carcinoma is a rare, cytologically bland variant of invasive urothelial carcinoma that is histologically characterised by disorderly proliferation of discrete to confluent irregular crowded large numbers of small nests beneath the urothelium.

The major problem is the distinction between nested variant of urothelial carcinoma and the benign proliferative lesions of urothelium, such as inverted papilloma, von Brunn nests, cystitis cystica, cystitis glandularis, nephrogenic adenoma, and paraganglioma.

The bland appearance of the cells can give a misleading impression and the tumours are sometimes misdiagnosed as benign lesions, leading in some cases to a significant delay in concluding the correct diagnosis and therefore diagnosed at higher stage.

We review the case of a 76-year-old male, with low grade papillary urothelial carcinoma associated with nested variant of urothelial carcinoma.

## IS TISSUE THE ISSUE? OPTIMISING THE REFERRAL PATHWAY OF GLIOMAS FOR CGH-SNP ARRAY

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**Background:** cIMPACT-NOW guidelines state optimal assessment of WHO grade II/III gliomas requires analysis of copy number variations (CNVs). SydPath has pioneered a referral pathway for affordable, validated comparative genomic hybridisation single nucleotide polymorphism (CGH-SNP) array for CNV analysis of gliomas.

**Aim:** To optimise the referral pathway of gliomas for CGH-SNP array, enabling scalability to external centres.

**Methods:** Consecutive adult patients with glial neoplasms received at SydPath over two years to June 2019 were retrospectively analysed. Referral processes and outcomes of CGH-SNP array were recorded.

**Results:** Of 77 patients with glial neoplasms, six IDH-wild-type gliomas with grade II/III morphology were upgraded to grade IV following CNV analysis as per cIMPACT-NOW guidelines. Identification of high-grade morphology on subsequent histological examination enabled timely cancellation of four tests. Ten cases with available tissue were not referred, all prior to cIMPACT-NOW guideline publication. Thirteen cases lacked tissue for referral; only four tests failed due to insufficient tissue.

**Discussion:** Referral for CGH-SNP array provided clinically relevant CNV analysis of gliomas. Improved efficiency can be achieved with our optimised tissue and case selection criteria, including complete morphological and IDH status assessment prior to testing. This will enable referral from external centres, allowing widespread adoption of cIMPACT-NOW guidelines using an affordable, validated test.

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## EXTRANODAL ROSAI-DORFMAN DISEASE, A RARE DIAGNOSIS IN SOFT TISSUE PATHOLOGY

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Rosai-Dorfman disease is a rare non-malignant proliferation of histiocytes typically involving the cervical lymph nodes. A small subset of cases present with extranodal manifestations. Case series and individual case reports discuss occurrences of Rosai-Dorfman disease in virtually every anatomical site. We discuss a case of a 63-year-old male presenting with multiple raised nodular lesions on multiple cutaneous sites. Biopsy of these lesions ultimately suggested a diagnosis of cutaneous extranodal Rosai-Dorfman disease. We discuss the histopathological, clinical and immunohistochemical features that allowed for this diagnosis. This is a rare pathological diagnosis with variable manifestations. Clinical suspicion and recognition of its classical histological features are essential for correct diagnosis, and in avoiding unnecessary treatment.

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## CLEAR CELL CARCINOMA OF THE HARD PALATE – A CASE REPORT

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Salivary gland neoplasia is a challenging area of diagnostic surgical pathology due to significant histomorphologic overlap between benign and malignant entities with the resultant risk of misdiagnosis and inappropriate treatment.

Clear cell carcinoma is a rare infiltrative, low grade salivary gland neoplasm with an indolent clinical course, little metastatic potential and a propensity for local recurrence.

This case reports a 32-year-old woman who presented with a 1-year history of a mass on her hard palate. The clinical history, histomorphologic, immunophenotypic and molecular features are described and discussed with emphasis on diagnostic pitfalls.

## A LIPOMATOUS VARIANT OF SCROTAL ANGIOMYOFIBROBLASTOMA – A CASE REPORT

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Angiomyofibroblastoma-like tumour of the male genital tract is a rare benign mesenchymal tumour arising in the scrotum, perineum or inguinal region. It is usually seen in females of reproductive age. Clinical presentation has no pathgnomic findings. In the largest series to date, Iwasa and Fletcher[1] reported 25 cases in men with the mean age being 52 years. This case report is of an 18-year-old male with a scrotal angiomyofibroblastoma that was 35 cm in maximum dimension, in the paratesticular tissue separate from testicular parenchyma. Macroscopically, the lesion was a fibrous, fatty and mucoid mass. Histologically, it showed a lobulated pattern of epithelioid and spindle cells arranged around various calibre vessels. Other differential diagnoses including myxoid liposarcoma and rhabdomyosarcoma were ruled out with the help of FISH studies for FOX 10 and PAX3. DDIT3 and FUS were negative. To date, in all open-access literature, there has only been 34 cases reported of this rare tumour, of which there is only one reported case <20 years of age; this will be the second case in the <20 age group in men. The poster will describe the clinical presentation, imaging, macroscopic findings, histology and immunohistochemistry along with a literature review.

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## EXTRAMAMMARY PAGET'S DISEASE WITH LYMPH NODE METASTASIS – ROLE OF IMMUNOHISTOCHEMISTRY AND DIAGNOSTIC PITFALLS

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Extramammary Paget's disease (EMPD) is an uncommon skin disease that is limited to the epidermis but has the potential to invade the dermis and metastasise. We describe a case of primary scrotal EMPD with lymph node metastasis.

A 78-year-old male presented with an irregular thickening of the right scrotal skin with lymphadenopathy. Fine needle aspiration (FNA) of the inguinal lymph node revealed a poorly differentiated metastatic malignancy. Metastatic melanoma and poorly differentiated adenocarcinoma were considered in the differential diagnosis.

Subsequently, an incisional biopsy of the scrotal lesion showed epidermal acanthosis, acantholysis and elongation of the rete ridges with atypical cells. The tumour cells were diffusely positive for CK 5/6 and CK7, and p63 highlighted the basal cells. Acantholytic squamous cell carcinoma was our initial diagnostic consideration. However, in view of coexpression of CK5/6 and CK7, and a metastatic lymph node, the case was reviewed and additional immunohistochemical stains were performed. The lesional cells were immunoreactive for mCEA, BerEP4 and GATA3, and negative for CK20 and MelanA stains.

Immunohistochemistry was helpful in arriving at the final diagnosis of EMPD. EMPD although rare, should also be considered in the differential diagnosis of metastatic poorly differentiated adenocarcinoma in appropriate clinical settings.

## PARATHYROID ADENOMA WITH PROMINENT LYMPHOCYTIC INFILTRATION: A POTENTIAL PITFALL IN FROZEN SECTIONS AND CYTOLOGY REPORTING

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**Introduction:** Parathyroid adenoma with prominent lymphocytic infiltration is rare, with only 12 cases reported in the English scientific literature. All these cases were not related to synchronous autoimmune or IgG4-related disease and presented clinically with primary hyperparathyroidism.
**Case presentation:** A 65-year-old woman presented with hypercalcemia and a neck mass, suggestive of parathyroid adenoma. She underwent parathyroidectomy and histopathological examination of the specimen showed a hypercellular parathyroid nodule comprising mature lymphoid cells admixed with parathyroidal chief cells. A comprehensive immunohistochemistry panel confirmed the benign nature of the lesion. The patient remains asymptomatic a year after the surgery.
**Discussion:** Parathyroid adenoma with prominent lymphocytic may be misdiagnosed as a lymph node at frozen section or cytology smears by an unsuspecting pathologist or cytologist, if the lymphoid component is predominant on the slide examined. Additionally, the morphology could be misinterpreted as a metastasis of parathyroid carcinoma into a peri-thyroidal lymph node. For this distinction, correlation with clinical and radiological findings is crucial and clues to adenoma include presence of a rim of uninvolved parathyroid parenchyma, low mitotic activity (<5%) and positive staining for parafibromin, bcl-2 and MDM2 on immunohistochemistry.

## EOSINOPHILIC SOLID AND CYSTIC RENAL CELL CARCINOMA WITH MONOSOMY OF CHROMOSOMES X AND 3

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**Introduction:** Eosinophilic solid and cystic renal cell carcinoma (ESC-RCC) is a recently described sporadic counterpart to tuberous sclerosis complex (TSC)-associated RCC that is not yet included in the 2016 World Health Organization (WHO) classification of renal neoplasms. The first series was reported in 2016 and, to date, just over 60 cases have been reported in the literature. The tumour is often asymptomatic and almost exclusive to female patients with a median age of 57 years. ESC-RCC constitutes approximately 0.2% of all renal cell carcinomas and most cases reported have shown a better prognosis than clear cell renal cell carcinoma. About 10% of reported cases have metastasised with four of them dying of the malignancy.
**Case report:** A 63-year-old woman presented with an incidental 40 mm, ill-defined nodule in the lower pole of the right kidney. Partial nephrectomy was performed and gross examination of the tumour showed a well-circumscribed neoplasm with solid-cystic cut surface. Microscopy revealed acinar and nested architecture with the neoplastic cells showing intracytoplasmic stippling ('Leishmania bodies-like') within the deeply eosinophilic cytoplasm. Macro- and micro-cysts in other fields were lined by hobnailed, eosinophilic tumour cells. Immunohistochemically, the neoplasm showed strong and diffuse staining for CK20 and AE1/AE3. CK7 was negative. Karyotyping of tumour cells showed previously unreported monosomy of chromosomes X and 3. The patient remains alive and well, without evidence of disease progression a year after surgery.

## CLINICAL UTILITY OF THE TFE3 BREAK-APART FLUORESCENCE *IN SITU* HYBRIDISATION (FISH) ASSAY IN MALIGNANT TUMOURS

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TFE3 break-apart FISH probe, located on Xp11.23 is designed to detect TFE3 gene rearrangements in many tumours including renal cell carcinomas (RCC) and alveolar soft part sarcoma (ASPS), and some variants of perivascular epitheloid cell neoplasm (PEComa). FISH test may be deployed as an adjunct tool for diagnosis. Generally, the FISH probe will give a typical FISH signal pattern but unusual patterns can also be encountered. We aimed to evaluate the break-apart FISH patterns and incidence of TFE3 gene rearrangements in soft tissue tumours such as RCC and ASPS.
As the morphological assessment may have overlapping features, TFE3 FISH test is a useful ancillary tool in the confirmation or exclusion of differential diagnosis.

## MALIGNANT SOLITARY FIBROUS TUMOUR OF UTERINE CERVIX, MIMICKING HIGH GRADE ENDOMETRIAL STROMAL SARCOMA

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Solitary fibrous tumour (SFT) is an uncommon mesenchymal neoplasm of fibroblastic origin which can be found in any organ, however, its occurrence in the female genital tract (FGT) is extremely rare. To date, around 50 cases of SFTs originating in FGT have been reported (as case report or small case series) of which 12 are in the uterus and 5 in the cervix. These are rare tumours and should be considered in the differential diagnosis of spindle cell lesion in the female genital tract when the immunohistochemistry is not supportive of common lesions. We are reporting a case of a malignant SFT involving primarily the cervix and extending into the isthmic uterus, involving the bladder, presenting with recurrence and distant metastasis to the lung and mesentery.

## OLFACTORY NEUROBLASTOMA WITH DIVERGENT DIFFERENTIATION

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Olfactory neuroblastoma (ONB) is an uncommon malignant neoplasm of the nasal cavity that arises from olfactory epithelium. Rare cases of focal histologic changes of divergent cell populations have been reported in ONB. However, these changes are seen mainly in tumours treated with chemo radiation or with distant metastases.

To date, only four cases of ONB associated with non-neuroendocrine tumours have been reported. We describe a case of ONB with divergent differentiation in a 68-year-old male who presented with a nasal cavity mass extending into the brain and base of the skull. The pathology showed the presence of two distinct cell populations showing features of high grade ONB and poorly differentiated / undifferentiated carcinoma with focal abrupt keratinisation. The differential diagnosis included NUT carcinoma and teratocarcinoma which were excluded since the immune markers and morphology were not supportive.

## EPITHELIOID SCHWANNOMA – A RARE VARIANT OF A COMMON LESION

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Epithelioid schwannoma is a rare variant of schwannoma arising in dermis or subcutis of limbs as a circumscribed lesion. Less than 100 cases of epithelioid schwannoma have been reported so far. They are considered benign despite the presence of atypical features such as nuclear atypia.
We present a case of a 26-year-old female who presented with a left posterior thigh lump with the clinical diagnosis of lipoma. The microscopic examination, however, is in keeping with epithelioid schwannoma.
This case demonstrates a very rare variant of a common lesion which can mimic few other soft tissue tumours including some malignant tumours. Hence, this may help pathologists to become familiar with this entity and avoid potential wrong diagnoses.

## NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA – CASE REPORT IN A 6 YEAR OLD

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Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL) is a rare subtype of Hodgkin lymphoma in children accounting for 10–20% of paediatric cases of Hodgkin lymphoma. In the paediatric population the reported median age at diagnosis is 13 years with a male preponderance and patients typically presenting with low stage disease.[1–3] It has a generally good prognosis with less aggressive treatment strategies compared to classical Hodgkin lymphoma. Histologically it is characterised by the presence of atypical Reed-Sternberg cells known as the lymphocytic and histiocytic variant (L&H) which have a vesicular polylobulated nucleus which is referred to as popcorn cells. A 6-year-old boy presented with a single rubbery lymph node mass in the neck with no other systemic symptoms. An excisional biopsy of the node was performed. Microscopically there was a nodular proliferation of small lymphocytes and scattered popcorn cells with the typical morphology and immunohistochemistry of L&H cells. No further treatment was performed and the patient was for regular follow up. One year later the patient is well and free from recurrence.

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## *ASPERGILLUS* AORTITIS IN A BIOPROSTHETIC AORTIC ROOT AT POST MORTEM

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*Aspergillus terreus* is a rare cause of endocarditis. Fungal endocarditis represents less than 2% of all cases of endocarditis and of these 20–25% are represented by *Aspergillus* species.[1] *Aspergillus terreus* is especially rare with only one reported case in the literature between 1950–2010.[2] Immunocompromise and previous cardiac surgery are well recognised risk factors for fungal endocarditis.[3] Complications are common and include embolisation to pulmonary, ophthalmic, renal, and other arterial systems. This is a report of an 80-year-old male with a history of *Aspergillus terreus* aortitis treated with aortic root replacement and coronary artery bypass grafting that subsequently died of culture negative sepsis. He was found at autopsy to have extensive *Aspergillus terreus* endocarditis involving a bio prosthetic aortic root replacement complicated by thrombosis of the left renal artery.

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## INVASIVE BREAST CARCINOMA OF NO SPECIAL TYPE WITH OSTEOCLAST-LIKE STROMAL GIANT CELLS: A CASE REPORT

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Invasive breast carcinoma of no special type (NST) with osteoclast-like stromal giant cells (OSGCs) is a rare tumour type. The literature available for this entity is predominantly limited to case reports and small retrospective studies. The patient is a 46-year-old female who presented to her GP with a 4-month history of a palpable mass in the left breast. An abnormality seen on a mammogram was confirmed to be an invasive cancer on core biopsy. She subsequently underwent a wide local excision of the lesion and sentinel lymph node biopsy. Histopathology showed a grade 2 invasive breast carcinoma NST with OSGCs and focal lymphovascular space invasion. Sentinel lymph node biopsy demonstrated involvement of one in seven lymph nodes with minimal extra-nodal spread. Immunohistochemistry showed a strongly ER/PR positive, HER-2 negative,

phenotype. The patient declined chemotherapy due to concerns about tolerability, and instead elected for adjuvant radiotherapy and endocrine therapy. A search of the Mater Hospital Kestral Pathology Laboratory System identified 3 further cases between 2009 and 2019. In this case report, we describe the morphological and immunohistochemical features of this rare but interesting entity.

## HISTOPATHOLOGIC FEATURES OF COLCHICINE TOXICITY IN THE GASTROINTESTINAL TRACT, A REVIEW OF 6 CASES

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**Background:** Colchicine is an alkaloid drug predominantly used in the treatment and prevention of gout. It has a narrow therapeutic index and toxicity may be associated with gastrointestinal symptoms. Characteristic histopathologic features may be identified in gastrointestinal biopsies.
**Aim:** To describe the histopathologic features of colchicine toxicity in the gastrointestinal tract.
**Methods:** Cases were identified using a database search at Envoi Pathology (2007–2019). Demographic data, clinical history, endoscopic features and histopathologic findings (presence of acute and chronic inflammation, ring mitoses and apoptosis) were documented.
**Results:** Thirteen gastrointestinal biopsies from six patients on oral colchicine therapy were included for analysis. Five patients were male and one was female. The mean patient age was 66 years (range 31–79). Treatment was for gout ($n$=5) and pericarditis ($n$=1). Two patients presented with symptoms of colchicine toxicity, including severe diarrhoea ($n$=1), nausea and abdominal pain ($n$=1). Four patients did not have clinically suspected colchicine toxicity. Histopathologic features included ring mitoses and chronic inflammation with eosinophils in all biopsies. Crypt apoptosis was present in four cases with associated neutrophils in one case.
**Conclusion:** Colchicine toxicity is characterised by distinct histopathologic features in gastrointestinal biopsies and may be an incidental finding in patients without clinical symptoms.

## ENDOMETRIOID BORDERLINE TUMOUR OF THE OVARY ARISING FROM ENDOMETRIOSIS – A CASE REPORT

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Endometrioid borderline tumour of the ovary is rare and constitutes 0.2% of all epithelial ovarian tumours. These tumours are considered as low malignant potential. These tumours often arise in association with endometriosis and endometrioid adenofibroma and often coexists with endometrial pathologies. The prognosis for ovarian endometrioid borderline tumour is excellent including that with features of intraepithelial carcinoma and microinvasion. Here, we describe a case of 45-year-old female with a history of endometriosis who underwent bilateral oophorectomy. Her preoperative CA-125 was 152 (KU/L) (ref range <36) and CA19.9 3073 KU/L (ref range <38). Macroscopically, there was a single cyst without solid or papillary areas. Microscopic examination revealed glandular proliferation with endometrioid morphology resembling complex endometrial hyperplasia without cytologic atypia and stromal invasion. There are foci of endometriosis and transitional and mucinous metaplasia. These features were diagnostic of endometrioid borderline tumour arising from endometriosis.

## FOAMY GLAND VARIANT OF PROSTATIC ADENOCARCINOMA (FGVPA), DIAGNOSTIC PITFALLS: A CASE REPORT AND LITERATURE REVIEW

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A transurethral resection of prostate (TURP) specimen was received from a 72-year-old male who presented with a recent history of urinary tract infection and increased serum prostate specific antigen (PSA) of 15 ng/mL.
There was an atypical glandular proliferation of which a predominant population demonstrated abundant pale xanthomatous cytoplasm with small hyperchromatic nuclei and inconspicuous nucleoli. A minor component of conventional prostatic acinar adenocarcinoma was identified focally in the background. Immunohistochemistry was used to confirm the diagnosis of adenocarcinoma.
FGVPA is a rare variant, with foamy cytoplasm due to intracytoplasmic vesicles not lipid or neutral mucin, and usually with small pyknotic nuclei with minimal atypia. Gleason scoring is performed by the underlying architectural pattern. Immunohistochemistry of basal cell markers and AMACR are often used to confirm a diagnosis of prostatic adenocarcinoma; however, it is to be noted that variants of prostate cancer including FGVPA are labelled with AMACR in only 60–70% of cases. It is important for the pathologist to be aware of FGVPA as in its pure form can easily be missed especially on needle core biopsy. The differential diagnoses of benign mimics with clear cytoplasm include xanthoma, Cowper's glands, clear cell cribriform hyperplasia and mucinous metaplasia.

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## A COLLISION TUMOUR OF BASAL CELL CARCINOMA AND MELANOMA – REPORT OF TWO CASES

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Basal cell carcinomas (BCC) are known to co-exist with other cutaneous lesions, but the collision of BCC with malignant

melanoma is rare. The most common combinations are BCC with squamous cell carcinoma, BCC with seborrhoeic keratosis and BCC with neurofibroma. The prognosis of each tumour must be considered separately. Melanoma colonising the BCC should still be considered as 'in situ' and not as invasive if no atypical melanocyte is found outside the BCC nests.

Here we report two cases of BCC associated with melanoma. In the first case, BCC was associated with melanoma *in situ*. The atypical melanocytes were confined to the nests of basal cell carcinoma. In the second case, BCC was admixed with invasive melanoma. In this case, the atypical melanocytes were present within the BCC nests, but were also identified within the dermis, outside the nests of BCC. The presence of two coexisting neoplasms was confirmed on immunohistochemistry.

In addition, we compared these cases with a pigmented BCC showing benign melanocytes colonising the tumour cell nests.

The key diagnostic features of this collision tumour, its pathogenesis, differential diagnosis and its prognosis will be discussed.

## MINERAL OIL INDUCED SCLEROSING LIPOGRANULOMA OF THE PENIS – A CASE REPORT

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Injection into the subcutaneous tissues of the penis for augmentation has been practiced throughout history. With the recognition of complications and sequalae the practice has died out in the developed world. However, it is still practiced in parts of Europe and Asia today, though the extent of the practice is unknown, and today's published literature may only scratch the surface. We report a case of mineral oil induced sclerosing lipogranuloma of the penis in a 55-year-old male from Papua New Guinea who presented with a mass involving the penile prepuce and shaft skin. This case demonstrates the diagnostic challenges and interesting pathology seen in developing countries. The treatment of choice is radical excision of the lesions with skin grafts.

## A RANT ABOUT A SANT: A RARE MIMIC OF SPLENIC HAEMANGIOMA

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Sclerosing angiomatoid nodular transformation (SANT) of the spleen is a rare, benign, vascular lesion with characteristic histological features. Often an incidental finding, full excision of the lesion has been shown to be curative. We describe a case of SANT in a 35-year-old woman who presented with a purported splenic haemangioma with atypical imaging features including an uncharacteristic enlargement over a two-year period. Gross examination of the splenectomy specimen revealed a circumscribed 42 mm white, lobulated mass with prominent central sclerosis and dilated vascular spaces at the periphery. Histological examination showed a hyalinised lesion with a nodular architecture imparted by nodules of small capillary channels with red cell extravasation, and scattered admixed chronic inflammatory cells. A rare lesion of indeterminate aetiology, SANT remains a curiosity and an essential diagnostic consideration among vascular lesions of the spleen with features not typical of haemangioma.

## A REVIEW OF BRAIN BANK QUALITY ANALYSIS PROCEDURES FOR HUMAN POST-MORTEM TISSUE SAMPLES

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There are currently 139 international brain bank facilities which collect, store and provide nervous system samples for research purposes. The human post-mortem brains within these brain banks have underpinned the basic understanding of disorders affecting the central nervous system (CNS) and continue to support ongoing work in the fields of neuropathology and neuroscience. Without such services there would be major limitations in the capability of neuroscience research to accurately translate findings from animal models to those in human subjects. As a result, there are tens-of-thousands of published research articles which utilise samples from established brain banks for research, with the goal of gaining a better understanding of the aetiology, pathogenesis and mechanisms of progression of neurological diseases as well as providing advancements in diagnosis and treatments. Contrastingly, there has been little work done to compare the quality control analysis protocols currently being used in different brain banks; including which neurological biomarkers and proteins are commonly analysed. This literature review aims to identify which sampling protocols and analytical methods are currently used in the literature to assess the quality analysis of neurological tissue and to compare the standardisation of these procedures between different brain banks.

## MYOID GONADAL STROMAL TUMOUR: A CASE REPORT

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Myoid gonadal stromal tumour is an emerging entity composed of spindle-shaped cells showing features of smooth muscle and gonadal stroma. These are rare tumours (<10 described in the literature), occur over a wide age range (4–59 years), but are typically found in middle-aged men,[1] with a median age of 41 years, who present with a mass.

Here we report a case of a 47-year-old man, NZ European/Pakeha, who presented with 5 weeks of tenderness in the right testicle.

Ultrasound scan showed an incidental, but suspicious 9 mm solid hypoechoic mass in the mid testis and he came forward for orchidectomy. Macroscopic findings revealed a 10 mm well circumscribed, pale soft, solid lesion within the hilar region of the testis. Microscopic examination showed an unencapsulated tumour, centred within the rete testis, composed of densely packed spindled cells which arranged in interweaving fascicles

within collagenous stroma. The spindle cells have uniform tapered nuclei and ill defined cytoplasm. Only one mitotic figure was identified. No lymphovascular or perineural invasion was seen.

Immunohistochemistry expressed markers of smooth muscle actin (SMA) and S-100. Inhibin showed weak positive staining. The tumour cells were negative for CD99, CD34, desmin and broad spectrum cytokeratin.

The histopathology and immunohistochemistry was consistent with a myoid gonadal stromal tumour and this is distinctly different from other sex cord-stromal tumours.

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## 'FIJI BELLY' CULMINATING IN COLECTOMY: A CASE REPORT FROM NEW ZEALAND WITH BRIEF REVIEW OF LITERATURE

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Traveller's diarrhoea due to *Entamoeba histolytica* is a worldwide problem due to growing popularity of international travel to exotic locations. Acute fulminant or necrotising amoebic colitis is a rare but potentially fatal complication of intestinal amoebiasis, reported in only less than 0.5% of cases. Misdiagnosis as inflammatory bowel disease can result in inappropriate steroid therapy which can worsen the amebiasis.

We report the case of a 55-year-old male who became unwell after travelling to a rural area in Fiji. He was initially treated as diverticulitis and subsequently had appendectomy due to suspected appendicitis. Symptoms persisted and subsequent colonic biopsies revealed features of acute colitis and revealed no microorganisms. The patient was treated for inflammatory bowel disease with Pentasa and prednisone, but continued to deteriorate. Fulminant colitis was suspected based on imaging findings and a subtotal colectomy was performed. Histopathological examination revealed flask shaped ulceration and areas of necrosis containing abundant microorganisms morphologically consistent with *Entamoeba*. The patient recovered well after antiamoebic medication.

A high index of suspicion is essential for early diagnosis of amoebic colitis to prevent misdiagnosis, inappropriate steroid treatment and prevent complications such as acute necrotising colitis.

## CHARACTERISING THE IMMUNE RESPONSE IN BRAF V600E AND BRAF WILD TYPE MELANOMA

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**Background:** BRAF V600E mutation may confer immune evasion through upregulating immunoregulatory cytokines and decreasing expression of melanoma differentiation antigens, thus being a target in cancer immunotherapy.[1]

**Aim:** To analyse the lymphocytic immune response in BRAF V600E and BRAF wild type (WT) primary melanoma.

**Methods:** Cases were selected through the Victorian Melanoma Service and the Molecular Laboratory Database, Alfred Health. BRAF V600E ($n$=11) and BRAF WT ($n$=11) primary cutaneous melanoma were matched according to subtype and Breslow thickness. Density and distribution of infiltrating lymphocytes were analysed following immunoperoxidase studies using CD3, CD4, CD8 and CD20 antibodies performed on serial sections, quantified by Image J analysis, and analysed using a one-way ANOVA with Tukey's multiple comparisons test.

**Results:** CD8+ T cells were the predominant infiltrating cell type [mean density and 95% CI (cells/mm$^2$) WT: 325 (200–450) vs V600E: 480 (317–643)], while infiltration with CD4+ T cells and CD20+ B cells were less prominent as compared to CD8+ T cells ($p$<0.01). The mean difference of cell density was not significantly different between matched BRAF V600E and WT melanomas.

**Conclusion:** There was no significant difference in the cell type, density or distribution of the immune infiltrate between matched BRAF V600E and WT melanomas.

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## ORBITAL IgG4 RELATED DISEASE IN A PATIENT WITH IRKA VARIANT GENE: A CASE REPORT

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To our knowledge there are less than 30 reported cases of IgG4 related disease (IgG4RD) in the paediatric population.[1]

We report a case of orbital IgG4-RD in a 14 month male infant with IRKA variant gene. He underwent an incisional biopsy for exophthalmos with a clinical suspicion of rhabdomyosarcoma. Prior to this admission the patient had multiple episodes of infection with possible immunodeficiency. Frozen sections demonstrated fibroinflammatory tissue with no evidence of malignancy. Paraffin sections revealed fragments of a mass with extensive fibrosis and a focally dense lymphoplasmacytic infiltrate with obliterative phlebitis, and increased absolute and relative numbers of IgG4+ plasma cells, in keeping with IgG4-RD. Immunosuppressive treatment was initiated but his clinical course was complicated by multiple infections including Pseudomonal meningoencephalitis, Candidaemia and CMV viraemia (PCR positive), and by intestinal pseudo-obstruction likely IgG4 related. In view of multiple infections and early presentation with an immune mediated disease, immunodeficiency gene panels were performed. An IRKA variant gene was detected, which was consistent with patient`s phenotype.

According to current literature, there is not a specific association between IgG4-RD and immunodeficiency. This case demonstrates IgG4-RD at an earlier age than usual can be an unusual presentation of an immune dysregulatory/immunodeficiency disease.[2]

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## MICRONODULAR THYMOMA WITH LYMPHOID STROMA – A CASE REPORT

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We report the case of a 68-year-old male with a background history of smoking, who presented with left sided abdominal pain. A CT scan of abdomen was performed which showed a small 6mm pulmonary nodule in right lower lobe. A subsequent CT chest performed 4 months after the index CT scan showed no change in the size of previous nodule but an additional 5 mm nodule, multiple calcified and non-calcified pleural plaques (presumably related to work in construction industry in 1970s) and more significantly a 35 mm well circumscribed solid mass in anterior mediastinum with no invasion into adjacent structures. There was no past history of any malignancy. The clinic/radiological differential diagnosis was thymic tumour, lymphoma or a metastatic malignancy. The core biopsy showed features of a thymoma and the histology and immunophenotype of subsequent resection specimen confirmed the tumour to be a micronodular thymoma with lymphoid stroma. Micronodular thymoma with lymphoid stroma is a very rare subtype of thymoma, accounting for about 1% of all cases. The tumour is usually diagnosed as stage I/II disease. There have been no reports of recurrences, distant metastases or tumour related deaths.

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## GLOMANGIOMA OF THE LUNG – A RARE DIFFERENTIAL DIAGNOSIS OF A PRIMARY LUNG TUMOUR

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We report the case of a 77-year-old male who presented with exertional dyspnoea on a background of history of smoking. A solitary lung mass was found on subsequent CT scan which was PDG avid on PET consistent with malignancy. Initial core biopsies suggested features of a glomangioma. Histopathology of the subsequent surgical resection confirmed the tumour to be a benign glomangioma, which was completely excised. The immunohistochemical phenotype was considered diagnostic of a benign glomangioma, an extremely rare entity in lung.

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## A NOVEL CASE OF A BENIGN PAROTID ADENOMA WITH DIVERGENT FEATURES

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**Introduction:** The parotid gland is the most frequent site of salivary gland tumours, most of these are benign.
**Case:** We present a novel case of an 86-year-old gentleman with a benign adenoma showing divergent features. He presented with a painless swelling in his left parotid gland, which showed scant oncocytic cells on fine needle aspiration. Parotidectomy was then undertaken for definitive diagnosis and treatment. The surgical specimen showed a 43 mm well circumscribed, heterogeneous tumour expanding the parotid gland. There were solid tan areas intermixed with friable yellow nodules in a background of adipose tissue. Microscopic assessment showed sheets, small nests and single oncocytic cells scattered throughout a background of mature adipose tissue. There were expanses of lymphoepithelial tissue with squamous metaplasia and variable cystic change alongside sebaceous metaplasia, and Warthin's tumour-like areas. Mitotic activity, necrosis and malignancy were not seen.
**Conclusion:** Our case is unique as it describes a benign adenoma demonstrating multiple histological tumours sub-types including sebaceous lymphadenoma, Warthin's tumour, oncocytoma, sialolipoma / lipoadenoma. Similar cases, with such wide morphology, have not previously been described in the literature. Although exact prognosis is not known, it is thought likely to behave in a benign fashion.

## MAMMARY MYOFIBROBLASTOMA: A CASE REPORT OF A RARE BENIGN TUMOUR IN AN ELDERLY MAN

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Mammary myofibroblastoma is a rare benign stromal tumour, predominantly occurring in menopausal women and older men. We present a case of a 73-year-old man with a tender right breast lump. He underwent a core biopsy assessment followed by a wide local excision. The lesion was a well circumscribed spindle cell nodule with interlacing fascicles and intervening collagen. The cells are elongate with pale cytoplasm and regular nuclei. There are scattered cells showing mild pleomorphism. Mitoses are uncommon. Multiple immunohistochemical stains were performed which were the key to diagnosis of myofibroblastoma. Completely excised lesions are not known to recur.

## INVASIVE CARCINOMA OF NO SPECIAL TYPE WITH FOCAL SEBACEOUS DIFFERENTIATION IN BREAST

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Sebaceous carcinoma which is defined as breast carcinoma with prominent sebaceous differentiation in no less than 50% of cells is very rare.[1] Breast carcinoma with sebaceous differentiation is also very rare with only 9 cases reported in the literature to our knowledge.[2,3] Sebaceous differentiation has been reported in association with invasive ductal carcinoma, adenoid cystic carcinoma and metaplastic carcinoma.[2] Hormone receptors and lymph node status vary between cases but none of the cases reported positive HER2 status. Here, we report a case of invasive carcinoma of no special type with focal sebaceous differentiation which is ER positive, PR positive, HER2 negative with two involved sentinel lymph nodes.

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## EBV-POSITIVE DIFFUSE LARGE B CELL LYMPHOMA, NOT OTHERWISE SPECIFIED IN A MAN WITH CROHN'S DISEASE

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EBV-positive diffuse large B cell lymphoma (DLBCL), not otherwise specified (NOS) is an uncommon aggressive lymphoma subtype associated with a worse prognosis in the elderly.[1,2] EBV-positive DLBCL has been reported in <5% of Western patients with no documented predisposing immunodeficiency.[2] There are many lymphoproliferative disorders associated with EBV infection such as lymphomatoid granulomatosis, plasmablastic lymphoma, DLBCL associated with chronic inflammation, EBV positive mucocutaneous ulcer, primary effusion lymphoma, and classical Hodgkin lymphoma.[1] EBV-positive DLBCL, NOS is a diagnosis of exclusion and clinicopathological correlation is required to differentiate between these differential diagnoses. Patients with inflammatory bowel disease (IBD) on immunosuppressive medications are at increased risk of developing Hodgkin and non-Hodgkin lymphomas and EBV has been reported in both.[3] Here, we report a case of EBV-positive DLBCL, NOS involving the bowel wall associated with perforation and partial involvement of one lymph node in a 73-year-old man with Crohn's disease.

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## EMBRYONAL RHABDOMYOSARCOMA – A CASE SERIES

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Rhabdomyosarcoma is a malignancy derived from primitive mesenchyme with propensity toward myogenesis, which is the most common soft tissue malignancy of childhood. There are four histologic subtypes: embryonal rhabdomyosarcoma (ERMS), alveolar rhabdomyosarcoma, spindle cell/sclerosing rhabdomyosarcoma and pleomorphic rhabdomyosarcoma. ERMS includes the typical, dense and botryoid patterns of rhabdomyosarcoma. ERMS presents as a mass lesion in the head and neck region and genitourinary system. The exact cause of rhabdomyosarcoma is not known. There is no evidence of correlation between ERMS and any specific gene fusions. Diagnosis and prognosis of rhabdomyosarcomas are determined by histologic features, presence of anaplasia, which in ERMS is associated with worse outcome, fusion status and clinical stage.

We present a case series of three paediatric patients who were diagnosed with ERMS at Sydney Children's Hospital, as follows:

- Case 1: 17-month-old female with clitoral ERMS metastatic to an inguinal lymph node.
- Case 2: 15-year-old male with testicular ERMS.
- Case 3: 15-year old male with prostatic ERMS.

We highlight the clinicopathologic features of rhabdomyosarcoma and demonstrate how to differentiate this malignancy from other paediatric small blue cell tumours.

## METASTATIC GLIOBLASTOMA FOLLOWING REDO BILATERAL LUNG TRANSPLANTATION – A CASE REPORT

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Extracranial metastases of glioblastoma are uncommon, with those occurring post solid organ transplantation being an extremely rare occurrence.

This case study reports a 67-year-old male with a history of bilateral lung transplantation, presenting with significant weight loss and associated worsening shortness of breath. A CT scan of the chest was performed, showing a 3.8 cm lesion within the right upper lobe, with multiple accompanying grossly enlarged bilateral lower mediastinal and hilar lymph nodes. A subsequent core biopsy of the lesion demonstrated an atypical spindle cell lesion, with immunohistochemical stains and specialist opinion in keeping with metastatic glioblastoma. We will discuss the diagnosis and differentials, and review the literature of this rare occurrence post lung transplantation.

## LANTHANUM DEPOSITION IN THE GASTRIC MUCOSA

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Lanthanum carbonate is a phosphate binding agent used for the management of hyperphosphataemia in patients with chronic renal failure. Cases of lanthanum deposition within the gastrointestinal tract, first recognised in gastric mucosa, have been reported since 2015. However, lanthanum deposition remains a relatively novel entity with potential for under-recognition and confusion with a variety of other processes. This case study reports a case of lanthanum deposition involving the gastric mucosa in a renal transplant patient. Biopsies taken from the gastric antrum demonstrated appearances of reactive gastropathy together with an accumulation of histiocytes, including occasional multinucleated forms, containing deposits of amphophilic to brown finely granular to coarse material within the superficial lamina propria. The differential diagnosis included gastric mucosal calcinosis, iron therapy-induced gastric injury, an infectious aetiology, or the accumulation of exogenous materials related to medications including resins/crystalloids. Investigation of the patient's medication history revealed oral lanthanum carbonate use; this finding taken in conjunction with the morphologic findings was most in keeping with lanthanum deposition. The identification of lanthanum deposition in gastric biopsies is important as the long-term consequences are currently unknown, and the use of this medication is increasing.

## HAEMOSIDEROTIC FIBROLIPOMATOUS TUMOUR – A CASE REPORT

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In our case we describe a 46-year-old woman who presented with 6 months of right dorsal foot swelling. Examination revealed sharp aching pain over the dorsal first metatarsophalangeal joint. Multi-modality imaging with plain radiography, CT and ultrasound showed a heterogenous solid subcutaneous mass of the dorsal forefoot. Subsequent MRI reported dilated slow flow vascular spaces interposed with fat, favouring haemangioma. Core biopsy performed favoured spindle cell lipoma.

Progressive growth of the lesion with functional impairment led to excision at 18 months follow up. Sections of the excision specimen showed mature fat with spindle cell proliferation and myxoid areas. Fibrotic and collagenous appearance were identified. The spindled cells formed fascicles and nodular aggregates between the adipocytes. Spindle cells were atypical and showed haemosiderin staining in keeping with haemosiderotic fibrolipomatous tumour (HFLT).

HFLT is a rare mesenchymal tumour. As seen in this case, it is locally aggressive with an associated 30–50% recurrence rate. Immunohistochemistry of the spindle cell component is typically positive for CD34 and calponin. The chromosomal translocation t(1;10)(p22;q24) with the fusion gene TGFBR3-MGEA5 is associated with this lesion, as well as pleomorphic hyalinising angiectatic tumours and myxoinflammatory fibroblastic sarcoma.

## HUNTING FOR SNAKES AND RUBIES

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**Background:** Digital pathology is increasingly part of diagnostic workflow.[1] RCPA Anatomical Pathology small biopsy slide exam already uses whole slide images (WSI), with plans to similarly digitise the cytopathology slide exams. Granulocytes are historically difficult to assess on WSI.[1] Chronic rhinosinusitis (CRS) is a heterogenous inflammatory condition. CRS subtype is diagnosed via histopathology.[2] Targeted biologic therapies are being studied for eosinophilic CRS, the most common and severe subtype in Australia, and accurate endotyping is important. Thus, on glass slides and WSI, differentiating eosinophils, with their bilobed nuclei and ruby-red cytoplasmic granules, from neutrophils, with their snake-like multilobate nuclei, is required to guide management.

**Aims:** To quantify eosinophil number on sinonasal tissue WSI, and validate WSI against the equivalent glass slides.

**Methodology:** On WSI, eosinophils were independently counted by two independent assessors. An anatomical pathologist validated eosinophil counts on WSI against equivalent glass slides after a washout period.

**Results:** Interobserver scoring for the assessors of tissue eosinophil count on WSI demonstrated excellent agreement [intraclass correlation coefficient (ICC) 0.963, $p<0.001$]. Intraobserver tissue eosinophil count on WSI and the glass slide indicated excellent agreement (ICC 0.988, $p=0.009$).

**Conclusion:** Eosinophil morphology and colour were accurately and consistently identified on WSI.

**Acknowledgements:**
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## A DECEPTIVE CASE OF GASTRIC CARCINOMA WITH LYMPHOID STROMA

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Gastric carcinoma with lymphoid stroma is a rare variant of gastric carcinoma characterised by tumour cells dispersed within a lymphocytic background.[1] This case reports a 67-year-old male

who presented with anaemia and melena. He proceeded to have an endoscopy which identified an ulcer suspicious for carcinoma. Histological examination showed sheets of lymphoid cells along with abundant Helicobacter organisms. The case was initially worked up as a case of lymphoma with an immunohistochemical panel of lymphoid markers being completed. The dense lymphoid infiltrate was distracting from the inconspicuous epithelioid cells camouflaged in the dense inflammatory infiltrate. The tumour cells were found to be EBER-ISH and cytokeratin positive, supporting the clinical impression of gastric carcinoma. Gastric carcinoma with lymphoid stroma is critically important to recognise and communicate to the treating clinicians as it provides prognostic information that may affect surgical management.[1,2] This rare variant should always be considered in cases with dense inflammation, even when a presumed cause such as *Helicobacter* infection is found.

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## DIFFUSE LARGE B-CELL LYMPHOMA MASQUERADING AS A PROSTHETIC JOINT INFECTION

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Diffuse large B-cell lymphoma (DLBCL) is a well-reported form of non-Hodgkin's lymphoma (NHL) which arises in extranodal sites in up to 40% of cases, producing an array of non-specific signs and symptoms.[1] Although the cause of DLBCL is unknown, many of the described risk factors ultimately cause immunodeficiency.[1] Metallic joint prosthetics are of common use in Australia, however some studies have suggested metallic prosthetics may be associated with malignancy due to the theorised carcinogenic properties of metallic ions and the chronic inflammation related to both joint disease and replacement.[2] Herein we report a rare case of DLBCL in a woman who presented three years post-total knee replacement for rheumatoid arthritis related joint disease. She presented with vague symptoms that were in keeping with prosthetic joint loosening or infection, however light microscopy and immunohistochemical analysis of bone biopsies identified DLBCL as the cause. Some studies have suggested there may be a cohort of metallic-joint prosthetic related lymphomas which could be likened to the well-recognised breast-implant associated anaplastic large cell lymphoma (ALCL).[3] This case discussion highlights the need for further international cohort studies that include a broad analysis of potential patient and prosthetic specific risk factors for malignancy.

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## A RARE CASE OF METASTATIC BALLOON CELL MELANOMA

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The balloon cell melanoma is one of the rarest variants of malignant melanoma with a distinctive but non-specific morphology.[1] Balloon cells are typically large cells with abundant amphophilic to eosinophilic granular cytoplasm. The diagnosis of this variant is made when more than fifty percent of tumour cells are ballooned.[1] This is a case of metastatic balloon cell melanoma in a 42-year-old male with a known history of melanoma who self-detected an enlarging axillary lymph node. The primary cutaneous lesion was described as having both spindled and ballooned cells, in contrast to the nodal disease which was almost entirely composed of melanocytes with balloon cell morphology. The exact mechanism and trigger that results in this morphology is still unclear, however electron microscopy analysis has identified the granular-appearing cytoplasm to be composed of dilated and merging melanosomes.[2] This case highlights the importance of considering this rare variant, even in cases where the primary melanoma has more classical features and does not meet the criteria for balloon cell melanoma.

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## INVASIVE STRATIFIED MUCIN-PRODUCING CARCINOMA. A CASE SERIES WITH ASSOCIATED PATHOLOGICAL FINDINGS

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**Background:** Stratified mucin producing intraepithelial lesion (SMILE) is associated with high risk HPV carcinogenesis and morphologically overlaps with cervical intraepithelial neoplasia (CIN) and adenocarcinoma in situ (AIS). In 2016, Schoolmeester *et al.*[1] described a case series of SMILE in which they observed unambiguous invasive adenocarcinomas resembling SMILE and proposed the term 'invasive SMILE' for such lesions.

**Aims:** To describe a case series of a recently named group of endocervical adenocarcinomas.

**Methods:** A retrospective search of the practice records was performed using the last year of records. Eight cases were identified, 3 of which had a component of invasive carcinoma resembling SMILE.

**Results:** We identified 3 cases of invasive SMILE and described their pathological features.
**Discussion:** All cases showed cytologically bland nuclear features and distinct palisading. Mitotic figures and apoptosis were easily identified in all 3 cases. 2 out of 3 cases were mucin rich and showed a neutrophilic infiltrate. One case was mucin poor and lacked a neutrophilic infiltrate. We found co-existent CIN in 66% of cases and ACIS in 33% of cases. There are clear morphological and immunohistochemical features supporting the designation of invasive SMILE as a distinct entity in the spectrum of cervical neoplasias.

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## OSTEOCHONDROMA OF HOFFA'S FAT PAD

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Infrapetellar osteochondroma is a rare benign osteochondromatous proliferation involving the infrapatellar fat pad. The pathogenesis of these lesions is unclear, but is thought to result from metaplasia of mesenchymal cells as a consequence of chronic infra-patella fat pad infringement or end stage of Hoffa's disease[1]. Given its uncommon occurrence, it can be mistaken for more common conditions about the knee. The extra-articular location is distinct from cartilaginous loose bodies and synovial chondromatosis, which involve the joint space. Despite the name, this condition is not related to osteochondroma of bone. We report a case of infrapatellar fat pad osteochondroma and discuss features to distinguish this condition from morphologically similar lesions.

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## TACTILE CORPUSCLE-LIKE BODIES IN LARGE BOWEL MUCOSA – AN UNUSUAL BUT HARMLESS INCIDENTALOMA

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Tactile corpuscle-like bodies (TCLB) are lesions that morphologically resemble Wagner-Meissner corpuscles occurring in sites where these mechanoreceptors are normally absent.[1] They are rare, but have been described in multiple sites, either in isolation or as a component of other neurally-derived lesions.[1] It has been suggested that they may represent a reactive neural proliferation.[1] It is important to distinguish TCLB from granulomata, amyloid or other lesions of neural origin, such as ganglioneuroma, as they have no known syndromic associations or clinical sequelae.[1] We present a case of TCLB occurring in the sigmoid colon.

A 57-year-old female with ulcerative colitis of twelve years duration was found to have a long-standing scarred-looking area of the sigmoid colon with a slightly undulant architecture. Biopsies from this area showed multiple lesions in the lamina propria and one submucosal lesion. The lesional cells had bland, eccentric, spindled nuclei partly encircling lamellated and fibrillary-looking eosinophilic cytoplasm. Immunohistochemistry showed strong, diffuse staining with S100 and SOX-10, weak non-specific staining with CD56, and no staining with EMA, CD163, synaptophysin, Claudin 1, NeuN, NFP, ERG, SMA, CD117 and Glut 1. The morphological and immunohistochemical features were of tactile corpuscle-like bodies.

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## A RARE CAUSE OF AN ADRENAL INCIDENTALOMA

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**Case summary:** A 65-year-old gentleman was referred for consideration of adrenalectomy for an adrenal mass. This mass was initially incidentally discovered 13 years prior. The most recent CT scan reported the enlarging large adrenal mass of soft tissue density with areas of calcification and irregular peripheral enhancement with possible necrosis, measuring 58×45×41 mm (TRxAPxCC).

A laparoscopic adrenalectomy was performed, given the enlarging nature of the mass and subclinical hypercortisolism. Histopathological examination showed adrenal cortex surrounding a central area of haemorrhage and necrosis. Surrounding the area of haemorrhage were some atypical ectatic vessels, extending into the cortex. The findings were consistent with an adrenal haemangioma.

**Discussion:** Adrenal incidentalomas are an increasingly common finding with the rising availability and quality in medical imaging. Less than 100 case reports of adrenal haemangiomas have been reported in the English literature. In the majority of cases, adrenal haemangiomas are detected incidentally.

**Conclusion:** With the increasing detection of adrenal incidentalomas, it is important to consider the differential diagnoses of such masses. Although rare, adrenal haemangiomas are a well-documented cause, and may be associated with non-specific symptoms, and electrolyte and endocrinological abnormalities. Once resected, they can be diagnosed by their characteristic histological features.

## WARTHIN-FINKELDEY GIANT CELLS IN AN AXILLARY LYMPH NODE DISSECTION SPECIMEN FOR BREAST CARCINOMA – A CASE REPORT

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Warthin-Finkeldey giant cell is a distinctive but lesser-known giant cell of lymphoid origin, which is classically associated with the prodrome of measles infection. However, its presence is not pathognomonic for measles, and the cell has been reported in a variety of reactive and neoplastic lymphoid conditions. We report a case where Warthin-Finkeldey giant cells were found in a lymph node dissection specimen for breast carcinoma in a patient who has no concurrent viral infection or lymphoproliferative disorder.

## MORE THAN MEETS THE EYE: ADENOSQUAMOUS CARCINOMA OF THE CONJUNCTIVA – A REPORT OF TWO CASES

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Adenosquamous (mucoepidermoid) carcinoma of the conjunctiva is a rare tumour with dimorphic differentiation, showing the morphology of both squamous and adenocarcinoma. In small biopsies or partial resection, the diagnosis can be missed. We report two cases of adenosquamous carcinoma arising from the bulbar conjunctiva; both cases were initially diagnosed as squamous cell carcinoma on superficial excisions because the adenocarcinoma component was only present within the deeper tissue on subsequent resections. The histologic features and immunohistochemical profiles are discussed, followed by a review of the literature.

## CALCIFYING PSEUDONEOPLASM OF THE NEURAXIS (CAPNON) – A CASE REPORT

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We report a case of a 32-year-old male with chronic headaches due to two calcified cerebellar lesions. The patient underwent surgical resection. Under microscopy, the tumour consisted of a calcified mass with prominent fibrillary architecture and associated chondroid matrix. The mass had a distinct interface with adjacent cortex, with areas showing a palisaded rim of epithelioid macrophages mixed with occasional meningeal cells. Immunohistochemistry showed that the palisaded rim of macrophages were CD68 positive and the occasional meningeal cells positive for EMA and PR. The morphology and immunoprofile is consistent with a calcifying pseudoneoplasm of the neuraxis (CAPNON).

## INFLAMMATORY MYOFIBROBLASTIC TUMOUR OF THE BREAST – A CASE REPORT

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We report a case of a 27-year-old female with a palpable right breast lump. The patient underwent core biopsies of the palpable lesion. Under microscopy, the cores showed a relatively circumscribed lesion composed of spindle cells arranged in haphazard and intersecting short fascicles in a fibrous stroma. The cells have elongate nuclei with mild nuclear pleomorphism and inconspicuous nucleoli. Immunohistochemistry showed positivity for ALK and SMA. The morphology and immunoprofile were consistent with an inflammatory myofibroblastic tumour.

The patient underwent excision biopsy of the lesion and the diagnosis of inflammatory myofibroblastic tumour of the breast was subsequently confirmed.

## EBV POSITIVE INFLAMMATORY FOLLICULAR DENDRITIC CELL SARCOMA OF THE SPLEEN – A CASE REPORT

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We report a case of a 64-year-old lady with a splenic mass. On imaging (CT) multiple lesion splenic lesions within the upper, mid and lower pole of the spleen. The largest was centered at the lower pole and measured 10.3×7.5×7.9 cm with central low density. The lesions were identified 4 years ago and had recently increased in size by 4 cm in the most recent scans. The patient underwent a laparoscopic splenectomy. Under microscopy, the tumour cells showed a proliferation of myofibroblastic and fibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes and eosinophils. Immunohistochemistry showed positivity for the follicular dendritic marker CD35 and in situ hybridisation analysis for Epstein-Barr encoding region (EBER) showed numerous strongly stained spindle cells throughout the lesion. The diagnosis of EBV positive inflammatory follicular dendritic cell sarcoma was established.

## LANGERHANS CELL SARCOMA – A CASE REPORT, LITERATURE REVIEW AND DISCUSSION

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Langerhans cell sarcoma is a rare, high-grade malignant neoplasm of the Langerhans cells, characterised by overtly malignant cytologic features, multiorgan involvement and an aggressive clinical course with a poor prognosis. It is generally considered to be a malignant variant of histiocytosis that can develop *de novo* or from antecedent Langerhans cell histiocytosis. Transdifferentiation of non-Langerhans cell lymphoid neoplasms to Langerhans cell neoplasms is not well documented. We report a case of Langerhans cell sarcoma in a 66-year-old male with a history of a stage IIIa follicular lymphoma who presented with multiple lesions in the liver and lung. A biopsy was performed of one of the liver lesions, which yielded lesional tissue composed of discohesive sheets of medium-to-large tumour cells staining positively with CD1a, S100, bcl-2 and CD68 immunohistochemical stains. BRAF V600E mutation analysis yielded negative results. We postulate our case to be an

example of Langerhans cell sarcoma transdifferentiating from a follicular lymphoma and will discuss the limited literature in this rare entity. The role of BRAF V600E mutation in prognosis and treatment will also be discussed.

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## IS IT MYCOPHENOLATE INDUCED COLITIS OR FLARE-UP OF CROHN'S DISEASE? A DIAGNOSTIC DILEMMA FOR HISTOPATHOLOGISTS

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Mycophenolic acid (MPA) is an immunosuppresive drug commonly used in patients with solid organ transplant. It inhibits the *de novo* pathway of purine synthesis that is crucial in cellular rejection of grafts. The same pathway is utilised by enterocytes for regeneration. MPA is a well-known cause of gastrointestinal mucosal injury which can take many forms and closely mimics other gastrointestinal diseases histologically including inflammatory bowel diseases, opportunistic infections and graft-versus-host disease. This case study reports a patient with a background history of Crohn's disease and lung transplant who is on mycophenolate therapy, presenting with diarrhoea and abdominal pain. Endoscopy revealed large confluent ulcers and severe pancolitis. Infective aetiologies including opportunistic infections have been carefully excluded. Histologically, the colonic biopsies demonstrate patchy active chronic colitis with ulceration and focal cryptitis. Mild crypt architectural distortion and focal crypt atrophy are seen. Eosinophils are inconspicuous. All of the above features can be observed in both mycophenolate-induced colitis and Crohn's colitis. This case report highlights the diagnostic dilemmas of histopathologists in this situation, followed by a review of latest literature and discussion on a meaningful differentiation of the two entities.

## CASE REPORT: PRIMARY BASAL CELL CARCINOMA OF THE PROSTATE – HISTOPATHOLOGICAL AND BIOLOGICAL FEATURES AND RECENT NEW FINDINGS IN ITS MOLECULAR PATHOLOGY

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Primary prostatic basal cell carcinoma is a rare entity. Worldwide, there are 98 reported cases with the largest case series comprising only 29 cases.[1,2] Unlike conventional prostatic acinar adenocarcinoma, primary prostatic basal cell carcinoma presents typically with nocturia, urinary urgency and acute urinary retention, on a background of normal serum PSA levels. In a minority of cases, elevated serum PSA levels have been observed, but only in those with concomitant prostatitis or acinar adenocarcinoma.[1,3] Digital rectal examination (DRE) findings are usually negative, except in cases with extra-prostatic extension or metastatic disease.[1]

To date, histopathology with immunohistochemical analysis remain the gold standard for its definitive diagnosis. Clinical suspicion of a prostatic malignancy in the setting of normal serum PSA level however, should alert the clinician to consider primary prostatic basal cell carcinoma as one of the possible differential diagnoses.

Here, we present a case of primary prostatic basal cell carcinoma in a middle-aged gentleman and discuss its histopathological and biological features, and recent new findings in its molecular characteristics (MYB rearrangements, PTEN expression loss and EGFR over-expression), which could present opportunities for the utilisation of novel therapeutic targets in the rapidly advancing field of biologic therapy.

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## HOW COMPARABLE ARE SERUM INDICES MEASUREMENTS BETWEEN LABORATORIES?

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As a routine quality measure, most laboratories now quantify serum indices on patient samples and selectively withhold reporting results when interferences are identified.

Data on how different measurement systems compare was somewhat limited by the lack of an external quality assurance (EQA) program for these parameters. In 2019, the RCPAQAP, in collaboration with ASE, developed a serum indices EQA program to address this.

**Methods:** Serum was pooled, supplemented and lyophilised to create six linearly related samples which were distributed to 70 laboratories enrolled in the program. The RCPAQAP performed data analysis on returned results using in-house software.

**Results:** There were 97 participants representing five different method groups in the program. Across all platforms, haemolysis performed consistently well with CV's averaging 4.7% for the high level, whereas icterus and lipaemia CV's averaged 15.7%. A bimodal distribution was noted for icterus. Up to half of all participants reported lipaemia with incorrect units.

**Discussion:** This new program demonstrates the need for an ongoing peer comparison when making decisions on accepting or rejecting patient results. The bimodal distribution observed for icterus may be of concern and the variability in reporting units for lipaemia is still an area for improvement.

## ASSAY INTERFERENCE CAUSING FACTITIOUS HYPERVITAMINOSIS D

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25-hydroxyvitamin D is most commonly measured with the use of automated immunoassay technology. It is well known that immunoassays are prone to interference from immunoglobulins present in the circulation. Here we present a case of a monoclonal IgM paraprotein interference in the Abbott Architect 25-hydroxyvitamin D assay, a quantitative delayed one-step competitive immunoassay using chemiluminescent microparticle immunoassay (CMIA) technology. A 68-year-old female with newly diagnosed lymphoplasmacytic lymphoma / Waldenstrom's macroglobulinaemia and a monoclonal IgM paraprotein of 44 g/L, had a 25-OH vitamin D measurement of >400 nmol/L on the Abbott Architect 25-hydroxyvitamin D assay. This result was inconsistent with clinical findings. A 1:2-dilution of the sample returned a non-linear 25-OH Vitamin D result of 84 nmol/L suggestive of an interferent present in the sample. The presence of rheumatoid factor was excluded with a measurement below the limit of quantitation of the assay. Referral of the sample for measurement of total 25-hydroxyvitamin D by liquid chromatography-tandem mass spectrometry (LC-MS/MS) returned a result of 75 nmol/L. The sample analysed was collected before the patient started chemotherapy and we concluded that the most likely interferent is the monoclonal IgM paraprotein.

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## THE ACCURACY OF BLOOD GAS ANALYSER RESULTS COMPARED WITH CENTRAL LABORATORY TESTING

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**Background:** Electrolyte and haemoglobin results from blood gas analysers are often used clinically before results from central laboratory testing are available. However, the accuracy of blood gas analyser results is uncertain.
**Methods:** Patients who presented to ED during 7 consecutive days and with blood gas analyses and central laboratory samples timestamped $\leq$20 minutes apart were included. Mean differences in sodium, potassium, bicarbonate, haemoglobin and haematocrit between central laboratory results and blood gas results were calculated. Differences were tested using t-tests and linear regression performed, with R^2 calculated.
**Results:** 55 sets of corresponding samples were analysed. Compared with venous blood gas results, mean central laboratory results were higher for sodium (5.0 mmol/L, 95% CI=4.4,5.5, $p<0.001$, $R^2=0.83$) and potassium (0.31 mmol/L, 95%CI=0.27,0.35, $p<0.001$, $R^2=0.96$). Mean central laboratory concentrations were lower for bicarbonate (−4.4 mmol/L, 95%CI= −4.9,−3.9, $p<0.001$, $R^2=0.93$) and haematocrit (−2.3%, 95%CI= −3.4,−1.2, $p<0.001$, $R^2=0.83$). Mean concentration did not systematically differ for haemoglobin but had lower correlation (3.6 g/L, 95%CI= −0.4,7.6, $p=0.074$, $R^2=0.72$).
**Conclusion:** Blood gas results may differ systemically and have moderate to excellent correlation with central laboratory testing. Analysers should be calibrated to minimise systematic errors and clinicians should be aware of differences to facilitate appropriate clinical decision making. The blood gas analyser involved has since been replaced.

## RECURRENT SEVERE RHABDOMYOLYSIS IN A PREGNANCY AFFECTED BY MYOTONIC DYSTROPHY TYPE 1

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An 18-year-old female G1P0 at 17+5 weeks pregnant with history of myotonic dystrophy type 1 (DM1) presented with bilateral leg ache, intermittent abdominal pain, and dark urine. Blood tests confirmed severe unprovoked rhabdomyolysis with CK 72546 U/L. CK remained higher than baseline throughout pregnancy and she had two further episodes of severe rhabdomyolysis requiring admission. Nonischaemic forearm exercise testing demonstrated normal response to exercise with no evidence of metabolic myopathy; having normal pre-exercise and post-exercise acylcarnitine profile and amino acid profile, appropriately rising lactate (1.0 mmol/L to 2.4 mmol/L), no significant increase in ammonia (29 μmol/L to 31 μmol/L), and appropriate deoxygenation (PvO2 36 mmHg to 32 mmHg). Three separate urine metabolic screens demonstrated normal glycosaminoglycans (6.0 mg/mmol; 8.6 mg/mmol; 6.3 mg/mmol creatinine; reference range <15.4) and no evidence of fatty acid oxidation defect. A rhabdomyolysis gene test panel involving over 50 genes revealed no underlying cause for rhabdomyolysis. At 33+4 weeks, our patient delivered a stillborn baby strongly affected by DM1 due to anticipation and unable to perform spontaneous respiration. Our patient's CK fell to 936 U/L one day after birth, lower than all levels during pregnancy, confirming pregnancy as the cause of rhabdomyolysis. We believe this is the first case of spontaneous recurrent severe rhabdomyolysis during pregnancy with DM1.

## INTERFERENCE OF ENZALUTAMIDE ON DIGOXIN IMMUNOASSAY: A CASE REPORT

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Androgen sensitive prostate cancer is a malignancy that may be treated with hormonal therapy. Enzalutamide, an androgen receptor antagonist, is indicated in patients with metastatic castration-resistant prostate cancer. The drug inhibits translocation of activated androgen receptors into the cell nucleus and prevents DNA binding, thereby inducing cell death and tumour regression.

Digoxin is a widely used cardiac glycoside to treat heart failure and reduce ventricular rate in atrial fibrillation. Therapeutic drug monitoring is essential due to its narrow therapeutic index. However, digoxin assays can be affected by many substances including digoxin-like immunoreactive substances (DLIS), medications such as spironolactone, canrenoate, various Chinese medicines and anti-digoxin antibody.

We present a case of falsely elevated digoxin levels due to enzalutamide interaction with the chemiluminescent microparticle immunoassay.

## A PATIENT WITH CHOLESTASIS, ELEVATED CHOLESTANOL, LDL-CHOLESTEROL AND LIPOPROTEIN X

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Biliary atresia is a rare liver disorder in children and is related with cholestasis. Lipoprotein-X and cholestanol are sensitive indicators of cholestasis in biliary cirrhosis and biliary atresia. We presented a child with elevated cholestanol, LDL-cholesterol and the presence of lipoprotein X due to cholestasis.

A 5-year-old girl with biliary atresia presented with raised total cholesterol (TC) 24.3, triglycerides (TG) 2.4, HDL-C 1.5, LDL-C 21.7 mmol/L. Blood works was cholestatic with total bilirubin 220 μmol/L, ALT 398 U/L, ALP 1367 U/L, GGT 714 U/L, bile acid 554 μmol/L. Coagulation, serum albumin and alpha-fetoprotein were normal. Lipid electrophoresis was reported as possible presence of lipoprotein X. Due to abnormally elevated cholesterol profiles, further inherited metabolic investigations were requested. 7-dehydrocholestanol was elevated at 191 μmol/L and reported as raised cholestanol, consistent with cerebrotendinous xanthomatosis. After treating with ursodeoxycholic acid and colesevelam, later with liver transplantation, her TC was reduced to 3.9 and TG 1.2 mmol/L. Offline measurement of Apo B on the sample of lipid electrophoresis was normal at 1.07 g/L.

This case highlighted abnormally elevated lipid profiles and cholestanol in a patient with cholestasis and the usefulness of Apo B to differentiate cholestasis from cerebrotendinous xanthomatosis.

## HOW A MONOCLONAL BAND SAVED THE DAY, IN AN APPARENT SAMPLE MIX UP FOR ALPHA-1-ANTITRYPSIN PHENOTYPING

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This is a case report on a 59-year-old male who was discovered to have a homozygous ZZ alpha-1-antitrypsin phenotype, as an incidental finding following a routine serum protein electrophoresis (SPE) investigation in 2013. In 2018 a respiratory clinician sent a repeat sample, questioning if the correct phenotype had been assigned as the level (40%) seemed too high for a homozygous ZZ diagnosis. Homozygous ZZ was again confirmed as the phenotype. In January 2019, the patient had another sample sent to our lab for routine SPE, and the laboratory noticed that the alpha-1-antitrypsin levels were now near normal. The patient had no inflammatory response so this was confounding given his homozygous ZZ diagnosis. Was this a case of a sample mix up? Unlikely, given that the patient, in addition to being a homozygous ZZ alpha-1-antitrypsin variant, also had a monoclonal IgA kappa paraprotein. Examination of the medical record revealed that the patient was undergoing alpha-1-antitrypsin replacement therapy. No mention of this fact was made on the blood request form. This case highlights the importance of supplying clinical information to the laboratory.

## DISTINGUISHING THERAPEUTIC MONOCLONAL ANTIBODIES FROM PATIENT MONOCLONAL PROTEINS BY ELECTROSPRAY TIME-OF-FLIGHT MASS SPECTROMETRY

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Monoclonal gammopathies are a group of disorders characterised by proliferation of clonal plasma cells. Monoclonal intact immunoglobulin (Ig), free light chain and heavy chain proteins are routinely detected using electrophoresis and are important for diagnosis, monitoring and patient management.

With the introduction of therapeutic monoclonal antibodies (tmAb), which are humanised monoclonal Ig proteins, for treatment of multiple myeloma and other disorders, protein electrophoresis is subject to interference from these therapeutics. They present as additional bands in the electrophoresis, complicating the interpretation of this investigation. The tmAbs cannot be distinguished from endogenous monoclonal proteins by current methods, which may lead to mis-diagnosis, and therefore incorrect patient management.

We have developed an electrospray time-of-flight mass spectrometry (TOF MS) method which is able to detect tmAbs in patient serum and differentiate these from endogenous patient clones using accurate mass assignment of Ig light chains. The unique light chain mass of the tmAb can be identified and distinguished from patient monoclonal light chains. TOF MS also offers the advantage of being more sensitive than protein electrophoresis, enabling a lower limit of detection to be achieved.

## SHOULD RCPAQAP BLOOD GAS PROGRAM INCLUDE INSTRUMENT CALCULATED PARAMETERS?

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A normal term baby girl was found to have low oxygen saturation on pulse oximeter (88–95%) on day 2 and did not respond to oxygen therapy. Cardio-pulmonary workup was uneventful.
Arterial blood gas on room air revealed normal pH, $pO_2$, $pCO_2$, bicarbonate and $sO_2$, but a high instrument-calculated p50 of 30–42 mmHg (RR 25–29) suggested a haemoglobin of low oxygen affinity. Haemoglobin HPLC analysis revealed an abnormal peak of 1.6% detected at RT 4.50 min which was shown by alkaline and acid electrophoresis, and subsequent DNA testing to be heterozygous HbA1:c.283G>A in the alpha1-globin gene (haemoglobin Titusville).
This is a rare haemoglobinopathy involving a single nucleotide change from G to A at codon 94 of the alpha globin gene, and results in a lower oxygen affinity, indicated by oxygen dissociation curve right shift and high p50.[1,2]
While RCPAQAP Blood Gas program monitors key analyser measurements, there is no attempt to probe the performance of calculated parameters which may be determined by sophisticated hidden software, e.g., for p50.
This case illustrates the importance of looking beyond the basic parameters of pH, $pCO_2$, $pO_2$ and bicarbonate and raises the desirability of RCPAQAP monitoring calculated parameters across various blood gas platforms which may be particularly vulnerable to haemoglobinopathies.[3]

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## A CURIOUS FAMILY OF STUNTED GROWTH

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A 4-month-old boy of non-consanguineous parents was referred to the Paediatric Endocrinology Department for growth failure complicated by hypoglycaemia. During hypoglycaemia, his GH and IGF-1 remained undetectable, and other causes of growth failure were excluded. He was commenced on recombinant-hGH (rhGH). After an initial good response, growth slowed despite increasing doses of rhGH, up to 7.5 mg/$m^2$/week. A poor IGF-1 response to rhGH was noted. Compliance issues were excluded. GH deficiency was re-confirmed by an Arginine-Glucagon provocation test. The rhGH was discontinued at 4 years 5 months because growth response criteria were not met.
The possibility of GH resistance due to autoantibodies to rhGH was confirmed using an $I^{125}$ competitive binding research assay at SydPath with an extremely high titre of 1:2,560.
Family history revealed an older sister who also had documented GH deficiency. She grew well on rhGH for 10 years followed by a slowdown in growth during puberty. She has now been off rhGH for 18 months and has a very low positive GH antibody titre. DNA testing of GH1 gene sequencing in the family is underway.[1]
Due to the rare combination of severe GH deficiency and high GH antibodies, a trial of recombinant IGF-1 appears to be the only therapeutic option.[2]

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## BASELINE PARAMETERS AND RESPONSE TO GNRH: CONCLUSIONS FROM AN AUDIT OF 136 SERIAL TESTS

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**Introduction:** The gonadotrophin-releasing hormone (GnRH) test is the gold standard for assessing pituitary responsiveness to the hypothalamic releasing hormone in precocious and delayed puberty; both conditions can affect the reproductive system as well as structural growth and psychosocial well-being.
**Methods:** GnRH tests were performed in 136 children (65% girls) aged 10 months to 21 years for precocious or delayed puberty. Leuprorelin (Lucrin, Abbott), a synthetic GnRH analogue, was given intramuscularly (0.02 μg/kg). Bloods were collected prior to injection and at 30, 60, and 120 minutes thereafter. Serum LH and FSH were measured at all time points using the paramagnetic particle, chemiluminescent immunoassay on Beckman Coulter UniCel DxI 800. Peak LH >5 IU/L was considered as pubertal. Baseline oestradiol and testosterone were measured by LC-MS.
**Results:** Peak LH response was only weakly correlated with baseline LH ($r^2$=0.21) or FSH ($r^2$=0.23). Girls with oestradiol >80 pmol/L (16% of girls) and boys with testosterone >4 nmol/L (16% of boys) all had peak LH >5.
**Conclusion:** Baseline LH or FSH levels are inadequate predictors of peak LH response. Girls with baseline oestradiol >80 pmol/L and boys with testosterone >4 nmol/L have reached the pubertal state and could possibly be spared the GnRH test.

## NEW CAUSES OF OLD DISEASES. ARE WE READY?

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A 67-year-old male with metastatic cholangiocarcinoma presented with dehydration and delirium approximately 6 weeks after participating into a Rare Cancer Trial utilising combination of immune checkpoint inhibitors (ICIs), i.e., ipilimumab and nivolumab.

His electrolytes were normal but cortisol was 36 nmol/L (185-625) and ACTH was 2 pmol/L (<10). Sixty-minute post-Synacthen cortisol was 153 nmol/L (>530). Secondary hypoadrenalism was diagnosed on the basis of low ACTH and baseline cortisol with poor response to Synacthen. Thyroid function tests revealed thyrotoxicosis, while TPO, thyroglobulin and TSH receptor antibodies were all negative.

ICIs have been increasingly implicated in autoimmune endocrinopathies. Combination of ipilimumab and nivolumab can give rise to hypopituitarism or hypophysitis, and thyroid dysfunction. In healthy individuals, immune checkpoints maintain immunological tolerance to self-antigens. By inhibiting these immune checkpoints, ICIs cause auto-immune like manifestations against multiple organs. Typically, complications develop in susceptible patients 6–15 weeks after introduction of ICIs. The preferred screening test for hypophysitis is morning cortisol and ACTH, followed by Synacthen test.[1]

In oncology, ICIs are the most rapidly expanding class of drugs alternatives to traditional chemotherapy. Therefore, oncologists, endocrinologists and pathologists need to understand their mechanism of action, side effects, importance of monitoring ICI usage to detect and investigate the associated endocrine disorders.

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## PARATHYROID HORMONE (PTH) IN HYPERCALCAEMIC PATIENTS. ANALYTICAL COMPARISON OF EIGHT PTH IMMUNOASSAYS

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**Introduction:** Modern PTH immunoassays can be classified as second (intact PTH) or third generation assays (PTH 1–84). It is generally considered that the performance in primary hyperparathyroidism (PHPT) of second and third generation assays is similar. The aim of this study was to compare PTH immunoassays in hypercalcaemic patients.

**Methods:** EDTA plasma from 112 hypercalcaemic patients with eGFR>60 was frozen prior to immunoassay. PTH assays were as follows: Roche (intact); Roche (PTH 1-84); Abbott Architect; DiaSorin N-Tact; DiaSorin 1-84 PTH; Beckman Access; Siemens Centaur; Siemens Immulite 2000; and SNIBE Maglumi 2000.

**Results:** Eighty-five patients had PTH levels > upper limit of the RI and 91/112 patients had PHPT.

Passing-Bablok analysis versus Roche Intact PTH slopes were as follows: 0.45 (DiaSorin 1-84 PTH); 0.89 (Beckman Access); 0.96 (Siemens Centaur); 1.08 (Abbott Architect); 1.28 (SNIBE Maglumi 2000); 1.28 (DiaSorin N-Tact); and 1.39 (Siemens Immulite 2000). Similar slopes were observed in normocalcaemic reference patients.

**Conclusions:** This study confirms observations that Intact PTH and PTH 1-84 assays have similar diagnostic utility in PHPT. Better standardisation of PTH assays would improve comparability of PTH assays in patients without renal disease. Standardisation of 3rd generation PTH 1-84 assays would result in comparable PTH levels regardless of eGFR.

## 'SILVER MAN' – A FIRST CASE REPORT OF SILVER ASSOCIATED STEATOHEPATITIS (SASH) AND DISCUSSION OF ITS PATHOMECHANISM

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A 47-year-old Chinese man, who worked as a clerk in the electronics industry, presented with gait instability and glove-and-stocking sensation. He had anaemia, deranged liver function, low ceruloplasmin (0.05 g/L; ref 0.18–0.35), high 24-urine copper (2.02 μmol/L; ref <0.5 μmol/L), low iron level (5 umol/L; ref 9–33), high ferritin (4521 pmol/L; ref 52–738) and low transferrin saturation (11%; ref 16–45). MRI liver and pancreas showed homogenous T2 hypointensity, a feature of iron deposition. MRI brain showed artefacts in bilateral globus pallidi that suggested mineralisation. Sequencing of *ATP7B* gene did not reveal any pathogenic variants. Further clarification of the clinical history revealed that colloidal silver was prescribed by his private practitioner for over a year. His blood silver level was about a thousand times above that of controls. In the liver tissues, there were patchy lymphocytic infiltrates with periportal and focal bridging fibrosis, moderate haemosiderin deposits and presence of silver. Clinical symptoms and biochemical results were improved after silver exposure was stopped. Silver binds with ceruloplasmin and loses its ferroxidase activity, so Fe2+ cannot be oxidised to Fe3+ and cannot be carried by transferrin. This leads to intracellular iron overload in the liver, pancreas and neuronal tissues.

## SEASONAL EFFECTS ON DEATH FROM DIABETIC KETOACIDOSIS

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During hypothermia, alteration of glucose metabolism can result in a hyperglycaemic and ketoacidotic state.[1] Conversely, diabetic ketoacidosis (DKA) can precipitate hypothermia by impaired thermoregulation and autonomic dysfunction.[2] Both DKA and hypothermia can demonstrate overlapping pathological and biochemical findings.[3]

**Aim:** Due to the related pathophysiology between hypothermia and DKA, we hypothesised that were would be a higher number of deaths from DKA in winter than in any other season.

**Method:** We performed a 12-year retrospective study on all deaths related to DKA at the Department of Forensic Pathology, Auckland City Hospital, New Zealand. The decedents' age and sex, and the season they died, were recorded. Statistical analysis was performed using R statistics.

**Results:** A total of 35 cases were included. Age and sex were not statistically significant between the seasons. Winter had the highest number of deaths from DKA ($n$=12), followed by summer ($n$=9), autumn ($n$=8) and spring ($n$=6).

**Discussion:** This study demonstrated that winter months had the highest number of deaths from DKA compared to other seasons. Given the similar pathophysiology and pathologic findings between hypothermia and DKA, this implies that winter may be a factor that can precipitate or exacerbate DKA that may be under recognised.

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## POST MORTEM COMPUTED TOMOGRAPHY (PMCT) LUNG CHANGES IN SUICIDE HANGING DEATHS: A CASE SERIES

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Hanging is the most common suicide method in New Zealand. Different structures in the neck, such as the airway, vasculature and nerves, are compressed during hanging and can individually or in combination cause death. The ligature characteristics may influence which neck structure is being predominantly compressed. Post mortem computed tomography (PMCT) is commonly included in a post mortem examination of a suspected suicide by hanging, especially when only an external examination is authorised. The majority of literature on PMCT findings in suicide hanging deaths focuses on the neck. We present a case series from the Department of Forensic Pathology, Auckland City Hospital, New Zealand, illustrating a range of PMCT lung findings in suicide hanging deaths. These include normal or congested lung fields, aspiration, air trapping and pneumomediastinum. We observe that PMCT lung findings appear to correlate with the ligature characteristics. This observation may have useful forensic relevance in matching potential ligatures in death from neck compression and warrants further investigation.

## ALCOHOL MEASUREMENT BETWEEN CEREBROSPINAL FLUID AND OTHER BODILY FLUIDS IN ABSORPTIVE AND POST ABSORPTIVE PHASES: TWO ILLUSTRATIVE CASES

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Post-mortem toxicology analysis for alcohol is a common adjunct post mortem biochemical test, although its interpretation can be challenging when establishing whether the presence of alcohol played a role in cause of death. Blood, urine and vitreous humor are commonly analysed for alcohol toxicology post mortem, but despite being a central nervous system depressant, cerebrospinal fluid (CSF) is not routinely analysed for this purpose. We present two deaths in which alcohol was detected in toxicological analysis, one in the excretory phase and one in the absorptive phase. In both cases, CSF alcohol levels lagged behind vitreous (and thus blood) but ahead of urine. This implies that CSF may be another matrix for use in determining the phase of alcohol metabolism, especially where other samples are limited or unavailable.

## WISCHNEWSKY LESIONS IN A MORBIDLY OBESE MAN WITH CIRRHOSIS, LIVER FAILURE AND CARDIOMEGALY: CAN THIS BE HYPOTHERMIA?

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Obesity is an increasingly prevalent co-morbidity that is associated with sudden unexpected death and is commonly encountered in post mortem practice. Due to the effects of increased body-habitus it is, however, uncommon to encounter a death in an obese individual from hypothermia, especially during

non-winter seasons. This case documents a hypothermic death in a setting of morbid obesity and subsequent liver failure and cardiomegaly where widespread Wischnewsky lesions and slightly elevated beta-hydroxybutyrate were noted, with non-elevated blood sugar levels. In this rare case, the only identifiable predisposing factor to hypothermia was metabolic derangement resulting in altered energy metabolism.

## BLACK DUODENUM – A 'NEW' ENTITY GONE UNNOTICED. FURTHER EVIDENCE OF SHARED PATHOPHYSIOLOGY BETWEEN BLACK OESOPHAGUS, WISCHNEWSKY SPOTS AND, NOW, BLACK DUODENUM

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We report a case of 'black' oesophagus / acute necrotising oesophagitis (ANE)-like 'black' duodenum / acute necrotising duodenitis in a man who died from diabetic ketoacidosis (DKA), which has not been previously reported in the literature. The morphological and histological features of this 'black' duodenum resemble closely ANE and erosive gastritis / Wischnewsky lesions of the stomach (WLs). The pathogenesis of this finding, given the similar location and manifestation, as well as the similar local blood supply, may be the same as AEN and WLs, but atypically manifested in the duodenum. In addition, we present further information on an additional four cases of black duodenum detected in the department since first recognising the entity, suggesting that this newly described entity may be missed at autopsy, where the duodenum is not closely inspected.

## RARE OCCURRENCE OF CEREBRAL METASTASES IN A YOUNG FEMALE WITH ADRENOCORTICAL CARCINOMA: FORENSIC PRESENTATION

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**Aim:** Adrenocortical carcinoma is a rare primary malignancy arising from the adrenal cortex. Metastases show predilection for the kidney, liver and abdominal viscera, with only rare reports of cerebral metastases in the literature. The aim of the study is to describe the atypical presentation of a non-secretory adrenocortical carcinoma.
**Method:** We reviewed the case of a young female with an adrenocortical carcinoma, initially presenting to the hospital with adrenal capsular rupture and abdominal pain. She passed away eight years after the initial diagnosis at home, following the excision of a scalp lesion. Forensic autopsy examination and imaging was performed.
**Results:** At autopsy, there were two previously uncharacterised metastatic lesions and multiple pulmonary metastases in the left parietal lobe and multiple pulmonary metastases. Internal examination also showed moderate mitral valve prolapse. The final cause of death was due to raised intracranial pressure because of the tumour mass effect.
**Discussion:** Cerebral metastasis is an uncommon presentation in patient with adrenal cortical carcinoma. The patient presents with a sudden death following a procedure and the post-mortem imaging and autopsy internal examination was crucial in unravelling the cause of death in this unusual situation.

## THE COMPOUNDING EFFECTS OF HEPATITIS C INFECTION WITH LIVER CIRRHOSIS, HEPATOCELLULAR CARCINOMA, AND BUDD-CHIARI SYNDROME IN FATAL GASTROINTESTINAL HAEMORRHAGE

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This case study reports a patient with hepatitis C infection with advanced liver cirrhosis, and undiagnosed hepatocellular carcinoma, who presented with acute Budd-Chiari syndrome and fatal gastrointestinal haemorrhage. Budd-Chiari syndrome is defined as hepatic venous outflow tract obstruction, and can present with signs of acute liver failure, including nausea and vomiting, abdominal distension, jaundice, coagulopathy, and abnormal liver function tests, and may progress to multiorgan failure and death. Budd-Chiari syndrome can arise in the setting of malignancy, via direct compression or invasion of vascular structures, with hepatocellular carcinoma most commonly described. The majority of hepatocellular carcinomas arise in the setting of liver cirrhosis, with chronic viral hepatitis (hepatitis B and C) a leading cause. Liver cirrhosis may result in portal hypertension, which promotes the development of oesophageal and gastric varices. Liver disease can also affect the production of clotting factors, which may increase the risk of potential haemorrhage. This case highlights the combined effects of potentially reduced clotting factors, oesophageal varices, and disseminated intravascular coagulation, and how their overlapping aetiologies may increase the risk of developing potentially fatal spontaneous gastrointestinal haemorrhage.

## AUTOIMMUNE PULMONARY ALVEOLAR PROTEINOSIS WITH CONCURRENT PULMONARY *CRYPTOCOCCUS GATTII* INFECTION

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This case study reports a patient with autoimmune pulmonary alveolar proteinosis (PAP), pulmonary cryptococcosis, and disseminated cryptococcaemia, and the associated histopathological findings. Autoimmune PAP is an uncommon condition characterised by excessive accumulation of surfactant within

alveolar spaces due to alveolar macrophage dysfunction. Autoimmune PAP is driven by circulating autoantibodies against factors involved in macrophage development and maturation. Affected macrophages have both impaired ability to clear surfactant, resulting in abundant surfactant deposition, and defective antimicrobial defence mechanisms, predisposing to atypical lung infections. *Cryptococcus gattii* is a fungal organism widely present in the environment, and is endemic to tropical and subtropical climate regions, including Australia. Infection is caused by inhalation of fungal spores, and commonly produces a range of clinical manifestations from minimal symptoms to disseminated disease with cryptococcaemia, the outcome of which is determined by a complex set of interacting pathogen and host factors. Cryptococcaemia is rare in those with intact immunity, and this case highlights how PAP and impairment in first-line antimicrobial defence mechanisms likely contributed to the progression to disseminated disease.

## DEATH DUE TO TENSION GASTROTHORAX

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The term 'tension gastrothorax' is used to describe the rare and life-threatening complication of a diaphragmatic defect and can present with non-specific symptoms. It develops when an intrathoracic stomach, which has herniated through a diaphragmatic defect, is distended, causing mediastinal displacement. Here, we present a case report of a previously healthy 2-year-old boy with tension gastrothorax as well as a review of the literature on this phenomenon. Although this condition is rare, it is an important differential to exclude in children presenting with non-specific symptoms.

## GEOMETRIC MORPHOMETRIC STUDY OF SEXUAL DIMORPHISM IN MALAYSIAN MANDIBLES

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**Background:** Geometric morphometric is the statistical analysis of form based on Cartesian landmark coordinates. In this study, geometric morphometric techniques were used to study sexual dimorphism of mandible. Aims: The objectives were to determine mandible variation in size and shape, to determine the relationship between size and shape of mandible in different sexes, and to visualise allometry patterns of mandible.
**Methods:** About 113 samples of adult human mandibles (65 males, 48 females) were analysed at the Universiti Kebangsaan Malaysia Medical Centre. Approximately 12 landmarks were placed on the 2-D image by landmarking software, and were analysed with MorphoJ.
**Results:** The first five principal components were taken to represent the morphological variance with 83.64% cumulative variance. The mandible shape was used to determine sex. The variance visualization showed significant variation between male and female. The classification accuracy was 91.96%.
**Conclusion:** Geometric morphometric is a good method to study sexual dimorphism of the mandible. Its potential may be developed in forensic anthropology to determine ancestry and age groups. MorphoJ and other softwares may be used in the application of geometric morphometric study of other bones.

## AN ANALYSIS OF CHILD AND ADOLESCENT SUICIDE IN THREE CENTRES FROM 2008-2017

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The overall suicide rate worldwide has been found to have changed little over the past 100 years,[1] but different trends have been observed over time for USA, Australia and NZ.[2,3] Few studies have focused on child and adolescent (<18 years of age) suicide, meaning there is little prior knowledge from which to determine trends. This project is an update on youth suicides in Adelaide, which were compared with the jurisdictions of Auckland (NZ) and Hennepin County (USA). Youth suicides between 2008–2017 in Adelaide and the other centres were included in this study. Demographic data (age, sex, ethnicity, BMI) and the method of suicide from these three regions were collected and analysed. There were 39 youth suicides in Adelaide (2.4% of 1661 total suicides), 50 in Hennepin (3.6% of 1404 total) and 105 in Auckland (6.4% of 1638 total) from 2008–2017. The most common method of suicide across all centres was hanging, occurring in >80% of cases in Adelaide and Auckland, and 56% in Hennepin. Hennepin County had a greater proportion of suicides using firearms (28%, compared with 1.9% for Auckland and 5.1% for Adelaide). Unusual means of suicide were used less frequently by youth than previously.

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## AN UNUSUAL CASE OF HYPOTHERMIA AND PARADOXICAL UNDRESSING IN WESTERN SYDNEY

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An 83-year-old lady, who was previously well and independent was found by her son in a state of partial undress in the lounge room in her home, after being seen well 1–2 days previously. The back door of the residence was open, some rooms in the house were in disarray, and blood was present in the living room. Police were contacted due to the possibility of an assault.

She was transferred to hospital, where she was found to have a temperature of 34.3°C and a fluctuating level of consciousness. She was found to have multiple, extensive bruising over her body with some intracranial injuries. No ano-genital injuries were present.

A forensic examination was carried out, with swabs finding male DNA on one of the skin swabs.

As the atmospheric temperature had been about 1°C over the previous two nights, it was deemed that an assault was less likely than hypothermia with confusion, paradoxical undressing and a fall with head injury. Terminal burrowing was also considered due to the position she was found in.

The patient had a rather stormy in-patient stay and was eventually discharged to a nursing facility due to residual neurological impairment.

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## FATAL PULMONARY THROMBOEMBOLISM: HOW FREQUENTLY MIGHT TESTING FOR HEREDITARY THROMBOPHILIA BE CONSIDERED?

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Testing for hereditary thrombophilia is currently not performed as a component of the South Australian Coronial post-mortem investigation of fatal pulmonary thromboembolism. This study sought to investigate the potential number of cases in which thrombophilia testing might be applied in the South Australian Coronial population. Fatal pulmonary thromboembolism cases were identified from 3 years of Forensic Science SA autopsy reports (2014-2016) and risk factors for pulmonary thromboembolism were recorded. A total of 188 cases were identified. A risk factor to explain the cause of fatal pulmonary thromboembolism was not identified in 8 cases. Additionally, one case had a family history of pulmonary thromboembolism. It could be suggested that post-mortem testing for thrombophilia should be performed in cases without identifiable risk factors, as testing may identify the apparently missing cause. Genetic testing could also be considered if there is a family history of pulmonary thromboembolism. Collectively, these groups would potentially require testing of approximately 3 cases per year. Testing for hereditary thrombophilia in these cases could explain the unexpected death from pulmonary thromboembolism and potentially prevent future pulmonary thromboembolism events in the next of kin.

## FATAL PULMONARY THROMBOEMBOLISM: DEEP VEIN THROMBOSIS INCIDENCE AT CORONIAL AUTOPSY

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Most pulmonary thromboemboli arise from deep vein thrombosis of the lower legs.[1] When pulmonary thromboembolism is identified as the cause of death at autopsy, it has been recommended that the calves should be dissected to locate the source of the embolus.[2,3] However, it is uncertain how often deep vein thrombosis will be found and if the incidence is altered by risk factors for pulmonary thromboembolism. This research aimed to determine how often deep vein thrombosis of the lower legs was found at Coronial autopsy when death had resulted from pulmonary thromboembolism, and to ascertain if risk factors affect the likelihood of finding deep vein thrombosis. Autopsy reports of pulmonary thromboembolism deaths in the year 2016 were identified on the National Coronial Information System. Dissection information and risk factors for pulmonary thromboembolism were recorded. Risk factors were analysed by logistic regression to determine if there was predictive value on the probability of finding deep vein thrombosis. A total of 235 pulmonary thromboembolism fatalities were identified. Deep vein thrombosis was found in 76.6% full-body autopsies. A recent hospital admission was found to have a statistically significant positive influence ($p$=0.01) on finding deep vein thrombosis of the lower legs.

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## GASTRIC INTRAMURAL HAEMORRHAGE SECONDARY TO PANCREATITIS

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Although rare, pancreatitis is known to be associated with vascular complications leading to life-threatening haemorrhage. Pancreatic inflammation and subsequent necrosis leads to the release of proteolytic enzymes that initiate vessel injury causing bleeding and damage to nearby structures.[1] Intramural gastric haemorrhage is also a rare occurrence and most frequently caused by trauma, coagulopathy or anti-coagulant use. Management is usually conservative.[2] We describe the case of a 56-year-old woman who died due to a large gastric intramural haemorrhage occurring in the context of acute on chronic pancreatitis. The deceased had a 6-month history of nausea, vomiting and abdominal pain. Investigations prior to her death did not reveal a cause for her symptoms. Post-mortem examination showed acute and chronic pancreatitis with inflammation and necrosis of the splenic artery. The damaged artery communicated with the gastric intramural haemorrhage. We review the vascular complications of pancreatitis, in particular gastric intramural haemorrhage.

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## SUDDEN DEATH DUE TO CARDIAC SARCOIDOSIS: A CASE REPORT

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Sarcoidosis is an infiltrative inflammatory disease of unknown aetiology, which can involve multiple organ systems in affected individuals. The disease is characterised by the histologic hallmark of non-caseating epithelioid granulomas, for which other causes of granulomatous infiltrates have been excluded. Cardiac involvement occurs in up to one-third of cases and indicates an adverse prognosis, with cardiac sarcoidosis being responsible for approximately one-half to two-thirds of sarcoid-related deaths. Clinical cardiac manifestations preceding death, such as arrhythmia, heart block or heart failure, only occur in approximately 5% of people with cardiac sarcoidosis, and therefore a diagnosis of cardiac sarcoidosis is often not made prior to death. We present a case of an older age Caucasian male who was unexpectedly found dead in his home. The cause of death in this case was cardiac sarcoidosis. Through this case we highlight the macroscopic and microscopic features of cardiac sarcoidosis and present a rationale for the importance of internal autopsy in cases that may otherwise be assigned a cause of death based on patient history, CT scan findings, and an external-only post-mortem examination.

## RAPID EXOME SEQUENCING AND ADJUNCT RNA STUDIES CONFIRM PATHOGENICITY OF A NOVEL HOMOZYGOUS *ASNS* SPLICING VARIANT IN A CRITICALLY ILL NEONATE

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Rapid genomic diagnosis programs are transforming rare disease diagnosis in paediatric acute care. Determining the pathogenicity of variants of uncertain significance within clinically relevant timeframes remains challenging. A ventilated newborn with cerebellar hypoplasia underwent rapid exome sequencing, identifying a novel homozygous *ASNS* splice-site variant (NM_133436.3:c.1476+1G>A) of uncertain significance in 75.5 hours. Rapid ASNS splicing studies using blood-derived mRNA from the family trio confirmed a consistent pattern of abnormal splicing induced by the variant (cryptic 5′ splice-site or exon 12 skipping) with absence of normal *ASNS* splicing in the proband. Splicing studies were reported within 10 days and led to reclassification of c.1476+1G>A as pathogenic at age 27 days, diagnosing asparagine synthetase deficiency (MIM 615574). Intensive care was redirected towards palliation. Time from initial exome sequencing report to variant reclassification was 22 days. Cost analysis based on hospitalisation length of stay for the proband and his similarly affected deceased sibling demonstrated that early diagnosis led to a reduction in hospitalisation costs by AU$117,800. We highlight diagnostic benefits of adjunct RNA testing to confirm pathogenicity of splicing variants identified via rapid genomic testing pipelines for precision and preventative medicine.

## MEASURING THE QUALITY OF PATHOLOGY REPORTS

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Pathology has traditionally used process-based tools to assure safety and quality. These include risk-based standards focussing on staffing competencies, equipment maintenance, procedure standardisation, and use of a quality management system (QMS). Within the QMS, quality is systematically monitored through quality control, quality assurance (QA) programs and audits.
We have previously shown that the major opportunities for error lie at boundaries between the pathology laboratory and the rest of the health system. Our previous work developed pre-analytical QA tools. We now describe the development of a post-analytical QA tool.
Our new tool allows quantitative measure of the quality of the final pathology report. Using genetic pathology as an example, we measured the quality of every final pathology report produced by a laboratory over a $2\frac{1}{2}$ year period. Statistical measures calculated the likelihood of an error being present, whether such errors were major or minor, and whether the rates of errors detected were statistically stable. Applying this tool to the laboratory resulted in a 2- to 5-fold reduction in frequency of errors and quantitative improvement in quality of pathology reports.
Although our tool has been piloted in genetic pathology, it is readily applicable to all pathology disciplines.

## PETER MAC EXPERIENCE WITH COMPREHENSIVE GENOMIC PROFILING – THE NEW STANDARD OF CARE IN TISSUE PATHOLOGY?

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Comprehensive genomic profiling (CGP) describes technologies that allow profiling of all major types of genomic alterations, including simple nucleotide variation (SNV and indel), somatic copy number alteration (SCNA), structural variation (SV), and aggregate markers of genome damage such as tumour mutation burden (TMB) and microsatellite instability (MSI). CGP could lead to improved access to molecularly targeted therapies for cancer patients but, aside from a few accredited commercial and academic providers, is not widely used in routine pathology practice. Aspects of CGP presenting barriers to broad adoption include cost, technical complexity, lack of reimbursement, and a perceived lack of clinical utility. Here we summarise the experience of Peter Mac's Pathology Department in providing CGP in the translation research setting over three years of testing for personalised medicine trials. We find that characterising tumours using a comprehensive in-house clinical research panel provides useful diagnostic and predictive information that impacts patient care in a number of cases, however at relatively high per sample cost. In comparison, we describe our experience with one of the first kit-based CGP research products on the Australian market meeting the requirements for routine CGP.

## IMPROVING GENOMICS AND BIOINFORMATICS LITERACY IN THE UNDERGRADUATE MEDICAL SCIENCE CURRICULUM

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**Background:** The growth of genetic sequencing requests for pathology diagnoses and personalised medicine demands that graduating medical scientists be cognisant of genomics and bioinformatics, in preparation for their future careers.
**Aim:** To improve the genomic and bioinformatics literacy of undergraduate Medical Science students.
**Methods:** QUT Bachelor of Medical Science students enrolled in a fourth-year core unit, studied a series of lectures and workshops covering genomic and bioinformatics analysis of bacterial, human germline and somatic case studies relevant to pathology diagnosis. The bioinformatics platform used was Galaxy. Students voluntarily and anonymously completed a survey prior and subsequent to the workshops to ascertain their growth in genomic literacy.
**Results:** Fifty-five students completed the pre-workshops survey: eight students declared 'very little' prior experience with bioinformatics, and four declared some experience in coding. The other students declared no previous experience. Fifteen students completed the post-workshop survey, of which 14 were 'a bit confident' or 'moderately confident' in their abilities. Eight students were moderately or strongly interested in continuing study in this area.
**Discussion:** Embedding and advancing teaching and learning of clinical genomics and bioinformatics in the undergraduate Medical Science curriculum is crucial for providing career-ready graduates in this burgeoning discipline of pathology.

## URINE ORGANIC ACID (UOA) ANALYSIS FOR THE DIAGNOSIS OF AROMATIC L-AMINO ACID DECARBOXYLASE (AADC) DEFICIENCY

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We describe the use of urine organic acid (UOA) analysis for the diagnosis of a CSF neurotransmitter defect, aromatic L-amino acid decarboxylase (AADC) deficiency in a 3-month-old boy. The patient presented with upper limbs spasm and abnormal eye movement. UOA was initiated for possible inborn errors of metabolism (IEM). Hyper-excretion of urine vanillactic acid (VLA) and N-acetyl-vanilalanine was detected in UOA which the pattern is pathognomonic to AADC deficiency. The diagnosis was subsequently confirmed by analysing the hotspot pathogenic variant in the *DDC* gene, i.e., IVS6+4A>T in <2 days. A CSF neurotransmitter profile was requested by the clinician and showed a classical pattern of AADC deficiency with markedly elevated 3-O-methyldopa of 2895 nmol/L (RI <300) and very low levels of 5-HIAA (<17 nmol/L; RI 114–335) and HVA (<67 nmol/L; RI 295–932). Because CSF sampling can be technically challenging and is also invasive, our case illustrates the potential of using non-invasive UOA to replace CSF neurotransmitter for the diagnosis of AADC. This is particularly useful clinically if sampling of CSF is practically infeasible. In conclusion, UOA is a simple and non-invasive test for AADC deficiency, and substantiate the previous work reported by Lee *et al.*[1]

**Reference**

1. Lee HC, Lai CK, Yau KC, *et al.* Non-invasive urinary screening for aromatic L-amino acid decarboxylase deficiency in high-prevalence areas: a pilot study. *Clin Chim Acta* 2012; 413: 126–30.

## IMPACT OF MATERNAL EXERCISE ON THE FRACTION OF FETAL CELL FREE DNA IN MATERNAL PLASMA

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**Aim:** Maternal exercise prior to non-invasive prenatal testing (NIPT) may reduce the fraction of cell free DNA attributable to the fetus ('fetal fraction'), a key determinant of NIPT performance. This pilot study aimed to assess the impact of maternal exercise on fetal fraction.
**Methods:** 15 pregnant women of gestational age $\geq$10 weeks were recruited from a public hospital antenatal service. Moderate exercise was undertaken (clinical exercise stress test as per Bruce protocol with target heart rate of 140 bpm), with peripheral blood collected pre- and post-exercise. Gestational age, maternal age, maternal body mass index (BMI), heart rate, and blood pressure were recorded. Fetal fraction was determined by the Harmony NIPT assay.

**Results:** As a cohort, there was no significant difference in post-exercise fetal fraction ($p$=0.38). However, women with BMI <25 had an average fetal fraction change of −2.3% ($n$=5, $p$=0.02), while women with BMI ≥25 had an average change of +0.5% ($n$=10, $p$=0.25). Change in fetal fraction was not influenced by gestational age, maternal age, change in heart rate, or change in systolic blood pressure.
**Discussion:** Moderate maternal exercise may only impact fetal fraction when maternal BMI is <25. Further studies are required to confirm this association.

## MEASURABLE RESIDUAL DISEASE (MRD) DETECTION BY NEXT GENERATION SEQUENCING (NGS) IN ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)

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**Introduction:** MRD, a key prognostic factor in ALL, is traditionally assessed by flow cytometry and/or allele specific oligonucleotide PCR (ASO-PCR). Here we describe validation and implementation of novel NGS technologies to measure MRD at clinically relevant time points.
**Methods:** Extracted DNA from bone marrow were analysed using the LymphoTrack® Diagnostic Assay Panel to detect IgH gene rearrangements. Sequence clonality was defined as >2.5% of total reads and >2x frequency of the third most frequent sequence. A 100 cell equivalent spike-in control (LymphoQuant™) was utilised for normalisation.
**Results:** Results were concordant (78.18%) between assay methods with the exception of 12 samples. In 10 cases, MRD was detected by NGS at a lower level than flow cytometry and ASO-PCR, which were negative. MRD positivity by NGS corresponded with poor clinical outcomes in these patients. We demonstrate that the use of spike-in controls deliver clinically meaningful results.
**Conclusion:** MRD detection by NGS is complementary to testing using flow cytometry and ASO-PCR. NGS has the potential advantage of increased sensitivity, detection of clonal evolution and a rapid turnaround time. Normalisation of MRD levels to cell equivalents is required to suitably compare results with flow cytometry and ASO-PCR.

## REVIEW OF 12 MONTHS OF COPY NUMBER VARIANT CALLING ON A CLINICAL NEXT GENERATION SEQUENCING PIPELINE

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**Background:** Next generation sequencing (NGS) provides the opportunity to detect not only single nucleotide variants and small indels, but also larger whole exon or whole gene deletions and duplications (CNVs).
**Method:** We implemented CNV calling in our NGS pipeline utilising the DECoN, XHMM and PanelCNV packages. We compared the performance with multiplex ligation-dependent probe amplification (MLPA) on our 1200 gene panel (R1kD) and with chromosomal microarray (CMA) on our whole-exome (WES) platform.
**Results:** On the R1kD, we reviewed 197 patient cases which had both NGS and MLPA. We detected 25 deletions and 7 duplications, all of which were detected by both methods. Seven other CNV calls from NGS were considered artefacts during IGV review due to the presence of pseudogenes and poor mapping. On the WES platform, we reviewed 37 patient cases which had both NGS and CMA and detected 11 deletions and 10 duplications by both methods. NGS called some additional smaller events which were not reported by CMA.
**Conclusions:** CNV analysis on NGS can be implemented in clinical pipelines. Based on review of the first 12 months of service we have moved some tests to NGS with MLPA only performed to check positive results.

## HEPARIN INDUCED THROMBOCYTOPENIA IN PATIENTS WITH SEVERE RHABDOMYOLYSIS: A CASE SERIES

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Heparin-induced thrombocytopenia (HIT) is a known immunological complication of heparin administration which can cause life threatening thrombosis. Here, we report a series of three cases of HIT in the context of acute kidney injury due to rhabdomyolysis that presented to Launceston General Hospital, Tasmania, between December 2017 and December 2018. During this time, there were a total number of four patients with HIT, out of which three had rhabdomyolysis. Patients were all men with age between 29 and 68 years old. The causes of rhabdomyolysis were statin therapy (in two cases) and ischemia induced by compartment syndrome (in one case). All patients received unfractionated heparin and continuous renal replacement therapy for 2–11 days. 4Tscore was 4 in one patient and 5 in two other patients. None of patients had thrombosis complication. In all patients, anti-heparin/PF4 antibody was detected by BioRad Heparin/PF4 gel column assay and the diagnosis was confirmed by serotonin release assay. Patients received non-heparin anticoagulation. Platelet count recovered after cessation of heparin. Since rhabdomyolysis is an uncommon condition, the concomitant development of HIT in our 3 cases raises the suspicion whether administration of unfractionated heparin in patients with rhabdomyolysis poses an additional risk for developing HIT.

## IDARUCIZUMAB RESISTANCE DUE TO A MARKEDLY ELEVATED DABIGATRAN CONCENTRATION – A CASE REPORT

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Dabigatran is a direct thrombin inhibitor licensed for treatment of venous thromboembolism and in stroke prevention for patients with non-valvular atrial fibrillation. It can be rapidly reversed when clinically indicated with idarucizumab, a humanised monoclonal antibody fragment.[1]

A 64-year-old male taking dabigatran 110 mg daily for management of atrial fibrillation presented with abdominal pain and acute kidney injury. On presentation he was found to have a markedly elevated dabigatran concentration of 2230 ng/mL and deranged coagulation profile with a thrombin time of >200 seconds (RR 10–12 seconds) and INR of 11.2. Idarucizumab 5 g was administered and continuous renal replacement therapy commenced for persistent bleeding from a central line. However repeat dabigatran concentration performed 6 hours following idarucizumab administration had increased to 3722 ng/mL. A further dose of idarucizumab 5 g was administered 14 hours following the initial dose. Dabigatran concentration performed 4 hours following the second dose was 1787 ng/mL.

This case highlights a markedly elevated dabigatran concentration with significant coagulopathy in the context of kidney impairment and possibly concomitant amiodarone use. Despite idarucizumab the dabigatran concentration was markedly elevated, indicating idarucizumab resistance. Although uncommon, idarucizumab resistance must be excluded by repeat dabigatran concentration testing, particularly when the initial dabigatran concentration is elevated and/or kidney impairment.

**Reference**

1. Pollack CV Jr, Reilly PA, van Ryn J. Idarucizumab for dabigatran reversal—full cohort analysis. *N Engl J Med* 2017; 377: 431–41.

## HYPEREOSINOPHILIA IN A PATIENT WITH REFRACTORY ECZEMA AND ALK-NEGATIVE ANAPLASTIC LARGE CELL LYMPHOMA

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A 41-year-old man with refractory eczema on immunosuppressants developed swinging fever and dyspnoea, with left pleural effusion and left axillary and groin lymphadenopathy (2–3 cm) found in physical examination. Clinically there was no eczema flare-up.

Laboratory tests showed hypereosinophilia ($79.1\times10^9$/L) and elevated LDH (520 U/L) and ALP (187 U/L). Some dysplastic eosinophils showing hyposegmented nuclei and hypogranular cytoplasm were noted on blood smears. Workup for parasites, allergy and autoimmune markers was unremarkable.

Thoracentesis yielded exudative effusate with numerous lymphocytes (WBC >1000/mm$^3$) but no malignant cell was evident. FNAC of lymph nodes found eosinophilic infiltrate only. Bone marrow examination revealed marked eosinophilia with similar dysplastic features and megakaryocytic hyperplasia, raising suspicion of myeloproliferative neoplasms. Karyotyping, molecular tests for JAK2 mutation and BCR-ABL1 fusion, and FISH for FIP1L1-PDGFRA, PDGRFB and FGFR1 rearrangements were unremarkable.

Excisional biopsy of left groin lymph node was then pursued and demonstrated sheets of pleomorphic neoplastic cells with focal 'hallmark cells'. Anaplastic large cell lymphoma ($ALK^-$ $CD30^+CD3^+CD8^+$) was diagnosed. PET/CT scan revealed a stage-IV disease with extensive supra- and infra-diaphragmatic hypermetabolic lymph nodes and multiple bone involvements. The patient opted for brentuximab vedotin plus combination chemotherapy.

This case underscores the importance of exhaustive investigations and clinicopathological corroboration in the workup of hypereosinophilia.

## NEUTRALISATION OF RIVAROXABAN INTERFERENCE ON APCR, FVIII AND FIX ASSAYS BY DOAC-STOP AND ANDEXANET ALFA

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Rivaroxaban is a widely utilised direct oral anticoagulant (DOAC), indicated for thrombosis treatment and prevention. Rivaroxaban binds to Factor Xa, affecting many haemostasis assays, including activated protein C resistance (APCR) and APTT based factor assays, including factor VIII (FVIII) and IX (FIX). Andexanet alfa is a clinical 'antidote' for anti-Xa agents, including rivaroxaban, neutralising activity *in vivo* and *in vitro*. DOAC-Stop is a commercial product that neutralises *in vitro* activity of DOACs.

We investigated whether rivaroxaban would induce false positive APCR and/or falsely reduced FVIII and FIX activity, and whether this could be neutralised by andexanet alfa or DOAC-Stop.

Four lyophilised plasma samples were prepared: normal plasma, and normal plasma spiked with rivaroxaban (200 ng/mL); rivaroxaban + DOAC-Stop; rivaroxaban + andexanet alfa. These were distributed to laboratories performing APCR and/or FVIII and FIX testing in RCPAQAP surveys. Data was analysed using robust statistics (mean, SD and CV).

In rivaroxaban 200 ng/mL samples, most APCR assays appeared largely unaffected, while FVIII and FIX assays showed a substantive reduction. Where assays were affected, DOAC-Stop neutralised rivaroxaban effects. Andexanet alfa did not completely neutralise the rivaroxaban effect, for APCR or FVIII and FIX, and unexpectedly lead to higher rates of false APCR than rivaroxaban alone.

## THE CHANGING FACE OF TESTING FOR ACTIVATED PROTEIN C RESISTANCE (APCR) – A 10-YEAR RETROSPECTIVE

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Activated protein C resistance (APCR) is a hypercoagulable condition that increases the risk of venous thrombosis. The Royal College of Pathologists of Australasia Quality Assurance

Programs (RCPAQAP) offers quality assurance testing for APCR twice a year. Participants either used activated partial thromboplastin time (APTT) or Russell viper venom time (RVVT) to perform clotting assays, with the end point of identification or exclusion of APCR. We aimed to identify trends in APCR testing, which methods and reagent kits are better in the identification against those reagent kits at risk of reporting false positive and/or false negative APCR.

Data from 40 APCR samples over the past 10 years was analysed. False positive and false negative rates were calculated per sample, and reagent kits.

There was an 18% increase in participants performing APCR testing, with participants reporting fewer incorrect interpretations in 2019 (3.0%) than in 2010 (16.8%). There was a move from APTT to RVVT based methods, with 59% users in 2019, compared to 48% in 2010. This likely contributed to lower percentages of incorrect results, as it was found that participants using APTT based assays reported more false negatives (87.8% of total) and false positives (72.2% of total) than those using RVVT based assays.

## DRUG-INDUCED AUTOIMMUNE HAEMOLYTIC ANAEMIA IN A PATIENT TREATED WITH ARTESUNATE FOR MALARIA INFECTION

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A 54-year-old woman was diagnosed with severe *Plasmodium falciparum* malaria following travel to Guinea. Her haemoglobin (Hb) at presentation was 138 g/L (ref range 115–160), with an initial parasite density of 5% and otherwise normal red cell morphology. The patient showed a good response to second line anti-malarial therapy with artesunate but represented 16 days post treatment initiation with symptomatic anaemia (Hb of 64 g/L), and displayed typical laboratory features consistent with haemolysis. The direct antiglobulin test (DAT) was positive (3/4) showing IgG and C3d specificity. The antibody screen was also positive, with grade 4+ reactions against all screening cells. Drug-induced autoimmune haemolytic anaemia (DIIHA) from artesunate therapy was suspected.

Prednisolone 1 mg/kg therapy was commenced, and transfusion was avoided due to the presence of the autoantibody and high risk of transfusion reaction. Treatment was successful with rapid resolution of haemolysis and Hb completely normalised on follow-up testing within 2 weeks. Response was sustained with tapering of prednisolone.

Post-artesunate delayed haemolysis (PADH) is estimated to occur in about 15–30% of patients treated with the drug.[1] Cases with a positive DAT are less common but are increasingly being reported and raise the possibility that artesunate may cause DIIHA.

**Reference**

1. Camprubi D, Pereira A, Rodriguez-Valero N, *et al.* Positive direct antiglobulin test in post-artesunate delayed haemolysis: more than a coincidence? *Malar J* 2019; 15: 123.

## HIGHLIGHTING THE NEED FOR HARMONISATION OF G6PD REPORTING FOLLOWING THE INTRODUCTION OF NEW ANTIMALARIALS

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The recent introduction of new antimalarial drugs (e.g., tafenoquine)[1] comes with a recommendation to ascertain G6PD deficiency in order to avoid drug induced haemolysis.

A recent review of RCPAQAP G6PD survey results revealed a degree of variation in the interpretation of assay results in the range of 2.0–9.0 U/g Hb.

**Aim:** To assess the current status of G6PD testing and reporting with a view to providing additional information to laboratories and clinicians when assessing patients prior to prescribing antimalarial drugs.

**Method:** An online survey was forwarded to laboratories participating in the 2019 RCPAQAP Haematology G6PD program seeking further information about their testing, interpretation and reporting of G6PD results. 76 of the 144 participating labs (53%) responded.

**Results:** The key findings were:

- A wide variation in reference intervals being reported (lower limit of normal ranging from 4.6 to 11 U/g Hb).
- 69% of respondents did not normally refer G6PD results for haematologist review.
- 93% of respondents do not specify a cut-off level of G6PD and/or interpretive comment below which it is not advisable to administer antimalarial drugs.

**Conclusion:** The key findings highlight the need to harmonise the reporting and interpretation of G6PD, particularly in light of new antimalarial treatments.

**Reference**

1. Tse EG, Korsik M, Todd MH. The past, present and future of anti-malarial medicines. *Malar J* 2019; 18: 93.

## MICROSCOPY AND ICT VS LAMP ASSAY IN THE DIAGNOSIS OF MALARIA: A REAL-WORLD TIME AND COST-EFFECTIVE ANALYSIS

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**Background:** Malaria has traditionally been diagnosed using microscopy and immunochromatographic (ICT) assay. However, they are not without limitations including limited sensitivities.[1] Alethia Malaria is a DNA assay using LAMP (loop-mediated isothermal amplification) for the direct detection of *Plasmodium* spp. Studies have shown good sensitivity and specificity with a higher level of detection compared to microsocopy.[2]

**Aim:** To determine a time and cost effective analysis of malaria diagnostic testing using microscopy and ICT vs LAMP assay in a community laboratory.

**Methods:** Malaria requests were identified at Australian Clinical Laboratories, Clayton, until 20 samples were obtained. All samples had microscopy, ICT and LAMP assay performed. The duration for the preparation of each test, microscopy review by

two scientists, and LAMP analyser time were recorded. Consumables, equipment and labour cost were calculated.
**Results:** The median time to result for microscopy and ICT was 49 min (including 14 min microscopy review). The cost per sample was AU$19.45 or AU$42.95 for 3 samples. The median time to result for the LAMP assay was 53 min (13 min sample preparation, 40 min analyser time) with a cost of AU$21.50 per sample.
**Conclusion:** The LAMP assay is a time and cost effective malaria diagnostic screening tool and should be considered for implementation in the laboratory.
**References**
1. Mathison BA, Pritt BS. Update on malaria diagnostics and test utilization. *J Clin Microbiol* 2017; 55: 2009–17.
2. Rypien C, Chow B, Chan WW, *et al.* Detection of Plasmodium infection by the Illumigene Malaria Assay compared to reference microscopy and real-time PCR. *J Clin Microbiol* 2017; 55: 3037–45.

## EVALUATION OF A T-CELL PROLYMPHOCYTIC LEUKAEMIA (T-PLL) EQA CASE STUDY

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Morphology continues to be a key diagnostic tool in identifying haematological disorders. The Royal College of Pathologists of Australasia Quality Assurance Program (RCPAQAP) offers an external proficiency program (EQA) in diagnostic morphology. The aim of the program is to assess the ability of participants to diagnose a case study through recognition of key morphological diagnostic features. Findings on a T-cell prolymphocytic leukaemia (T-PLL) case study were reviewed as a potential indicator of diagnostic capability among participating laboratories.
**Method:** The morphology program consists of 4 runs per year and three case studies per run. This case study featured a T-PLL. Participants were assessed using a predetermined scoring system for both the morphological and diagnostic component.
**Results:** The expected key morphological diagnostic features were a marked lymphocytosis with a predominance of small abnormal lymphoid cells containing prominent cytoplasmic blebbing. In addition, mature nuclear chromatin with a high magnification comment indicating highly convoluted nuclei with most containing a single small nucleolus.[1] Of the 499 participants, 76% (379) indicated the presence of the abnormal lymphocytes (T-cell prolymphocytes). However, only 45% (223) submitted a diagnosis of T-PLL.
**Conclusion:** This case study highlights an ongoing need for EQA programs to provide challenges to improve education and training in morphology.
**Reference**
1. Swerdlow SH, Campo E, Harris NL, *et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues.* Revised 4th ed. Lyon: IARC, 2017; 346–8.

## GUIDELINES FOR REPORTING BLOOD CELL MORPHOLOGY – ARE LABORATORIES FOLLOWING?

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In 2015, the International Council for Standardization in Haematology (ICSH) released a report outlining recommendations for the standardisation of nomenclature and grading of peripheral blood cell morphological features. Based on these, lymphoid cells with a suspected malignant or clonal aetiology should be classified as abnormal lymphocytes with an accompanying description of the cells.[1] We sought to evaluate if laboratories were following the ISCH reporting recommendations.
**Method:** Laboratories enrolled in the 2019 RCPAQAP Manual Differential program were provided with clinical notes, a stained blood film (which featured a T-cell prolymphocytic leukaemia case) and asked to categorise the different white blood cells. Assessment was based on robust statistical analysis and the clinical scenario.
**Results:** 79% (378/480) of labs reported the presence of abnormal lymphocytes, however, only 10% (41) provided a description of the abnormal cells. 23 participants included the abnormal cells as part of the lymphocyte count, while 15 participants counted the abnormal cells as 'others' without a description.
**Discussion and conclusion:** The main morphological features that were expected to be reported were the presence of abnormal lymphocytes and an associated description (T-cell prolymphocytes). Based on the results for this survey, either laboratories have a low uptake on the ICSH guidelines or they are missing important morphological features indicating the need for standardisation in blood film morphology reporting.
**Reference**
1. Palmer L, Briggs C, McFadden S, *et al.* ICSH recommendations for the standardization of nomenclature and grading of peripheral blood cell morphological features. *Int J Lab Haematol* 2015; 37: 287–303.

## DROPLET DIGITAL PCR FOR FETAL HPA-1A TYPING – NIPT PROOF OF PRINCIPLE STUDY

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**Background:** There is a clinical need for a non-invasive prenatal test (NIPT) that accurately assesses fetal HPA-1a status in feto-neonatal alloimmune thrombocytopenia (FNAIT) investigations. This is relevant for HPA-1bb women who have developed HPA-1a antibodies.
**Aims:** To establish proof of principal that droplet digital (dd) PCR is a suitable platform for NIPT, to detect fetal HPA-1 status.
**Methods:** Maternal blood samples were collected from four subjects, gestation ages ranges from $12^{+4}$ ,13, 22 and 39 weeks. Cell-free fetal (cff)DNA was extracted from maternal plasma for ddPCR. Cultured amniocytes or infant cord serology were used to confirm the findings.
**Results:** Optimisation demonstrated that the ddPCR assay could be performed using the same reaction and cycling conditions as NIPT assays developed for fetal red cell antigen predictions.
Fetal specific signals were detected for HPA1a sequences for three of the four cases: only the 13-week case lacked signals, predicting that the baby was negative. Genotyping outcomes correlated with cultured amniocyte genotype.

**Summary/conclusions:** This study provides proof-of-principle that ddPCR reliably detects fetal HPA-1a signals from early gestation, allowing clinicians time to assess the need for IVIg management. This assay has the potential to provide a safer approach for managing such alloimmunised antenatal cases.

## LIQUID BIOPSY FOR MANAGEMENT OF HAEMOLYTIC DISEASE OF THE FETUS AND NEWBORN

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**Background:** Haemolytic disease of the fetus and newborn arises from maternal allo-antibodies to red cell antigens, crossing the placenta. The most frequent antibodies after RhD, are Kell, Duffy and RhCE antigens.
Liquid biopsy in pregnancy management is concerned with the detection of cell-free fetal DNA (cffDNA) circulating in the maternal plasma. The accuracy for fetal *RHD* genotyping is well established.
**Aim:** To evaluate a maternal blood test to predict the fetal, non-RhD, blood group status.
**Methods:** A clinical collaborative study assessed the accuracy for a suite of assays to predict fetal Kell, Duffy, Rhc/C and Rhe/E status for women with respective antibodies ($n$=90, gestation age 8–37 weeks).
Droplet digital PCR technology, ddPCR, tested for single nucleotide variants (SNVs) associated with these blood group antigens. Infant cord blood serotypes were used as the primary outcome measure.
**Results:** Fetal specific signals were detected as early as 8 weeks gestation. Genotyping matched all available infant cord outcomes 45/45. Accuracy is 100% (95% confidence interval 91.96–100%).
**Discussion:** A clinical demand exists for liquid biopsy of maternal blood for fetal blood group genotyping. Droplet digital PCR is accurate and provides an evidence base to guide clinical care for at-risk pregnancies.

## UTILISING GENEXPERT TO IDENTIFY CML IN THE PRIMARY CARE SETTING: TRIGGERS FOR TESTING AND PREDICTORS OF POSITIVE RESULTS

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The GeneXpert utilises quantitative PCR to detect BCR-ABL fusion transcripts in the molecular monitoring of patient with chronic myeloid leukaemia (CML).[1] Although GeneXpert hasn't currently been validated for the diagnosis of CML, BCR-ABL PCR on peripheral blood is frequently requested for this purpose. We performed a retrospective audit of BCR-ABL results in patients without established CML to assess test indications, triggers for ordering and the pre-test predictors of a positive BCR-ABL result. From January to November 2019, there were 178 tests with ten positive cases identified. All positive cases were initiated by a general practitioner triggered by a previous abnormal full blood count and film and had leucocytosis, neutrophilia and myeloid left shift, with nine cases having a basophilia. The presence of basophilia and myeloid left shift amongst the 178 patients was highly predictive of an underlying myeloid neoplasm or clonal myeloid mutation on subsequent molecular testing (PPV 100% and 71%, respectively). This reinforces our laboratory protocol of contacting general practitioners when these features are identified on blood film to expedite further testing and referral. In order to reduce unnecessary ordering of BCR-ABL, education is required regarding the low yield of this test in the absence of leucocytosis or neutrophilia.

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## METASTATIC GERM CELL TUMOUR PRESENTING AS ACUTE MEGAKARYOBLASTIC LEUKAEMIA AND DISSEMINATED MELANOMA: A CASE REPORT

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Since first recognised in 1985, studies have described the unique and rare association between haematological malignancies and germ cell tumours, most commonly acute megakaryoblastic leukemia (AMKL) and non-seminomatous germ cell tumours. A recent molecular study identified mutations in PTEN and TP53 in both tumours, supporting the theory that distinct genomic alterations underlie this rare association. It is also recognised that teratomatous components of mediastinal germ cell tumours have a tendency for secondary transformation to other malignancies including melanoma. We report a case of a 38-year-old man presenting with severe back pain. An MRI spine demonstrated diffuse marrow replacement and bony lesions concerning for metastatic disease. The patient had recently completed chemotherapy for a mediastinal germ cell tumour with teratomatous components on histopathology. A staging CT identified liver and splenic lesions suspicious for metastatic deposits. A peripheral blood film performed on admission was found to have circulating blasts with an immunophenotype consistent with megakaryoblasts. He subsequently underwent a bone marrow biopsy confirming AMKL with a TP53 mutation. A liver biopsy revealed necrotic tumour with immunohistochemistry consistent with metastatic melanoma. In summary, we describe a case of treated mediastinal germ cell tumour with secondary transformation to metastatic melanoma with synchronous AMKL.

## UNKNOWN UNKNOWNS: LIMITATIONS IN DETECTING TYPE II ANTITHROMBIN DEFICIENCY BY THE XA-BASED CHROMOGENIC METHOD

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Inherited deficiency of antithrombin (AT) occurs as a heterozygous quantitative reduction (type I) or qualitative reduction (type

II), and causes a high risk of thrombotic complications, including venous thromboembolism and obstetric morbidity. Recently updated international guidelines recommend incorporating a combination of a chromogenic thrombin or Xa-based functional assay, a progressive (heparin-independent, prolonged incubation) functional assay and a quantitative assay (e.g., latex agglutination or ELISA) in the evaluation of AT deficiency, however only chromogenic functional assays are routinely performed in Australian laboratories.[1] These functional assays have varying sensitivity to the wide variety of AT mutations, especially type II lesions, depending on the serine protease, incubation time and reagents used.[2,3]

We describe four cases of suspected type II AT deficiency which demonstrated discrepant results between functional assays/reagents, and compare our historical cohort data of reduced AT activity before and after changing between commercial reagents. Trends in sensitivity of different assays/reagents reported in local and international quality assurance programs are also reviewed. These findings highlight the potential for under diagnosis of AT deficiency, the importance of fully characterising assay performance and understanding limitations in assay sensitivity – especially in these uncommon but clinically significant variants.

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## BLOOD GROUP EXOME SEQUENCING DEFINES NULL AND WEAK KIDD (JK) PHENOTYPES: EVIDENCE FOR TRANSFUSION MANAGEMENT

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**Background:** The rare Jk(a-b-) Jk:-3 phenotype of the clinically significant Kidd blood group system (ISBT 009) is frequently encountered in the Polynesian population (0.272% compared to 0.002% in Caucasians).[1] Discrepancies between phenotype and genotype have revealed the limitations of conventional methods in differentiating true Jk(a-b-) phenotypes from those with variable antigen expression caused by genetic variants. We report two cases that were resolved by massively parallel sequencing (MPS).

**Methods:** The testing algorithm comprises red cell phenotyping plus genotyping using SNP array to determine Jk(a/b) antigen status. Sequencing using a targeted blood group exome panel on the Illumina MiSeq is applied when discordant results are obtained.

**Results:** Case 1: Phenotype Jk(a-b-), genotype predicted Jk(a+b+). Sequencing indicated homozygosity for a silencing splice site variant, c.342-1G>A, predicting the 'null' Jk(a-b-) phenotype.

Case 2: Phenotype results were equivocal, suggesting either Jk(a+$^{w}$b-) or Jk(a-b-). Genotype results predicted Jk(a+b-). Sequencing indicated heterozygosity for nucleotide substitution, c.130G>A, defining the JK*01W.01 allele, consistent with weakened Jk(a) expression, therefore reported as phenotype Jk(a+$^{w}$b-).

**Discussion:** MPS defined blood group allelic variants to distinguish between null and weak antigen expression. This provides evidence to guide patient transfusion management and the precise provision of rare Jk(a-b-) blood inventory only when required.

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## USE OF MOLECULAR MUTATIONS IN HIGH RISK MPN FOR ASSESSMENT OF BLASTIC TRANSFORMATION

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BCR-ABL negative myeloproliferative neoplasms are a heterogenous group of clonal haematopoietic stem cell disease all of which have an intrinsic risk of evolution into acute myeloid leukaemia.[1] The frequency of leukaemia transformation varies according to the subtype with primary myelofibrosis estimated at 10–20% at 10 years followed by polycythemia vera at 2.3% in 10 years and essential thrombocytopenia varying widely from <1% to up to 10%.[1] Although blastic transformation often progress to acute myeloid leukaemia, transformation to acute megakaryoblastic leukaemia is rare in adult population being <1% of all AML.[2] We report a case of a 58-year-old lady who presented with progressive symptoms of fevers, back pain and fatigue with a 10 year history of polycythemia vera/essential thrombocytosis overlap. Laboratory testing showed neutrophilia, mild anaemia with elevated lactate dehydrogenase and uric acid. Bone marrow biopsy showed marked infiltration of megakaryoblasts of various size and maturity with cytogenetics demonstrating hypertripody. Myeloid gene panel demonstrated mutations of JAK2, TP53 and TET2 which have been reported to concur high risk of blastic transformation in myeloproliferative neoplasms.[3] In summary, we describe a case of PV/ET overlap with rare transformation into acute megakaryoblastic leukaemia.

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## ATYPICAL PRESENTATION OF IGA-RELATED IMMEDIATE REACTION WITH BACK PAIN AND RELATIVE HYPOTENSION – ANAPHYLAXIS OR NOT?

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Anaphylactic transfusion reactions are rare, occurring in approximately 1 in 50,000 red cell transfusions.[1] One aetiology includes the development of antibodies against transfused IgA in patients with severe IgA deficiency. Diagnosis of IgA-related anaphylaxis involves the measurement of IgA levels and anti-IgA antibodies.[2] Recently, the evidence underlying this entity and the causal relationship between laboratory tests and clinical manifestation has been questioned.[3] We describe a case of a 50-year-old man with chronic anaemia with an infected enterocutaneous fistula. He received six red cell transfusions where he developed severe back pain and relative hypotension within 15–30 minutes of transfusion, settling after transfusion was ceased. He was afebrile with no respiratory, dermatological or gastrointestinal manifestations typical of anaphylaxis. Direct antiglobulin test was negative, and blood cultures were sterile. Tryptase taken 2.6 hours after symptom onset was raised 16 μg/L (0.0–11.4 μg/L). IgA level was <0.10 g/L (0.80–4.40g/L). Anti-IgA titre was 400 U/mL (0–7 U/mL). IgA deficient components were prepared pre-operatively. He subsequently received three washed red cells uneventfully, one during a laparotomy for the enterocutaneous fistula.

This case describes an atypical presentation of a rare but important complication of blood transfusion, as well as the diagnostic process and subsequent management.

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## UTILISATION, OVER-ACTIVATION, PRODUCT NON-UTILISATION AND OUTCOMES FROM MASSIVE TRANSFUSION PROTOCOL (MTP) ACTIVATIONS IN A NON-MAJOR TRAUMA CENTRE

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**Background:** Locally adapted MTP is recommended to deliver blood products to patients with critical bleeding to improve outcomes.[1]

**Method:** Retrospective study of MTPs in a non-major trauma centre (Nepean Hospital) between January 2018 to October 2019. Clinical outcomes were retrieved from electronic medical records.

**Results:** There were 102 MTP activations during the study period. Non-trauma related bleeding accounted for 96.1%, with gastrointestinal (38.2%) and obstetric (21.6%) sources most common. Of first shipments, all four units of red cells (RC) were used in 79.4% of activations, and all four fresh frozen plasma (FFP) were used in 80%. An FFP:RC ratio of 1:1–1:2 was achieved in 85.3% of activations that required ≥4 RCs. Average product non-utilisation rate was 0.73 RC and 0.59 FFP per activation. Overall, 16.3% of MTPs required ≥10 RCs within 24 hours (62.5% of these were gastrointestinal related bleeding). Mortality at 24-hours and 30-days was 3.9% and 11.8% respectively.

**Discussion:** This study highlights differing indications of MTP activation and severity of clinical status compared to major trauma centres.[2] The impact of MTP and transfusion ratios on clinical outcomes in this population remains unclear.[3] Further research is needed to optimise product usage, particularly for gastrointestinal and obstetric related bleeding.

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## LABORATORY INVESTIGATION OF A RARE COAGULATION FACTOR DEFICIENCY

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We present a case report of a 30-year-old pregnant patient who presented for haematologist review following incidental finding of a prolonged APTT. There was no family history of bleeding or thrombosis. Lupus anticoagulant testing, mixing study and factor assays were requested. Laboratory testing revealed a deficiency of prekallikrein.

Prekallikrein is a serine protease which forms part of the contact activation phase of coagulation. Prekallikrein deficiency is an autosomal recessive trait, and patients with homozygous or compound heterozygous deficiency will present with plasma prekallikrein levels <1%. While it is understood that patients with prekallikrein deficiency do not have a bleeding tendency, the defect may have a role in the development of hypertension and other cardiovascular conditions. This case study will review the laboratory investigations necessary to diagnose prekallikrein deficiency, and the sensitivity of different APTT reagents to deficiency of prekallikrein.

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## PURE RED CELL APLASIA, IMMUNE THROMBOCYTOPENIA AND POST-TRANSFUSION COOMBS' TEST NEGATIVE HAEMOLYSIS DURING ANTI-PD1 THERAPY FOR METASTATIC LUNG ADENOCARCINOMA – CASE REPORT

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Anti-Programmed Death Ligand 1 (PD-L1) and Anti-Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) checkpoint inhibitors are increasingly important treatment modalities for solid organ and haematological malignancies. Immune-mediated cytopenias are a rare consequence of checkpoint inhibition and include autoimmune haemolytic anaemia (AIHA), immune thrombocytopenia (ITP) and pure red cell aplasia (PRCA).

We report the case of a 75-year-old woman with metastatic lung adenocarcinoma on first line pembrolizumab therapy, presenting with profound anaemia with reticulocytopenia, moderate thrombocytopenia and haemolysis post red cell transfusion. Bone marrow biopsy showed absence of erythroid precursors, in keeping with PRCA, and presence of megakaryopoiesis, consistent with ITP. Extensive testing for the aetiology of haemolysis did not reveal a clear diagnosis.

She was treated with prednisolone initially, and red cell transfusion withheld. Due to inadequate response she was given intravenous immunoglobulin therapy which resulted in vigorous reticulocyte response and improvement in haemoglobin and platelet count. To date she has required no escalation of therapy.

In summary, we describe a rare case of concurrent PRCA and ITP during treatment with PD-L1 inhibitor therapy, and haemolysis of cryptic cause. Treating clinicians should be vigilant for the development of autoimmune haematological syndromes during checkpoint inhibitor therapy. Treatment with conventional immunosuppression is usually successful.

## A RETROSPECTIVE ANALYSIS OF CORRELATION BETWEEN APTT AND ANTI-XA LEVELS USING *EX VIVO* PLASMA SAMPLES FROM PATIENTS ON INTRAVENOUS HEPARIN THERAPY

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**Background:** Intravenous heparin therapy is traditionally monitored according to activated partial thromboplastin time (APTT). Alternatively, monitoring by anti-Xa level testing may be less affected by pre-(analytical) variables. We analysed 105 samples from 46 patients who were on heparin infusions for concordance between APTT and anti-Xa levels. The existing therapeutic ranges (TR) were defined as 60–100 s (APTT) and 0.3–0.7 U/mL (anti-Xa).

**Results:** Patients were predominantly male, admitted for treatment of acute coronary syndrome. Warfarin co-administration occurred in 20%. Median heparin rate was 100 U/h. Overall, 43% of samples showed concordance, with 21% of samples having both APTT and anti-Xa levels within the existing TR and 22% of samples having both APTT and anti-Xa levels in the sub-TR. In 19% of samples, the APTT was therapeutic whilst anti-Xa was sub-therapeutic. Variations in intrinsic pathway factors, fibrinogen or antithrombin were not predictive of discordance between APTT and anti-Xa.

**Conclusion:** Poor correlation between APTT and anti-Xa levels for monitoring heparin therapy cannot be explained by variations in other coagulation factors. Clinical outcomes correlation studies are required to determine optimal monitoring strategy for heparin therapy.

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## RELAPSED/REFRACTORY ETP-ALL SUCCESSFULLY TREATED WITH NOVEL COMBINATION THERAPY VENETOCLAX WITH NELARABINE PRIOR TO ALLOGENEIC STEM CELL TRANSPLANT

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T lymphoblastic leukemia (T-ALL) is malignant neoplasm of immature T-cells that has characteristic immunophenotypic subtypes that correspond to T-cell maturation stages. Early T-cell precursor acute lymphoblastic leukaemia (ETP-ALL) is one such subtype, which is derived from thymic cells at the early T-cell precursor differentiation stage and make up 5–16% of T-ALL cases.[1] ETP cells are derived from haematopoietic stem cells that have recently migrated to the thymus, and retain multilineage pluripotency. They display reduced expression of T cell antigens; typically CD1a(–), CD5(–/dim) and CD8(–), and display aberrant expression of stem cell or myeloid antigens.[2] Congruently, the genetic mutations seen in ETP-ALL are similar to those found in poorly differentiated myeloid neoplasms.[2] ETP-ALL is historically thought to have a poor prognosis with standard chemotherapy, and a dismal prognosis in the setting of relapsed and refractory disease. Recent research has described how ETP-ALL is dependent on BCL2, and hence how antagonists such as ABT-199 (venetoclax) may offer a potential therapeutic benefit.[3] This case study reports a patient with relapsed/refractory ETP-ALL with multiple genetic variants, who had an excellent response to a novel combination therapy of venetoclax with nelarabine prior to allogeneic stem cell transplant.

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## VARIATION IN HAEMATOLOGY REPORTING – A DRAIN ON CLINICIAN TIME AND SOURCE OF CLINICIAN ERROR

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**Aim:** To review the variability in reporting formats of laboratory tests across Australian laboratories and assess the potential for resultant wasted clinician time and clinician interpretation errors.
**Methods:** Haematology reports (FBC, coagulation screen) were reviewed from 15 Australian laboratories (the majority in NSW) via convenience sampling. The formatting aspects of a total of 20 reports/views were reviewed for test name, sequence of results down or across page, units and reference intervals.
**Results:** There was wide variability across most formatting aspects. Six laboratories reported the most recent results at the left of the page and six on the right. There were 9 variations in FBC and 4 for coagulation screen test sequences down the page. There was variation in test names for the same tests e.g., 8 (slightly) different names for neutrophils. Multiple versions of reference intervals were observed e.g., 8 different reference intervals for white cell count and 10 for MCV. Different number of significant figures were used for reporting some tests.
**Discussion:** Improving the standardisation of laboratory reporting formats may reduce time expended by clinicians reviewing results and reduce the risk of clinician error when interpreting results. This can only be achieved by laboratories collaborating in standardising these factors.

## HISTIOCYTIC SARCOMA TRANSFORMED FROM A LOW GRADE B LYMPHOPROLIFERATIVE DISORDER – A CASE REPORT

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Histiocytic sarcoma (HS) is a rare and aggressive lympho-hematopoietic malignancy that represents less than 1% of all non-Hodgkin lymphomas with poor response to therapy. According to the World Health Organization classification it is defined on the basis of morphological and immune-histochemical properties of mature tissue histiocytes.[1] It can occur sporadically or in association with other haematological neoplasms such low-grade lymphomas (follicular lymphoma or chronic lymphocytic leukaemia among others).[2] Patients can present with either localised or disseminated disease involving organs such as the skin, central nervous system, spleen, gastrointestinal system, lymph nodes and the bone marrow. The pathogenesis of HS remains unclear and the presence of characteristic cytogenetic abnormalities such as PTEN, p14ARF and p16INK4A are currently non-contributory in the management or prognostication of the disease.[3] As a result of the rarity of the disease and lack of clinical trials, treatment strategies remain a challenge due to limited therapeutic options which are largely based on case studies. We report a case of a 65-year-old woman presenting with histioctytic sarcoma, transformed from a low-grade B lymphoproliferative disorder (LPD). This case aims to highlight the heterogeneity of this disease, aggressive course and the limited treatment options available.

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## IDENTIFICATION OF *TP53* ABERRATIONS IN CHRONIC LYMPHOCYTIC LEUKAEMIA USING DIFFERENT MOLECULAR DIAGNOSTIC TECHNIQUES

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*TP53* aberrations arise through deletion or mutation of *TP53* gene. Accurate identification of *TP53* aberrations is important in risk stratification of chronic lymphocytic leukaemia (CLL).
**Aim:** To identify *TP53* aberrations in CLL using different diagnostic techniques.
**Methods:** Next-generation sequencing (NGS) for *TP53* mutation was performed in 104 CLL patients. Duplication/Deletion (Dup/Del) identification tool was developed in NGS analytic platform to identify *TP53* deletions. *TP53* deletions were also screened by fluorescent *in situ* hybridization (FISH) and multiplex ligation-dependent probe amplification (MLPA) in 81 and 40 patients respectively.
**Results:** *TP53* aberrations were identified in 29 patients; 27 had mutations with or without deleted *TP53* and 2 had sole *TP53* deletions. Of 43 mutations identified in these 27 patients, 26 mutations showed variant allele frequency of $\leq$12%. Most patients with mutated *TP53* (19/27) had no *TP53* deletions whereas 80% (8/10) of individuals with deleted *TP53* had concurrent mutations. Compared to FISH, sensitivities of Dup/Del tool and MLPA in identification of *TP53* deletions were 20% and 80% respectively.
**Discussion:** *TP53* mutation is the most frequent cause of gene inactivation. NGS should be offered to all CLL patients requiring treatment for proper prognostication. Regarding detection of *TP53* deletion, FISH is the best available screening technique.

## METASTATIC MALE BREAST CANCER FOUND FROM BONE MARROW TREPHINE

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The prevalence of male breast cancer is approximately 1% of all breast cancers. The most common histological subtype is ductal carcinoma, non-specific type. They are typically oestrogen and progesterone receptor positive and HER-2 receptor negative. A 79-year-old man underwent bone marrow biopsy. He initially presented to a different hospital for right clavicular fracture. CT thorax showed diffuse lytic lesions around the fracture site and in his vertabrae. This triggered a typical work up for multiple myeloma. He had no recent constitutional symptoms or history of malignancy. H&E staining demonstrated diffuse acinar infiltration. Therefore, serial cytokeratin staining was performed. After the exclusions of multiple organs as the primary site based on multiple negative immunohistochemistry, breast remained as the final target. Biopsy of breast was performed. The finding was concordant with bone marrow biopsy finding. This case demonstrated a benefit of a stepwise immunohistochemistry utility to diagnose unexpected metastatic malignancy from bone marrow biopsy.

## INTENTIONAL 24-FOLD OVERDOSE OF LOW-MOLECULAR-WEIGHT HEPARIN

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There is no established consensus on the management of massive low-molecular-weight heparin (LMWH) overdose. We describe a case of a 37-year-old woman who presented with an intentional overdose of 24 subcutaneous injections of enoxaparin 100 mg (2,400 mg total, or 24 mg/kg). Significant past history included recurrent venous thromboembolism treated with therapeutic enoxaparin following warfarin instability, obesity, prothrombin G20210A mutation, and epilepsy requiring antiepileptics that significantly affected P-glycoprotein and cytochrome P450 3A4. Clinical examination was unremarkable. Initial laboratory evaluation 7 hours post-overdose revealed an elevated activated partial thromboplastin time (APTT) of 167 seconds (reference range 26–36 seconds), international normalised ratio (INR) of 1.7 (<1.3), fibrinogen of 3.0 g/L (1.5-4.0 g/L), thrombin clotting time (TCT) of 79 seconds (12–22 seconds) and unrecordable anti-Xa level. Renal function was normal. The patient declined prophylactic protamine sulphate administration and as such was observed. At 16 hours post-overdose, APTT was 166 seconds and TCT 49 seconds. At 26 hours post-overdose, APTT and TCT normalised to 34 and 18 seconds, respectively, and anti-Xa level was 1.38 IU/mL (therapeutic range 0.6–1.0 IU/mL). There was no overt bleeding or a fall in haemoglobin. Following psychiatric assessment, she was discharged home with a view to reinitiating therapeutic enoxaparin.

## USING THE BASOPHIL ACTIVATION TEST FOR THE DIAGNOSIS OF NUT ALLERGY IN A PAEDIATRIC POPULATION

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**Background:** Children being assessed for nut allergy undergo specific IgE (sIgE), skin prick testing (SPT) and oral food challenge (OFC) when required. The basophil activation test (BAT) in addition, may be able to identify patients at risk of an acute allergic reaction and reduce the need for OFC.
This pilot study recruited patients over an 18 month period from Immunology outpatient clinics at a tertiary paediatric hospital, attending for assessment of their nut allergic status.
**Method:** Whole blood from study patients was stimulated with PBS or peanut allergen using an in house assay method. Basophils identified by CCR3 expression were analysed for upregulation of activation markers CD63 and CD203. Correlation between BAT activation, peanut-sIgE, SPT and oral food challenge outcomes where recorded were analysed.
**Results and discussion:** CD203 showed significant upregulation in individuals who had positive peanut-sIgE results (>0.35 kU/L). Where OFC data was available, the BAT did not segregate patients into OFC pass and fail groups. Additional OFC data is required to clarify the utility of BAT in the diagnosis of nut allergy. The need for prompt processing following sample collection is a potential limitation to its use in the diagnostic laboratory.

## PROLIFERATING CELL NUCLEAR ANTIGEN ANTIBODY TESTING – GETTING THEM ALL

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Proliferating cell nuclear antigen antibody (PCNA) is associated with systemic lupus erythematosus (SLE) and characterises a cohort of patients at risk of renal or central nervous system involvement. The antibody has also been reported in patients with hepatitis B and C virus infection. It has a pleomorphic nuclear cell cycle dependant pattern on antinuclear antibody (ANA) testing by indirect immunofluorescence (IFA).
In this laboratory PCNA has been historically reported from the IFA pattern on Hep2000 cells (Immuno Concepts, USA) and not confirmed on a secondary test.
An audit of PCNA pattern reported from ANA testing and incidental characterisation by immunoblot was undertaken to determine the frequency of PCNA detected. Over 4 years, 34 PCNA results were reported. Clinical details provided included SLE, joint pain and acute hepatitis.
Extractable nuclear antigen antibody characterisation by immunoblot incidentally identified a further 20 samples with PCNA not reported on ANA. ANA patterns included speckled,

homogeneous and nucleolar. Clinical details in this group also included SLE and joint pain.
This investigation demonstrates that IFA testing alone for PCNA may miss clinically relevant cases due to a strong dominant ANA pattern. Clinical characteristics and correlation with IFA is required to validate the immunoblot PCNA result.

## EVALUATION OF A VIRTUAL ANA EXTERNAL QUALITY ASSURANCE CHALLENGE

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**Background:** Provision of an antinuclear antibody (ANA) EQA program which challenges laboratories with a range of potential autoantibody patterns is often limited by access to sufficient donor serum. RCPAQAP introduced a 'virtual sample' in its 2019 ANA program with the aim of widening the scope of potential patterns on offer.
**Methods:** A commercial control (Euroimmun IIFT Control for antibodies against PCNA Cyclin 2 IgG) was sent to a reference laboratory to prepare slides (using an Immuno Concepts Hep 2000® kit). The slides were returned to RCPAQAP and scanned in-house using a Zeiss Axio Imager Z2 microscope with MetaSystems scanning and imaging platform. An image was then loaded to the myQAP portal for participating laboratories to access and submit their comments.
**Results:** 69/77 (90%) of participants correctly identified the expected pattern as cell-cycle related proliferating cell nuclear antigen (PCNA-like) antibodies.
**Discussion:** The addition of a virtual sample with related images to the RCPAQAP ANA surveys has been well received by participating laboratories. These are also seen as a valuable educational resource to ensure the competency of staff performing ANA testing across the range of ANA patterns.

## UNDERSTANDING THE TUMOUR IMMUNE MICROENVIRONMENT (TIME) AT DIFFERENT SITES OF MELANOMA METASTASES (METS)

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**Background/Aim:** The site of melanoma metastases influences response to immunotherapy (IT), and also has prognostic impact; liver particularly is a uniquely IT-resistant site.[1,2] We aimed to characterise and compare the TIME at different sites of metastases.
**Methods:** Multiplex immunofluorescence was performed on FFPE samples from 139 untreated metastatic melanoma pts, from 5 anatomical sites [liver $n$=20; lung $n$=23; brain $n$=40; subcutaneous $n$=21; lymph node (LN) $n$=35]. T-cell (CD3, FoxP3, Tim-3, CD103, PD1) and myeloid-derived cell (CD14, PDL1, CD68, CD56, CD16) markers were stained and analysed.
**Results:** CD3+ T-cell densities were significantly lower in liver (median=154.3 cells/mm$^2$) vs lung (median=434.7 cells/mm$^2$) and LN mets (median=504.8 cells/mm$^2$) ($p$<0.01). The proportion of PD1+ T cells was lower in liver (0.7%) vs subcutaneous (7.5%), LN (7.4%) and lung (3.0%) mets ($p$<0.01). Tim-3+ T-cells were higher in liver (10.7%) compared to LN (1.2%) and subcutaneous (1.1%) mets ($p$<0.001). Liver mets presented higher CD68+ macrophage densities compared to LN mets (median=290.6 vs 99.75 cells/mm$^2$; $p$<0.05).
**Conclusion:** Melanoma liver mets have less immune T cell infiltration compared to other sites, and might hold unique mechanisms of immune tolerance. These data provide insights into the biology of melanoma mets at different sites and response to therapies.

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## BIOMARKERS FOR PREDICTING CLINICAL RELAPSE IN REFRACTORY PEMPHIGUS PATIENTS TREATED WITH RITUXIMAB

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**Background:** Rituximab is an effective treatment for inducing remission in pemphigus vulgaris (PV) refractory to conventional immunosuppression. Re-treatment is required on relapse, but there are currently no reliable biomarkers in predicting clinical relapse.
**Method:** We prospectively followed 18 PV patients previously treated with rituximab at Westmead Hospital over a 2-year period. Disease activity was assessed by pemphigus disease activity index (PDAI) along with desmoglein (dsg), intercellular cement substance (ICSA) antibody titres, total B-cell and memory B-cell (CD19+CD27+) counts.
**Results:** 9/18 patients relapsed requiring further rituximab administration. Of these, relapse was preceded by dsg elevation in 5/9 and B-cell return in 2/9 patients. Chronic elevation in dsg antibodies and B-cells were seen in the remaining 2/9 patients with no relationship to PDAI. Of the 9 patients in clinical remission, 5 had normal dsg antibody levels. Review of their clinical data prior to the study suggests correlation of dsg titre elevation with disease relapse. The remaining 4 patients had chronic elevation of dsg antibodies and B-cells. There was no additional information gained from measuring

memory B-cells and no correlation between PDAI and ICSA antibody levels.
**Discussion:** Both dsg antibody levels and B-cell counts can predict relapse in subgroups of rituximab-treated refractory PV patients.

## SOLUBLE FACTORS FROM PACKED RED BLOOD CELLS AUGMENTED LPS INDUCED MONOCYTE PRODUCTION OF IL-1B AND CASPASE-1

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**Introduction:** During routine storage packed red blood cells (PRBC) undergo biochemical and morphological changes, and soluble mediators accumulate which have been hypothesised to contribute to poor outcomes post-transfusion. Interleukin (IL)-1β is a pro-inflammatory cytokine critical for cell proliferation and differentiation. We investigated whether PRBC transfusion modulated IL-1β driven inflammation and assessed whether macrophage inhibitory factor (MIF) was involved.
**Methods:** Isolated monocytes were co-incubated with PRBC supernatants (collected at D2, D14, D28, D42) +/− lipopolysaccharide (LPS, 1 μg/mL) or LPS+ATP (positive control) for 4 hours, 37°C, 5% $CO_2$. IL-1β and caspase-1 were quantified in PRBC-SN and culture SN. MIF was quantified in PRBC-SN and then recombinant MIF (rMIF) +/− LPS added to model 2-3 unit of transfusion. Results were analysed by ANOVA (compared to untreated or LPS alone, $p<0.05$).
**Results:** PRBC-SN increased LPS-induced monocyte production of IL-1β ($p<0.05$) and caspase-1 ($p<0.05$). MIF was present in D2 (19 ng/mL) and D42 (247 ng/mL) PRBC-SN. rMIF did not modulate LPS-induced IL-1β or caspase-1 production from monocytes.
**Conclusions:** Soluble factors in PRBC augmented LPS-induced IL-1β and caspase-1 production in monocytes suggesting inflammasome activation. There was no evidence that MIF was responsible for modulating IL-1β production and further investigation into the other immunomodulatory mediators from PRBC is warranted.

## SEQUENTIAL INVOLVEMENT OF URETERS AND KIDNEYS WITH IGG4 DISEASE LEADING TO NEPHRECTOMY: A CASE REPORT

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We present a 63-year-old male with IgG4-related retroperitoneal fibrosis, causing secondary obstructive pyelonephritis. Imaging of the retroperitoneum was not informative, and prior to the diagnosis being made a left, simple nephrectomy was performed for the obstructive uropathy.
The diagnosis was later suspected because of progression to contralateral obstructive uropathy with subtle medial displacement of the ureter. It was established based on serum IgG subsets, retrospective immunostaining of the nephrectomy tissues, and supported by FDG-PET showing low-level uptake in the retroperitoneum.
This case highlights the importance of awareness of IgG4 disease in the context of obstructive uropathy, and the need for clinical/imaging correlation when histologically assessing a nephrectomy. The histological pattern of established ureteropelvic mural fibrosis depositing circumferentially, associated with ongoing mural inflammation including plasma cells, but sparing the urothelium as well as showing a relative paucity of fibroblasts and histiocytes may be clues to the diagnosis.
The management of IgG4-related disease is immunosuppression (trying to stall its progression), as well as managing the complications caused by the already-deposited fibrosis.
IgG4 retroperitoneal disease is often a multidisciplinary diagnosis, requiring a high level of suspicion and the assessment of multiple diagnostic parameters. Diagnosis at its earlier stages is challenging.

## A FIVE-YEAR RETROSPECTIVE AUDIT OF ANTI-MYELOPEROXIDASE ANTIBODY TITRES MEASURED USING A COMMERCIAL CHEMILUMINESCENT IMMUNOASSAY

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**Background:** In 2015, ACT Pathology transitioned to a commercial chemiluminescent immunoassay (QUANTA-Flash MPO, Inova Diagnostics) to measure anti-MPO IgG antibodies. Monitoring of internal performance check sera identified discordant results following a change in reagent lot. To investigate this further, we conducted a five-year retrospective audit of all anti-MPO titres measured using this assay.
**Methods:** Samples were stratified according to titre (negative <6 IU/mL, low-positive 6–23 IU/mL and high-positive ≥24 IU/mL), clinical information provided on request forms, ANCA pattern as detected by indirect immunofluorescence (IIF), and reagent lot number.
**Results:** A total of 2005 anti-MPO titres were measured between 15 May 2015 and 13 August 2019. The mean number of tests performed each month doubled between 2015–2016 (25 tests/month) to 2017–2019 (50 tests/month). This was associated with increased testing of patients with known AAV. Some variation in the percentage of low-positive (5.8–16.4%) and high-positive (7.7–21.4%) results was observed between the 12 reagent lots used, however this may have been confounded by duration of use (range 2–296 days). The predicted probability of p-ANCA detection was significantly higher in patients with higher anti-MPO IgG titres (OR=17.66, 95% CI 13.72–21.13, $p<0.0001$).
**Conclusion:** Anti-MPO IgG testing at ACT Pathology has increased over the last five years. While some variation between reagent lots has been observed, this has not significantly affected overall assay performance.

## INTERCHANGEABILITY OF PD-L1 LABORATORY-DEVELOPED TEST BY 22C3 ANTIBODY CONCENTRATE AMONG IHC PLATFORMS IN GASTRIC CANCER

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**Background:** The PD-L1 IHC 22C3 pharmDx assay on the Dako Autostainer Link 48 (ASL48) platform has been established to measure PD-L1 expression in gastric cancer (GC); however, availability of this platform is limited. We developed an IHC laboratory-developed test (LDT) using the 22C3 antibody concentrate to determine PD-L1 expression in patients with GC.
**Methods:** PD-L1-stained tumour specimens ($N$=120) from patients with GC or GEJ adenocarcinoma were scored for combined positive score (CPS) $\geq$1 by 3 pathologists at 3 sites. The PD-L1 IHC 22C3 pharmDx assay on the Dako ASL48 served as the gold standard; the 22C3 antibody concentrate was tested on 3 platforms: Dako ASL48, Ventana BenchMark Ultra, and Leica Bond-Max.
**Results:** Intraclass correlation coefficient of CPS as a continuous variable between the gold standard and each platform ranged from 0.910-0.989. When CPS was dichotomised based on a score $\geq$1, the total agreement ranged from 87–98%, positive percentage agreement ranged from 81–99%, and negative percentage agreement ranged from 90–100%. Intra-pathologist concordances using the 22C3 pharmDx assay also showed substantial agreement (kappa value 0.779).
**Conclusions:** The 22C3 antibody concentrate can be successfully used on 3 IHC platforms to determine PD-L1 expression in tumour samples from patients with GC.

## PTEN PROTEIN LOSSES AND LOSS-OF-FUNCTION GENETIC VARIANTS IN GASTRIC CANCERS: THE RELATIONSHIP WITH MICROSATELLITE INSTABILITY, EBV, AND PD-L1 EXPRESSION

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**Background:** Inactivation of PTEN is caused by various mechanisms and is related to progression of cancer. In gastric carcinoma (GC), the relationship between PTEN protein losses and genetic variants is unclear and their effects on microsatellite instability (MSI), EBV, and PD-L1 expression are not studied.
**Methods:** We performed comprehensive cancer panel tests with 322 tumour tissues from advanced GC patients. In all cases, immunohistochemistry for PTEN protein was performed, and loss of protein expression is defined as a complete absence of nuclear staining.
**Results:** In total, 34 cases (10.6%) had *PTEN* mutations and 13 of them (55.9%) showed PTEN protein losses. In 288 wild-type GC for *PTEN*, protein losses were found in 35 cases (12.2%). PTEN protein losses were significantly associated with *PTEN* mutations ($p$=5.232e-10), MSI-high ($p$=3.936e-08), and EBV-negativity ($p$=0.0071). The most common *PTEN* variants with protein losses were p.R130 found in 4 cases, p.R335 in 2 cases, and all cases with nonsense mutation showed PTEN inactivation.
**Conclusions:** *PTEN* loss-of-function mutation is an important genetic mechanism of PTEN inactivation.

## NON-STANDARDISED REPORTING OF AUTOANTIBODY ASSAYS AMONGST AUSTRALIAN AND NEW ZEALAND LABORATORIES: RESULTS OF A SURVEY

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**Background:** Autoantibody results only slightly above established cut-offs are considered to have lower specificity and provide lower likelihood ratios; their clinical significance may therefore be uncertain, which is not readily communicated with dichotomous qualitative reporting.
Line immunoblots have become a common method for detecting autoantibodies due to a streamlined methodology. However, the manufacturer's recommended positive cut-off, which is uniform for all antibodies, is contentious.
**Methods:** We distributed a survey via e-mail to Australasian immunopathology laboratories to investigate how autoantibody assays are currently being interpreted and reported, with a focus on line immunoblots. The survey was developed using www.surveymonkey.com.
**Results:** There were 31 responders, comprising immunopathologists and scientists from at least 17 unique laboratories across Australia (8 public, 5 private) and New Zealand (4 laboratories). Autoantibody reporting was not standardised; there were significant differences in reporting practices, particularly regarding the interpretation of and positive cut-offs used for line immunoblots, which were often contrary to manufacturer's guidelines. Interpretative qualitative reporting based on results from other investigations and clinical history was a common theme.
**Conclusions:** There is a need for standardised guidelines regarding reporting of autoantibody assays. A collaborative effort from immunopathologists, clinicians and industry is required. Assay manufacturers must justify recommended cut-offs.

## SPOT ON! EVALUATION OF T-SPOT.TB FOLLOWING INDETERMINANT QUANTIFERON TB-GOLD PLUS IN SCREENING FOR LATENT TUBERCULOSIS

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**Background:** Current guidelines recommend screening for latent tuberculosis in at risk patients, including immunosuppressed patients, particularly those receiving anti-TNF-alpha therapy.[1] Interferon-γ release assays (IGRA), including T-SPOT.TB (TS) and QuantiFERON TB-Gold Plus (QFG), are one method for case identification. Our lab suggests requesting TS after indeterminant QFG, although evidence for this approach is limited.[1]
**Methods:** A retrospective audit of TS tests from November 2018 to October 2019 was performed to identify the results of testing after indeterminate QFG. Additional details, including QFG mitogen response, source of referral, and interval between QFG and TS, were also examined.
**Results:** Eighty TS tests with a history of indeterminant QFG result were identified. Seventy-two (90%) had a clear result, with the majority being negative (69 tests, 86%) and three positive results (3.8%). Of the remaining requests four (5%) were not performed due to low cell counts, three (3.8%) had an indeterminant result, and one (1.8%) was uninterpretable due to high background.
**Discussion:** Our current strategy utilising a second IGRA (TS) after indeterminant QFG led to clarification of indeterminant results in the vast majority (90%) of cases. This outcome supports continuing our testing strategy and provides some evidence to inform changes to guidelines.

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## DEMONSTRATION OF ECULIZUMAB DEPOSITION BY DIRECT IMMUNOFLUORESCENCE ON A RENAL BIOPSY IN A CASE OF ATYPICAL HAEMOLYTIC URAEMIC SYNDROME

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Eculizumab is an IgG2/IgG4 kappa monoclonal antibody that blocks C5 and subsequent terminal complement pathway activation. It can be useful in complement-mediated atypical haemolytic uraemic syndrome occurring as a consequence of complement dysregulation. We report a case demonstrating direct immunofluorescence (DIF) findings suggestive of eculizumab binding to renal tissue.

A 40-year-old man with primary focal segmental glomerulosclerosis underwent deceased donor renal transplantation. After an unremarkable post-transplant period, he developed thrombotic microangiopathy (TMA) complicated by graft dysfunction and ischaemic ileal ulcers. Despite commencing eculizumab for possible complement-mediated aHUS, he had progressive renal impairment and persistent haematological features of TMA, and proceeded to graft nephrectomy five days post-eculizumab administration. On DIF, renal tissue demonstrated sparse focal lobular aggregates of IgG within glomeruli and bright IgG deposition within walls of tubules, which was kappa light-chain restricted. Serum free light chain ratio was normal, and no serum paraprotein was detected. Renal biopsies pre-eculizumab administration did not demonstrate this binding pattern. Further examination revealed IgG2 and IgG4 subclass restriction, suggestive of eculizumab binding to C5 in renal tissue. Similar renal biopsy staining patterns have been attributed to eculizumab deposition.[1,2] Pathologists should be aware that therapeutic monoclonal antibodies may be detected on biopsy specimens.

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## HEPATITIS C-ASSOCIATED GLOMERULONEPHRITIS MASQUERADING AS GOODPASTURE'S SYNDROME

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Anti-glomerular basement membrane (GBM) autoantibodies are associated with Goodpasture's syndrome, characterised by lung and kidney involvement. We report a case with clinical disease demonstrating discrepant anti-GBM antibody results between assay platforms.

A 39-year-old male presented with an eight-week history of haemoptysis and acute renal impairment, on a background of active hepatitis C infection. Creatinine was 256 μmol/L with haemoproteinuria, hypocomplementaemia, and positive anti-GBM level (65 U/mL Phadia ELiA; reference range >10 U/mL) which was confirmed on repeat testing. Treatment for Goodpasture's syndrome was initiated with plasma exchange (PLEX) and intravenous cyclophosphamide. However, renal biopsy performed in parallel to treatment did not demonstrate characteristic linear GBM binding on direct immunofluorescence. Findings were instead consistent with hepatitis C-associated glomerulonephritis. ANCA by immunofluorescence was negative. Anti-PR3, anti-MPO and anti-CCP tested retrospectively by Phadia ELiA methods were also positive, raising suspicion for an interfering factor. Pre-treatment sera tested for anti-GBM antibodies via indirect immunofluorescence (INOVA primate kidney) and chemiluminescence assay (INOVA BIO-FLASH)

were negative. Unfortunately, pre-treatment cryoglobulins had not been tested. However, testing 6 months after presentation confirmed type 2 cryoglobulins, and anti-GBM levels had normalised. Cryoglobulins or another interfering factor may have caused platform-specific assay interference, affecting anti-GBM and other autoantibody detection on the same platform.

## RETROSPECTIVE REVIEW OF TCR-Vβ ANALYSIS BY FLOW CYTOMETRY AND PROPOSED USE OF SCREENING METHOD

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**Background:** Flow cytometric analysis of the TCR-Vβ repertoire can help to determine T cell clonality. The most useful application is in the early diagnosis of T cell neoplasms.
**Methods:** All TCR Vβ assays performed between 2010–2019 at John Hunter Hospital Laboratory were included. 24 Vβ families were tested, gated on CD4 or CD8 cells.
**Results:** 37 Vβ assays were performed on 36 patients. 35 tests were performed on blood, with 2 on tissue. 3 cases were paediatric.
The distribution of results were: 20 monoclonal, 5 suspected and 12 polyclonal. The final clinical diagnoses will be presented.
**Discussion:** In the monoclonal and suspicious groups, abnormalities in Vβ4, Vβ14 and Vβ17 were most frequently found. If screening using only these specificities, a total percentage of <3% or >58% was suspicious of clonality and should prompt full TCR-Vβ testing. Based on the samples audited, this screening method has a sensitivity of 96% and specificity of 91%.
**Conclusion:** TCR-Vβ analysis by flow cytometry is a rapid quantitative method to determine T cell clonality. We propose the use of a screening method using 3 Vβ antibodies in one tube, with further characterisation if warranted. Further studies are needed.

## SEROPREVALANCE TO *COXIELLA BURNETTI* IN THE RAMU VALLEY OF PAPUA NEW GUINEA

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**Background:** In Papua New Guinea (PNG) most febrile illnesses are attributed to malaria. However, recent studies have confirmed the presence of other fever producing illness like dengue and rickettsia. The purpose of this study was to establish serological evidence to *C. burnetii* the causative bacteria of Q fever, another fever producing illness in the human population of PNG in the Ramu Valley.
**Methods:** 327 blood samples were sent to the Australian Rickettsial Reference Laboratory in Geelong, Australia, for serology and PCR testing.
**Results:** There was only phase II positive serological results, none of the samples had phase I reactivity. This study considered a cut off of phase II titer of ≥50 of either IgA, IgM or IgG as seropositive. The seroprevalence of Q fever in the Ramu Valley was 4.9% (16/327). The proportion of females (62%) was higher than males (38%). In age distribution, the largest proportion 7.2% (7/97×100) of seropositive was in the 21–30 year age group. Residential areas and cattle exposure were found to be the main risk factors associated with exposure to *C. burnetii*. All PCR results were negative.
**Conclusion:** There is serological evidence of exposure to *C. burnetii* in the Ramu Valley of PNG. Health workers can consider Q fever as a differential diagnosis in patients with fever, generalised body aches, malaise and a suggestive history.

## FATAL *E. COLI K1* MENINGITIS AND VENTRICULITIS IN AN ADULT

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*Escherichia coli K1* is known as highly virulent pathogen, commonly causing neonatal meningitis. It is an extremely uncommon aetiological agent as a community acquired meningitis in adults, which has 25% mortality and neurological complications in over 50% of patients.
Many routine clinical microbiology laboratories lack facilities for molecular diagnosis and or serotyping to identify this organism. Our current CSF diagnostic platform includes a 14 target multiplex PCR assay including the PCR target for *E. coli K1* capsular antigen. This resulted in us picking up rare, possibly previously underdiagnosed cases of *E. coli K1* meningitis.
An elderly female, found in a collapsed state at home with fever, vomiting, urine and faecal incontinence was brought to our emergency department. Urgent CT scan demonstrated ventriculitis with extensive pus formation.
CSF analysis has demonstrated neutrophil leucocytosis, elevated protein, very low glucose and moderate Gram-negative bacilli, which were identified soon after as *E. coli K1* by Biofire film array ME panel. All other cultures of the patient were unremarkable except urine culture which grew extremely susceptible *E. coli K1 strain.* Despite being treated with meropenem, ceftriaxone, aggressive neurosurgical treatment and intensive care, the patient passed away on day 9 of illness.

## AN EVALUATION OF SYNDROMIC MULTIPLEX PCR TESTS FOR THE DETECTION OF PATHOGENS ASSOCIATED WITH GASTROENTERITIS

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A broad spectrum of enteric pathogens can cause infectious gastroenteritis. Conventional diagnostic procedures such as culture, biochemical identification, immunoassay and microscopic examination currently used by many laboratories are time consuming and typically lack sensitivity and specificity. Syndromic multiplex polymerase chain reaction (PCR) based testing allows for the detection of a greater number of gastrointestinal (GI) pathogens with greater sensitivity and specificity within a relatively short time-frame.

We present an evaluation of the AusDiagnostics Faecal Pathogens M (16-well) PCR assay (AusDiagnostics) against another commercial multiplex PCR assay, the BioFire FilmArray GI Panel (bioMérieux). Each assay was performed in accordance with the manufacturer's instructions. The results of each assay were compared to existing laboratory methods, including culture, rapid antigen and in-house PCR assays.
Both assays exhibited high positive and negative percent agreements (≥96%). The AusDiagnostics Faecal Pathogens M (16-well) PCR assay can be used within a high throughput clinical laboratory setting whereas the BioFire FilmArray GI Panel is suited to low-volume or urgent clinical settings. By having a broader spectrum of detectable pathogens, syndromic multiplex PCR tests can deliver improved support for clinicians in the diagnosis and management of gastrointestinal infections.

## EPIDEMIOLOGY, CLINICAL FEATURES AND LABORATORY TESTING OF *NEISSERIA GONORRHOEAE* INFECTIONS IN THE AUSTRALIAN CAPITAL TERRITORY IN 2014–2018

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Gonorrhoea is most commonly diagnosed by nucleic acid amplification tests (NAATs), however culture remains important for providing information on antimicrobial susceptibilities. This study describes the epidemiology of gonorrhoea in the Australian Capital Territory (ACT), clinician compliance with the performance of culture, and sensitivity of culture relative to NAAT.
Positive *Neisseria gonorrhoeae* NAATs and culture and demographical information were identified from the ACT public pathology laboratory information system for a 5-year period (2014–2018). NAAT positive cases were reviewed to determine if a specimen had also been taken for culture. Repeat detection of *N. gonorrhoeae* from one or more sites within a 29-day period were regarded as a single episode.
917 episodes of *N. gonorrhoeae* involving 1,233 positive NAATs/cultures from urogenital (30%), throat (37%), anal (32%) and other sites (0.4%) were observed; 89% in males. An increase in number of episodes and test positivity rate were observed over time. 81% of NAAT positive specimens had culture performed, of which 64% isolated *N. gonorrhoeae*. Culture positivity was poorest for throat (57%), anal (65%), and vaginal (54%) specimens.
Until other methods of detecting antimicrobial resistance are available, clinicians should be targeted to collect appropriate specimens for culture to inform treatment and surveillance.

## *PARACOCCUS YEEI* – AN EMERGING PATHOGEN OR INCIDENTAL FINDING?

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*Paracoccus yeei* is an aerobic Gram-negative coccobacilli that is found in soil. There are increasing reports of infection in the literature. The organism can appear under-decolourised on Gram-stain and thus be inadvertently reported or dismissed as a Gram-positive cocci. We report two cases of identification of the organism in our laboratory and the associated clinical findings. The first case is of a 5-month-old girl with unilateral ulcerating groin crease lesions who cultured *P. yeei* in blood culture, identified on MALDI-TOF-MS. Treatment in this case was directed at a *Pseudomonas aeruginosa* cultured from the wound, although Gram-positive cocci seen on the Gram-stain of the wound were never cultured. The second case is a 49-year-old woman with *P. yeei* cultured from a left knee joint aspirate with a polymorph count of $16{,}500\times10^6$/L, again identified on MALDI-TOF-MS. In this case, no directed treatment was administered. Identification of *P. yeei* may be increasing due to inclusion in the database of rapid microbiological identification systems such as the MALDI-TOF-MS and automated biochemical systems such as the VITEK-2 GN cards. Ongoing case publication is required to elucidate the prevalence and pathogenicity of this organism.

## A CASE OF *PSYCHROBACTER SANGUINIS* BACTEREMIA IN A MIDDLE-AGED MAN

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*Psychrobacter sanguinis* is a Gram-negative obligate aerobe first identified in 2012. *Psychrobacter* species are cold-tolerant and often associated with marine environments.[1] They are known to cause opportunistic infections. Here, we report the first known case of *Psychrobacter sanguinis* bacteremia in Singapore in a middle-aged man with no known exposure to seawater or seafood. The organism was initially identified by MALDI-TOF, and confirmed with 16S rRNA sequencing. We also describe further phenotypic studies of this isolate. The patient was admitted with fever, marked hyponatremia, rhabdomyolysis, and altered mental state, and his condition improved with IV ceftriaxone.

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## EPIDEMIOLOGY OF CULTURE-POSITIVE MUCORMYCOSIS IN QUEENSLAND: 2013–2018

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Mucormycosis is an uncommon, but serious, invasive mould infection associated with rapid progression and high morbidity and mortality. Infection can occur in a broad range of hosts,

including the immunocompetent. This retrospective observational study of culture-positive proven and probable cases between November 2013 and November 2018 identified a total of 48 cases (34 proven and 14 probable) out of 215 patients with positive cultures.

*Rhizopus* spp. were the most common aetiology (22, 45.8% of cases). Patients who sustained trauma were most likely to have non-*Rhizopus* species as were patients from outside south-East Queensland. *Saksenaea* spp. infection were most commonly associated with trauma, cutaneous infection and with residence in tropical regions. Haematological malignancy, diabetes and trauma were the most common risk factors. Disseminated infection was rare (4%) though extensive localised spread was common in those with both cutaneous and rhino-orbital-cerebral manifestations (ROCM).

The 30-day and 1-year mortality were 17% and 33.33% respectively. The strongest predictors of mortality were rhino-orbito-cerebral site of infection (OR 11.67, $p$=0.01, CI 2.05–66.41), diabetes mellitus (OR 4.2, $p$=0.04, CI 1.06–16.58) and haematological malignancy (OR 5, $p$=0.02, CI 1.38–21.21). The strongest factor associated with survival was cutaneous site of infection (OR 0.15, $p$=0.01, CI 0.04–0.59).

## CHOLERA RISK FACTORS, PAPUA NEW GUINEA, 2010

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**Background:** The study was conducted during an outbreak of cholera in Lae, Papua New Guinea, beginning in August 2009. Cholera was seen as a new or emerging disease in the context of Papua New Guinea (PNG) as it was unknown prior to the outbreak.

**Aim:** The aim of the study was to identify risks factors in order to control and prevent further spread of the disease and to evaluate point of care test for cholera.

**Method:** This study was a hospital based case-control study conducted at Angau Memorial Hospital, Lae, PNG. The study subjects included 176 participants (54 cases and 122 controls), selected according to prescribed selection protocols. The information was collected in the form of a questionnaire/s. Stool culture was a standard method used in this study.

**Results:** The major independent risk factors noted were: mobile population above the age of 20 years, defecating in open air, rivers or streams, contacts who have travelled to affected areas. Of note, hand washing with soap was protective to individuals connected to piped running water.

**Conclusion:** It was concluded that access to safe and clean water and improved sanitation were likely to limit the spread of cholera in the communities. Mobile population and settlement dwellers were high risks factors associated with the spread of cholera.

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## INTERNAL VERIFICATION OF BD BACTEC FX40 INSTRUMENT FOR RAPID DETECTION OF BLOODSTREAM INFECTIONS

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**Aim:** The BD BACTEC FX40 automated instrument was evaluated for use by Ballarat Australian Clinical Laboratory (ACL) to aid in the detection of blood stream infections.

**Method:** 20 organisms were chosen from the reference culture collection to be inoculated into two aerobic, two anaerobic and two paediatric blood culture bottles filled with designated volume of human blood. For each organism, 50 µL of the recommended dilution was aseptically added for each bottle with 5 mL of normal saline in each dilution tubes. There were 12 control bottles injected with sterile water. All bottles were loaded into the instrument. Bottles were removed as they flagged positive. A gram stain and culture were performed on each bottle that flagged positive. Identification by standard laboratory procedures was performed on all isolates.

**Result:** All bottles that were expected to flag positive, flagged positive within the specified time frame listed. The time to detection for each bottle type with the organisms seeded into the blood culture bottles was recorded.

**Conclusion:** All predicted positive blood culture bottles flagged positive except *Streptococcus pneumonia* in the anaerobic bottle. Controls remained negative. BACTEC FX40 instrument was fit for purpose given that it demonstrated acceptable agreement with inoculated organisms and culture.

## APPLICATION OF SINGLE PLATFORM METAGENOMICS SEQUENCING ALONGSIDE CONVENTIONAL TESTING FOR TWO ADULT CASES OF CENTRAL NERVOUS SYSTEM (CNS) INFECTION

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**Aim:** To evaluate clinical usefulness of metagenomics sequencing alongside conventional testing in two adult cases of CNS infection.
**Methods:** For both cases, bacterial microscopy and culture, herpes multiplex PCR, enterovirus PCR, parasitology multiplex PCR, *Acanthamoeba* culture, fungal culture, cryptococcal antigen and *M. tuberculosis* culture and PCR were done on the cerebrospinal fluid (CSF) with 4 mL required for each patient. Metagenomics sequencing required only 0.4 mL of CSF for each patient. CSF was subjected to particle enrichment (virus and ribosomes), random amplification of extracted RNA and DNA, library preparation and Ion Torrent next generation sequencing (NGS). Although clearly an experimental method, this method has been successful in detecting viruses and other microbes in a range of samples.
**Result:** All conventional testing as mentioned above was negative. NGS of sample 1 generated 3.7 million reads, mean read length 156 nucleotides; sample 2 generated 4 million reads, mean read length 185 nucleotides. Analysis of NGS reads focusing on finding an infectious aetiology, did not reveal any significant findings. Clinicians were reassured to prescribe immune-suppressive therapy with good response for Case 1 and have antibiotics ceased in Case 2.
**Conclusion:** Metagenomics sequencing alongside conventional testing may be useful for ruling out active infection in patients with possible CNS infection.

## A CASE OF BILHARZIAL TUBERCLE IN A MIGRANT FROM ZIMBABWE, DIAGNOSED LATE THROUGH CYSTOSCOPY AND HISTOLOGY, WITH NEGATIVE SCHISTOSOMIASIS SEROLOGY [INDIRECT HEMAGGLUTINATION (IHA)]

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We report a case of Bilharzial tubercle in a migrant from Zimbabwe, recognised 10 years later through flexible cystoscopy and histological findings. A 21-year-old female presented to her local doctor with six months history of supra-pubic pain and dyspareunia without systemic symptoms. Her past medical history included intermittent asymptomatic haematuria since 2006 attributed to thin membrane disease, migraine and sinusitis. She had freshwater exposure in a rural region in Africa prior to migration to Australia 11 years ago. Her urine dipstick showed erythrocytes count of $137\times10^6$/L. Schistosomiasis serology (IHA) was negative. Pelvic ultrasonography showed a focal 8×5 mm lesion in the posterior bladder wall suspicious for neoplastic aetiology. Cystoscopy demonstrated patchy changes on bladder mucosa and a persistent bladder wall mass, which was nodular and suspicious for Bilharzial tubercle. A 7 mm fragment of the bladder lesion showed urothelium with mucosal ulceration and dense mixed inflammation with large numbers of eosinophils. Numerous calcified schistosoma eggs were present within the mucosa and lamina propria. The mucosa showed reactive changes and there was benign squamous metaplasia without evidence of malignancy. She was treated with praziquantel 20 mg/kg orally with food, for 2 doses and 4 hours apart with resolution of her symptoms, haematuria and lesion.

## EVALUATING COMMUTABILITY OF EQA SAMPLES FOR EPSTEIN-BARR VIRUS SEROLOGY

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**Background:** Providing 'patient-like' commutable samples is an ongoing challenge for all EQA providers. RCPAQAP sources human serum and plasma from commercial suppliers, donated de-identified pools and consenting donors. For some assays plasma is not the recommended specimen type for testing.
**Aim:** In 2019, RCPAQAP performed plasma to serum conversion for EBV surveys previously distributed as a plasma sample to investigate the effect of sample type on results.
**Methods:** A single source plasma sample (from Physicians Plasma Alliance collected in sodium citrate) was distributed for two EBV surveys. RCPAQAP subsequently performed a plasma to serum conversion using an in-house method and redistributed the defibrinated sample for a third survey. A comparison of the replicate samples was performed to identify any discrepancies.
**Results:** A shift in reporting for qualitative results (positive/negative) for EBV VCA IgM was noted over the three surveys. The two surveys using plasma samples had less than 80% agreement across methods whereas a consensus of 90% was achieved for the defibrinated sample.
**Discussion:** There are many contributing factors that can lead to variation in results including sample type. For serological testing, it is important to be aware of any limitations for the assay in use. RCPAQAP now routinely defibrinates plasmas where required to improve the commutability of the sample.

## EVALUATING A STRONGYLOIDES EQA PROGRAM: OUTCOMES OF A TWO-YEAR PILOT STUDY

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**Aim:** While an initial Strongyloides pilot survey in 2018 showed a high concordance in reporting of qualitative results, there was a high variation in the reporting of quantitative results within and between method groups. In 2019, RCPAQAP Serology distributed a second Pilot Program to assess the reporting of low-level positive results.
**Method:** The 2019 survey (comprising two duplicate negative, one high-level and one low-level positive serum samples) was distributed to 12 Australian and 5 international laboratories for Strongyloides IgG and total antibody testing. Qualitative (pos/neg) and quantitative (NTU, OD, and S/CO) data were subsequently analysed using RCPAQAP in-house software.
**Results:** 16 participants used a commercial assay and one an in-house assay. Qualitative results showed 100% consensus for the negative specimens, 81% consensus for the high-level positive samples, and no consensus for the low-level positive sample. A high variation in the reporting of quantitative results between and within method groups and inconsistencies in the reporting of cut-off values were identified.

**Conclusion:** The RCPAQAP Strongyloides pilot studies demonstrated the need for an ongoing EQA to enable laboratories to confirm the presence or absence of Strongyloides antibodies and assist in evaluating method performance for the accurate reporting of Strongyloidiasis, particularly low-level positive samples.

## SUPPLEMENTARY ASSAYS FOR THE DETECTION OF *NEISSERIA GONORRHOEA*, IS IT TIME TO REVIEW OUR PROTOCOLS?

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Nucleic acid amplification tests (NAAT) are widely employed in laboratories for detection of *N. gonorrhoea*. Due to false positive results from earlier generation NAAT assays, testing algorithms recommend a supplementary assay in addition to the initial screening test for all initial positive results - public health laboratory network guidelines.[1]

Our laboratory tests for *Chlamydia trachomatis* and *Neisseria gonorrhoea* on the Roche Cobas® CT/NG (6800/8000 systems) and uses the AusDiagnostics Urogenital 8-well assay for supplementary testing. Over a 3 month period in 2019, 730 initial positive gonorrhoea results were obtained of which 57 (7.8%) were negative on supplementary testing. Throat swabs were the sample type least likely to have concordant results, with 23/125 (18.4%) negative on the supplementary assay. This is compared to 8/50 (16%) of rectal swabs, 9/99 (9.1%) of genital-site swabs and 14/414 (3.4%) of urine specimens. With the exception of throat swabs, all initial positive results with a cycle threshold <35 cycles were also positive on the supplementary assay.

Results suggests that routine supplementary testing for all samples may not be necessary and that this two test algorithm could be reconsidered.

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## AN ASSESSMENT OF THE CLINICAL IMPACT OF POSITIVE BIOFIRE FILMARRAY MENINGITIS/ ENCEPHALITIS (ME) PANEL RESULTS

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**Introduction:** BioFire FilmArray ME Panel is a rapid multiplex polymerase chain reaction (PCR) panel for 14 meningeal pathogens with results available in about one hour. The introduction of this rapid diagnostic platform revolutionised the workflow in our laboratory with a significant impact on patient management.
**Aims and methods:** Fifty positive CSF results were retrospectively analysed to determine turnaround times (TATs) and contribution of a positive CSF results to clinical care of the patient such as early cessation of antibiotics and early discharge from the hospital.
**Results:** Average TAT for a positive CSF multiplex PCR was 4 hours. Early cessation of antibiotics and almost immediate discharge was noted for the majority of positive results (25/50) caused by enteroviral meningitis. In the bacterial meningitis cases the result enabled clinicians to quickly switch over to directed therapy.
**Conclusion:** This audit demonstrates BioFire FilmArray ME panel facilitated rapid diagnosis of bacterial meningitis followed by early switching of empirical antibiotics to the pathogen specific directed therapy and early discharge of meningitis.

## RAPID ANTIFUNGAL SUSCEPTIBILITY TESTING FOR YEAST STRAINS USING A COMBINATION OF VITEK 2 AST YS08 AND E TEST AND SENSITITRE YEASTONE METHODS

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**Introduction:** Candidaemias and other invasive yeast infections has a significantly high mortality. Therefore clinical microbiology laboratories should be able to offer quick antifungal susceptibility testing especially for isolates from sterile sites. Current gold standard reference method take at least 2–4 days to obtain a result. According to current Australian antibiotic guidelines, patients often continue to receive broad spectrum echinocandins during this interim period. With the recent availability of Vitek 2 AST YS08 panel, we have opportunity to explore the option of quicker results.
**Aims:** Comparison of the results of the two systems in view of introducing Vitek 2 AST YS08 panel (bioMérieux) for routine susceptibility testing.
**Methods:** Thirty-five consecutive blood and sterile isolates of yeasts (predominantly *Candida* spp. were tested using Vitek 2 AST YS08 panel on site with results compared with the Sensititre YeastOne method (Thermo Fisher) in the reference laboratory. The former panel was supplemented by Fluconazole E test, whenever the Vitek-2 MIC was suppressed.
**Results:** Antifungal susceptibilities for 6 antifungal drugs compared well with a very high degree of concordance with the reference method.
**Conclusion:** Our results demonstrate that Vitek 2 YAST S08 panel supplemented with E test MIC for common antifungals such as fluconazole is a promising tool for routine use. However, we would like to continue our study longer to increase the number of strains and variation of yeasts.

## COMPARATIVE ANALYSIS OF ELECTRO-CHEMILUMINESCENCE IMMUNOASSAY (ECLIA), ELISA AND RAPID DIAGNOSTIC TEST (RDT) FOR DETECTION OF HEPATITIS B SURFACE ANTIGEN (HBSAG)

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**Introduction:** Chemiluminescence immunoassay (CLIA), ELISA and rapid-tests (RDTs) are commonly used for detection of HBsAg. However, larger comparative studies evaluating electro-chemiluminescence immunoassay (ECLIA) are still fragmentary. This study compares the above three tests for evaluating their diagnostic accuracy and suggested a diagnostic cut-off index (COI) for ECLIA.
**Methods:** A cross sectional investigation was conducted in Department of Microbiology, JNMCH, Aligarh from July to December 2018 and a total of 3846 samples were included in the study. Representative samples that showed discrepancy between ELISA and ECLIA (Cobas-e411) were confirmed by nucleic acid amplification test (NAAT).
**Results:** Of the tested samples, 259 (6.73%) were positive by ECLIA. Out of these 259 samples, 68 were positive by both ECLIA and ELISA and had cut off index (COI) >5 in ECLIA, whereas 191 were reactive by ECLIA only (COI between 0.9–5). The concordance rate of ECLIA and ELISA in detecting serum HBsAg was 26.25% while the same for ELISA and RDT was 31.57%. Representative samples with COI>9 were positive by NAAT and those with COI between 0.9–9 were negative by NAAT.
**Conclusion:** ECLIA is a highly sensitive test however positivity-COI be raised above 5. In doubtful cases combination of ECLIA and NAAT be used.

## BIOSYNTHESIS OF SILVER NANOPARTICLES FROM *PHYLLANTHUS NIRURI* LEAF EXTRACTS AND ITS ANTIBACTERIAL ACTIVITY AGAINST ANTIBIOTICS-RESISTANT CLINICAL ISOLATES

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**Objective:** Synthesis and characterisation of silver nanoparticles using *Phyllanthus niruri* leaf extracts and determination of antimicrobial activity against clinical bacterial isolates.
**Methods:** Silver nanoparticles (AgNPs) were biosynthesised with the aqueous leaf extract of *Phyllanthus niruri*. Synthesised nanoparticles were characterised by UV-vis, FTIR, XRD, SEM-EDX and TEM. Clinical and standard isolates characterised by VITEK 2 were used for screening of antibacterial activity. The clinical strains tested were *Streptococcus* spp, *Escherichia coli*, *Enterococcus faecalis*, *Enterobacter clocae*, *Citrobacter freundii*, *Burkholderia cepacia* complex, *Salmonella typhi*, carbapenem-resistant Enterobacteriaceae (imipenem-resistant strain of *E. coli*), MRSA and VRE. The standard strains were *E. coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 27853. Antimicrobial activities of the silver nanoparticles were tested by well-diffusion method.
**Results:** Nanoparticles showed significant activity against all the strains tested. Best activity was noticed against *Pseudomonas aeruginosa* ATCC with zone of inhibition (ZOI) of 30 mm followed by *E. coli* ATCC 25922 with ZOI 22 mm. Among the clinical isolates, the ZOI ranged between 12–16 mm with significant activity noticed against antibiotics-resistant bacteria such as MRSA, VRE and CRE.
**Conclusion:** *Phyllanthus niruri*-nanoparticles showed promising antibacterial results; especially, the activity against MRSA, VRE and CRE is quite promising and may be utilised in developing newer antimicrobial compound.

## INTESTINAL MICROBIOTA PREDICT RESPONSE AND TOXICITIES DURING ANTI-PD-1/ANTI-CTLA-4 IMMUNOTHERAPY

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Immunotherapies targeting PD-1/PD-L1 and CTLA-4 have revolutionised the treatment of malignant melanoma. Whilst combining strategies is associated with improved response rates, this is accompanied by increased incidence of severe immune related adverse events (irAEs). Given the ability of the gut microbiota to modulate both local and systemic immunity, this study aimed to examine the association of the gut microbiome with the subsequent efficacy and development of irAEs during combination immunotherapy in the neoadjuvant setting. Pre-treatment faecal microbiomes of stage III melanoma patients ($n$=38) were analysed using 16S sequencing. Low microbial diversity and a reduction in the abundance of butyrate-producing *Ruminococcaceae* and methanogenic-archaea were associated with lack of response and the development of severe irAEs. Machine learning applied to the data was able to predict patients who would develop severe irAEs in the absence of tumour efficacy with 87% accuracy. Mass cytometry of matched pre-treatment PBMCs indicated that differences in peripheral immune cells were associated with changes in microbial diversity. Together, the data suggests that pre-treatment microbiomes influence systemic immunity and can be used to predict immunotherapeutic outcomes, and the maintenance of a robust microbial ecosystem that supports barrier function is key to developing successful microbial interventions to improve patient outcomes.

## *STREPTOBACILLUS MONILIFORMIS* BACTERAEMIA AND SEPTIC ARTHRITIS IN A CHILD

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*Streptobacillus* species are zoonotic pathogens colonising the oral cavity and upper respiratory tract of rats and other rodents.[1] Transmission occurs via bites or scratches, referred to as rat-bite fever, or ingestion of contaminated food or water, referred to as Haverhill fever.[1,2] *Streptobacillus* species are rarely isolated due to fastidious growth requirements, inhibition by sodium polyanethol sulfonate anticoagulant in blood culture bottles, and susceptibility to commonly-used antibiotics.[1]

A 12-year-old immunocompetent female with pet mice and rats presented with fever, left shoulder pain, and rash for five days. Examination demonstrated left axillary lymphadenopathy and left glenohumeral joint restricted range of motion, swelling, and warmth. Ultrasound confirmed a moderate glenohumeral joint effusion and subacromial bursitis. Arthroscopic washout of the joint revealed diffuse, non-purulent, synovitis. The synovial fluid cell count was $15{,}300\times10^6$/L with a mononuclear cell predominance. *Streptobacillus moniliformis* was isolated in culture of blood (paediatric blood culture bottle) and synovial fluid specimens after approximately 72 hours at the microbiology laboratory at Nepean Hospital. The patient admitted to kissing her pet rodents on their mouths and sustaining scratches to the skin of her hands whilst bathing them. She recovered completely with intravenous ceftriaxone for one week then oral amoxycillin for three weeks.

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## IMPLEMENTATION OF EUCAST SHORT INCUBATION BREAK POINTS DIRECTLY FROM BLOOD CULTURE BOTTLES IN A PRIVATE MICROBIOLOGY LABORATORY

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**Background:** Traditional antimicrobial susceptibility results require overnight incubation. A faster turnaround time would allow earlier commencement of targeted therapy and minimise the use of broad spectrum antibiotics.

**Methods:** The Rapid Antimicrobial Susceptibility Testing (RAST) methodology published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) were applied to a representative sample of positive blood cultures from March to August 2019 and compared to the currently used Vitek 2 system and assessed for major [one method reporting sensitive (S) and the other resistant (R)] and minor errors [one method reporting increased exposure (I) and the other S/R].

**Results:** Nineteen isolates (12 *Escherichia coli*, 3 *Staphylococcus aureus*, 2 *Klebsiella pneumoniae* and 2 *Pseudomonas aeruginosa*) were tested. Six hour RAST results exhibited no major or minor errors. All 96 (100%) of the interpretable isolate/antibiotic combinations were concordant. Thirteen (12% of total) combinations fell in the area of technical uncertainty (ATU) and had to be tested using the pre-existing method.

**Conclusion:** The EUCAST RAST methodology was found to be useful at our laboratory for the commonly isolated blood culture pathogens. While ongoing testing of isolates will be required to fully validate this methodology, it holds promise for laboratories using EUCAST guidelines.