March 2020

Priceless

Clifford Craig FOUNDATION

Health • Research • Hope

The news bulletin for supporters of the Clifford Craig Foundation

$650,000 Commitment for Research in 2020

2020 Medical Research Grants

- Multidisciplinary approach to antenatal care - $62,606
- Acute Ischemic Stroke, multi-centre trial - $57,032
- Tasmanian Lung Cancer Registry - $80,000
- Type 2 diabetes, insulin resistance - $19,368
- Ear and lung infections, Haemophilus influenzae - $19,965
- Vaccines in the Elderly (extension grant) - $200,000
- Influenza in kids (extension grant) - $48,550

The Clifford Craig Foundation will provide funding for five new research projects in 2020, plus allocate additional funding for two existing trials that are being undertaken at the Launceston General Hospital and the North West Regional Hospital in Burnie.

The successful recipients of the five new medical research grants were announced late last year and support a broad range of health areas, including pregnancy, lung cancer, diabetes, acute stroke, and ear & lung infections. The funding allocation for the five new projects is $238,970.

Additionally, the Foundation has agreed to further funding of $200,000 for the Vaccine Trial to extend the project to 2021 and $48,500 to the Understanding of Immunity to Influenza in Children to the end of 2020. Both projects are led by infectious diseases specialist, Prof Katie Flanagan.

Chairman of the Clifford Craig Foundation, Associate Professor McTaggart said the combination of the newly announced grants, with the existing research program commitments, will see the Clifford Craig Foundation contribute approximately $650,000 for medical research in North and North West Tasmania this year.

"This announcement sees the Foundation building upon our reputation for facilitating an important collaborative clinical medical research program at the Launceston General Hospital which supports local research that is undertaken by medical professionals at the hospital, medical and nursing students, and university researchers", he said.

Associate Professor McTaggart acknowledged and thanked Clifford Craig's supporters and donors for their philanthropic support that enables the Foundation to facilitate research activity at a local level, that ultimately leads to better health outcomes for the people who live in our region.

Keep reading for a detailed overview of the newly funded projects.

From the CEO

Welcome to the Special Research Edition of the Clifford Craig newsletter *"Priceless"*.

This issue of *Priceless* highlights the very important medical research projects that are being undertaken here in our very own hospitals in Launceston, Burnie and Mersey. As you read the articles, I am sure you will agree that we have some wonderful and dedicated clinicians who not only provide vital patient care, but they are driven to finding better treatments and models of care.

It is extremely rewarding that our community enables research projects such as these to be undertaken here in Northern Tasmania. Through the Clifford Craig Foundation, your philanthropic support enables us to fill the hospital funding gap and provide the "extra gold nuggets" for innovative medical research, education of health staff and support the purchase of much needed medical equipment that is beyond the hospital budget.

Thank you once again for your on-going support. It is people like you that are our lifeblood and the reason we are able to continue to grow from strength to strength.

I hope you enjoy reading the newsletter.

Peter Milne
Chief Executive

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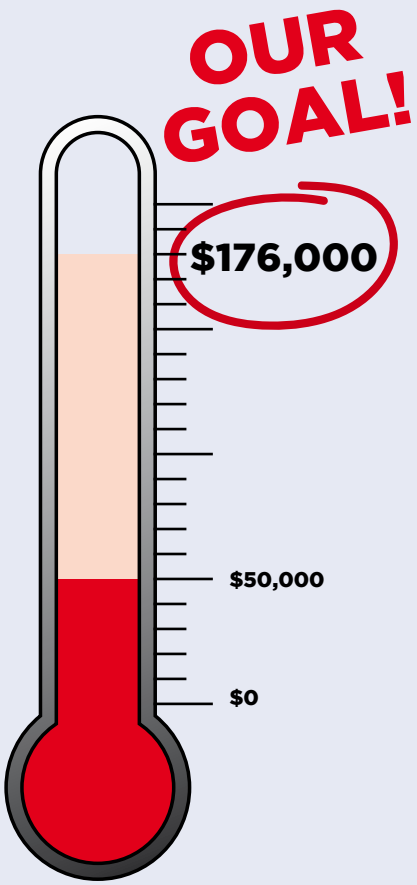
Fibroscan **Appeal**

We are so grateful for the wonderful support from all those who have generously contributed to our fundraising appeal to purchase a much needed Fibroscan for the Launceston General Hospital.

We are aiming to raise $176,000 for this vital "liver disease" diagnostic machine and the appeal has so far raised just over $50,000.

Thank you to everyone who has donated so far, and please encourage others to donate so that we can reach our goal and provide the LGH with its own dedicated Fibroscan.



Stroke - Dr Matt Lee-Archer

Randomised controlled Trial of Exenatide versus standard care in Acute Ischemic Stroke (TEXAIS)

Dr Matt Lee-Archer

$57,031.92

Stroke is one of Australia's biggest killers and a leading cause of disability. Stroke kills more women than breast cancer and more men than prostate cancer. In 2017 there were more than 56,000 new and recurrent strokes – that is one stroke every nine minutes.

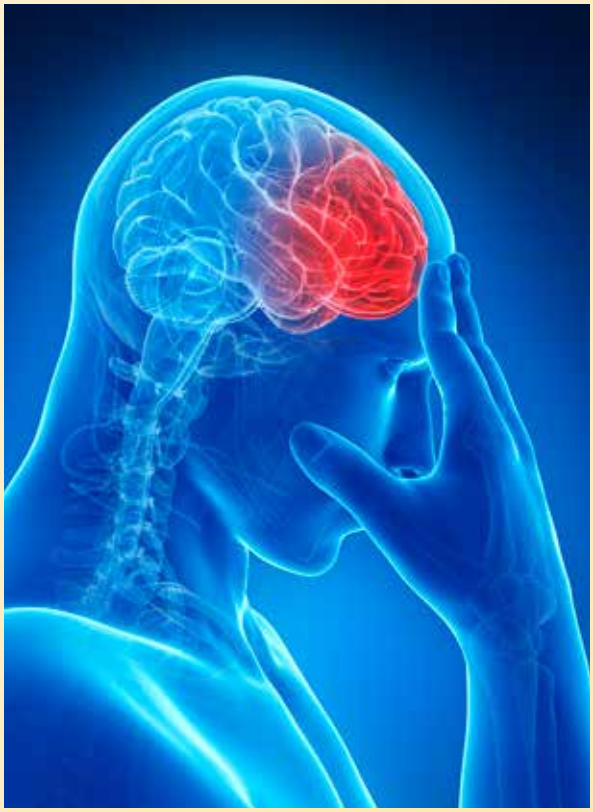
This project will enable the Launceston General Hospital to participate in a Neurology multi-centre trial that includes 15 hospitals in Australia, New Zealand and Finland. The trial will investigate Exenatide, a commonly used diabetes drug that increases insulin secretion.

In many acute diseases, there are worsening clinical outcomes for patients with elevated blood sugar levels, known as hyperglycaemia. In acute ischaemic stroke, post-stroke hyperglycaemia (PSH) occurs in up to 50% patients, reduces the efficacy of stroke thrombolysis with increased risk of bleeding, increases stroke size, and results in worse clinical outcomes and death.

At this stage, Insulin-based therapies have not proved beneficial in treating PSH as they are difficult to implement and maintain, cause frequent hypoglycaemia and have not shown to reduce mortality or improve clinical outcomes. It is hoped that an alternative, simple to use, treatment for PSH, such as Exenatide, may therefore have a significant impact for acute stroke care.

Exenatide is a commonly used diabetes drug, that among its effects, increases insulin secretion. Importantly, this action is glucose dependent – as blood sugar levels decrease, its stimulatory effect on insulin secretion subsides with a very low risk of hypoglycaemia.

A previous pilot study of 17 consecutive, unselected patients with acute ischaemic stroke compared subcutaneous Exenatide for 5 days versus routine standard care. The blood glucose levels remained consistently lower (and less variable) in the treatment group, most noticeably in those stroke patients with known diabetes. Exenatide was safe and well tolerated by all patients, with no symptomatic hypoglycaemia.



TEXAIS is a 3-year Phase 2, multi-centre, prospective, randomised, open label, blinded end-point trial comparing subcutaneous Exenatide to Standard Care. The number of patients to be recruited is 528 patients (264 in each group) with a primary end point of early neurological improvement at 7 days, and secondary end points of recovery at 90 days. Continuous glucose monitors will track the intra-day dynamic variability of glucose in acute stroke in all trial patients (treatment and standard care). These results will be important in informing the planning of a larger phase 3 study.

This will be the first research project undertaken by the new team of neurologists at the Launceston General Hospital.

Make Your Flu Shot Count

Become a Vaccine Trial Participant and contribute to important medical research

We'll provide you Influenza and Whooping Cough Vaccines for **Free**

We need research volunteers who are:

- 65 years and above
- Or 20-50 years old
- In good health
- Not had influenza vaccination this year
- Have not previously participated

For further information, please contact a **Clifford Craig Research Nurse.**

Phone: 6777 6001
Email: research@cliffordcraig.org.au

Reduction in Lung Infections

Enhancement and further in-vitro validation of a potential probiotic to reduce ear and lung infections caused by Haemophilus influenzae

Dr Stephen Tristram

$19,965

The bacterium Haemophilus influenzae commonly colonises the upper airways of healthy people, yet under certain predisposing conditions, it also causes various lower respiratory tract and ear infections. These infections cause significant disease in individuals, frequently becoming chronic, are a major burden on the healthcare system and are difficult to control by either antibiotic therapy or vaccination.

The practice of administering "good bacteria (probiotics)" to individuals, to maintain a healthy microbial balance in certain body sites and prevent disease is an emerging approach to controlling infectious diseases.

Dr Tristram's recent Clifford Craig Foundation funded projects have discovered a non- disease-causing bacterium (potential probiotic) that normally and harmlessly inhabits the human throat that is able to inhibit the growth of H. influenzae by starving it of access to critical nutrients. Preliminary studies on healthy volunteers show that the presence of this potential probiotic strain is protective against H. influenzae.

This project proposes to continue to investigate and optimise the use of this organism as a respiratory probiotic to minimise colonisation and subsequent infection with H. influenzae.

Type 2 Diabetes

What drives the regulation of the zinc transporter ZIP7 in insulin-resistant skeletal muscle? Implications for the treatment of insulin resistance and type 2 diabetes

Dr Stephen Myers

$19,368

Type 2 diabetes (T2D) is one of the fastest growing chronic diseases globally. It affected over 415 million adults in 2015 and is expected to rise to 642 million by 2040. Preceding the development of T2D is insulin resistance (IR), a disorder associated with compromised insulin action on regulating glucose metabolism. IR contributes to the development of type 2 diabetes (T2D) and several pathological conditions and complications including blindness, neurodegenerative disease, kidney failure and amputations.

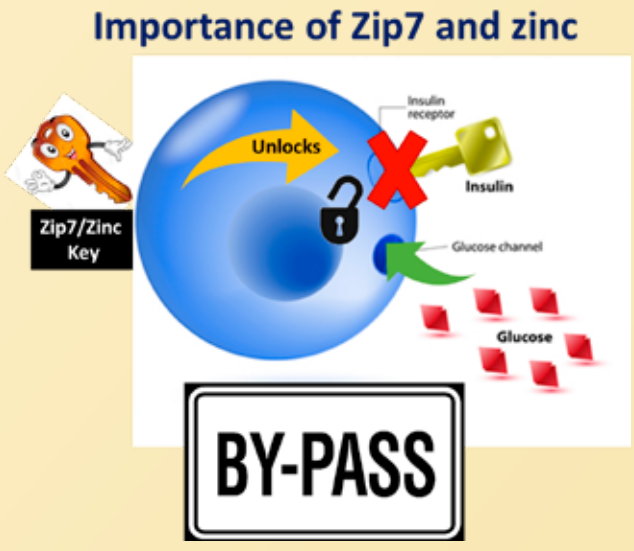
Insulin resistance can occur up to a decade before the development of T2D and therefore provides a therapeutic 'window of opportunity' to treat or better manage this disorder before the development of T2D. Accordingly, strategies to discover novel molecular targets that increase the efficacy and safety of therapeutic treatment options for IR and T2DM are critical. Zinc and the proteins that transport this metal ion in cells are now emerging as key molecular targets for the treatment of a variety of diseases, including T2D.

Zinc transporter proteins release zinc into cells which subsequently activates several cell signalling molecules involved in cellular maintenance. One specific zinc transporter, ZIP7, has been named the 'gate-keeper' of zinc release from cellular organelles and the zinc released by ZIP7 has been shown to activate cell signalling molecules involved in glucose and fat metabolism. However, the mechanisms whereby ZIP7 achieves this is not known.

Therefore, this project will assist in adding to the major 'gap' in the research on this subject. Thus, understanding the mechanisms of ZIP7 regulation of zinc and subsequent activation of pathways that contribute to glucose and lipid metabolism will lead to novel therapeutic strategies to target this transporter in a clinical setting to treat Insulin Resistance and Type 2 Diabetes.

Improving quality of life is at the forefront of this research through providing economic and societal impacts. For example, reducing insulin resistance and T2D in our communities will lessen primary healthcare and hospitalisation visits and increase the health and wellbeing of our citizens. This also fits well within Tasmania's Healthy Tasmania Five Year Strategic Plan to make Tasmania the healthiest population by 2025.

This research builds on Dr Myers previous work that has been funded by the Clifford Craig Foundation and is the next rational move forward to delineate the molecular mechanisms of zinc and ZIP7 in human IR and T2D.



Pregnant women and their offspring: Healthy Outcomes for the Future (HOFF)

Multidisciplinary approach to antenatal care to improve the health of pregnant women and their offspring: Healthy Outcomes for the Future (HOFF) program – NW Project

Mrs Sharon Lucciano – Specialist Diabetes Dietician

$62,606

Maternal obesity and gaining weight above recommendations, can result in adverse outcomes for both women and their babies including - gestational diabetes (GDM), pre-eclampsia, premature birth, macrosomia (large babies), postpartum haemorrhage and neonatal death. A recent audit estimates 54.6% of pregnant women presented at antenatal clinics in North West Tasmania were overweight or obese, approximately 10% greater than the reported national average.

This project will expand on the knowledge that pregnant women's dietary behaviour and exercise patterns are influenced by interpersonal, institutional and community factors showing nutrition education and lifestyle changes during pregnancy are linked to positive maternal and infant outcomes.

The primary objective of this project is to implement an evidence based, multidisciplinary, effective model of care and lifestyle interventions (Healthy Outcomes for the Future (HOFF) program) as part of routine care provided at antenatal clinics on the rural north west of Tasmania to improve the health of mothers and their offspring. The HOFF program will be led by Midwives who are in a unique position to provide nutrition advice to pregnant women due to their regular contact with women via their usual antenatal care.

The research project will utilise a co-design approach, amalgamating contributions from clinicians, research and primary care staff from North West Regional Hospital and Mersey Community Hospital. This will provide a collaborative approach between midwives, nutrition, exercise and education experts, with the view that this may provide an effective way forward. The implementation of the HOFF program will be evaluated and adapted to the specific requirements of the local community using continuous quality improvement methods.

This is a two-year project which will enable the antenatal team, as a by-product, to gain experience in formal methodologies of continuous quality improvement and establish a cohort of neonates for possible future research.

Lung Cancer Registry

Establishment of a Tasmanian lung cancer registry: a north and north-west collaborative initiative

Dr Sukhwinder Sohal

$80,000

Lung cancer is one of the most common forms of cancer in the world, with 1.8 million new cases detected annually (as of 2015) and 1.6 million deaths worldwide. The current average survival rate for patients with lung cancer varies from 4–18.6% depending on regional differences; the variation in outcomes being attributed to variations in treatment and diagnostics. Lung cancer is also responsible for the highest overall burden among cancers.

The major objective of this project is to establish a Tasmanian Lung Cancer Registry allowing collaborative dedicated lung cancer research across Tasmania with local, national and global benefits. This will be a multidisciplinary effort bringing together multiple stakeholders within the State's major hospitals to improve outcomes from this highly lethal disease. These include respiratory clinicians at the Launceston General Hospital, North West Regional Hospital and Royal Hobart Hospital.

The team aim to establish a registry database, collect clinical samples and undertake translational research, including early diagnosis of lung cancer. To support this, a comprehensive respiratory biobank has already been established with samples from smokers with normal lung function, smokers, never smoking normal controls and patients with chronic obstructive pulmonary disease (COPD).

The project will investigate biomarkers for early detection of lung cancer and mechanisms which lead to manifestations of this highly malignant condition. This will inform clinical practice, early diagnosis and disease mechanisms for new therapeutic targets.

It will provide direct benefits to patients through informing clinical practice through the formation of a lung cancer registry. It will also lay the foundation for future lung cancer research in Tasmania and enhance collaborations between major hospitals in the State.

Understanding immunity to influenza in kids

Prof. Katie Flanagan
Extension Grant - $48,550

Millions of people each year get infected with the influenza virus or flu, many of whom die. Young children are particularly susceptible to severe disease and death from flu. This is likely to be due to differences in the child's immune system compared to adults who are less susceptible, however very little is known about children's immune responses to flu.

Flu vaccination is currently the best protection against the virus, however it provides 60% protection at best and only works against certain types of flu. Therefore, better vaccines are needed, particularly for vulnerable children. We can only develop better vaccines if we understand what parts of the immune response to flu are important in protecting us.

This study aims to provide this information by studying the immune cells in blood, tonsils and adenoids of healthy children in order to understand how their immunity to flu differs from that of adults. Obtaining matched blood and tissue samples from humans is rare in immunology studies, even more so when derived from children, making this a very unique sample biobank.

Recruitment for the project in the first year (2019) was excellent with blood and tonsil tissue collected from most of the recruited participants. The samples have contributed to one recent publication in the Journal of Immunology. The Clifford Craig Foundation has agreed to provide extension funding to enable the project to continue for a further year and allow the research team to recruit up to 150 participants.

Dementia Study Published in the British Medical Journal Open

An extensive dementia research study undertaken by Launceston General Hospital physician Dr George Razay which developed a diagnostic tool to help medical practitioners to diagnose a treatable form of dementia has been published in the BMJ Open.

Funded by the Clifford Craig Foundation, the study found that Idiopathic Normal Pressure Hydrocephalus (INPH) may be more common than has been previously thought.

Idiopathic normal pressure hydrocephalus (INPH) is one of the few potentially treatable causes of dementia, but it is difficult to diagnose in older people, with patients often misdiagnosed with Alzheimer's disease or vascular dementia. The condition has previously been viewed as a rare condition.

INPH causes not only memory problems and dementia, but also balance and walking difficulties and urinary incontinence. The condition is diagnosed by brain CT scan showing enlarged ventricles (cavities of the brain). This probably results from difficulty in draining away cerebrospinal fluid, leading to build-up of fluid in the ventricles causing them to enlarge. Diagnosis is important because it can be treated by inserting a fine tube called a shunt in the ventricle to drain away excess fluid from the ventricles to the abdomen. Once the shunt inserted, it remains in place and regulate the flow of fluid from the ventricles.

The results of the Launceston Idiopathic Normal Pressure Hydrocephalus study, investigated the incidence of INPH, developed a simple diagnostic tool to help medical practitioners to diagnose the condition, and looked at the effect of shunting on cognitive, balance, gait and urinary functioning.

The study included 408 participants with memory problems, who attended the memory disorders clinic, the only clinic in Northern Tasmania.

This study is the first world-wide to report that INPH is more common than has been previously thought, and that at least 15% of participants with memory problem have INPH. Moreover, only 55% of patients with memory problems have dementia, of whom 40% had Alzheimer's disease and 10% had mixed dementia. In comparison to other studies, the study diagnosed less with Alzheimer's disease and other dementia syndrome, but more of INPH.

Photo courtesy of Examiner

The study developed a simple assessment to help the diagnosis of INPH in a non-specialised setting. The presence of balance and gait disorder with difficulty of standing on toes and heals, fear of falling, urinary urgency, nocturnal frequency and incontinence, enlarged ventricles with Evans ratio more than the combined diagnostic threshold strongly predict the diagnosis of INPH in patients with memory problems. Moreover, patients who had shunt surgery, showed improvement in cognition, balance, gait and urinary functions. In this study, 56% improved by at least 50% in mini-mental state examination and balance and gait functions in the first year.

There are currently an estimated 447,115 Australians with dementia and almost 50 million people worldwide. Based on the results of Dr Razay's research, it is estimated that INPH affects 67,067 of Australians with dementia and 7.5 million worldwide. There are, therefore, many patients with dementia who may have INPH, and they are denied a treatment that may improve cognitive, balance and gait functions and quality of life, and may delay institutionalization.

As the baby boomer generation reaches old age, the number of cases of dementia and INPH will grow significantly, but the good news is that INPH can be diagnosed and treated.

Glaucoma Inheritance Study Tasmania

In 1996, the Clifford Craig Foundation awarded a research grant of $50,000 to ophthalmologist, Professor David Mackey, to enable a major study into eye disease to be undertaken in Tasmania. David had been an intern and resident at the Launceston General Hospital in 1984 and 1985 and was a visiting Ophthalmologist to the LGH.

Glaucoma is the most common hereditary eye disease causing blindness in the world and Tasmania is well suited for studying inherited diseases. Hence, the Glaucoma Inheritance Study in Tasmania (GIST) was seen as a significant opportunity to support a potentially ground-breaking research study.

27 years later, the GIST study continues, and the research team has often attracted international recognition for the many major scientific discoveries relating to the genes that cause glaucoma.

Professor Mackey has kindly provided an update on his work with GIST.

Glaucoma affects 3% of the population over 40 years of age and untreated, causes loss of peripheral (side) vision and eventual blindness. Anyone can develop glaucoma, however, if you have an immediate family member with glaucoma, you are at a much higher risk than the rest of the population.

Since 1994, the Glaucoma Inheritance Study in Tasmania (GIST) has been working with families and individuals with glaucoma to help find the genes that cause glaucoma so that we can:

- Understand the disease better
- Predict those at risk of developing glaucoma, so that early detection and treatment reduces the risk of blindness
- Develop new treatments for glaucoma

Since starting the Glaucoma Inheritance Study in Tasmania (GIST) over 25 years ago, we have published over 150 papers describing major scientific discoveries relating to the genes that cause glaucoma.

In some families, we have been able to identify a specific glaucoma gene. Family members can then be tested if they carry the same specific glaucoma gene as their affected relative and help minimize blindness by regularly having their eyes examined.

Myocilin (MYOC), was the first gene associated with glaucoma and it was through our research that we were able to identify these genetic changes. To date (year 2020) we have identified over 100 genes that each contribute a small effect to the risk of developing glaucoma. This work has been part of the International Glaucoma Genetics Consortium (IGGC) with the Australian team members as leading contributors.

In some cases, glaucoma can be influenced by several gene changes, as well as environmental factors. Therefore, glaucoma is referred to as a "complex" or "polygenic eye disease". With the latest genetic discoveries, a new genetic risk scoring system has recently been developed for certain diseases. This system is called a polygenic risk score (PRS) 1. This can help determine whether people are at high or low risk of developing glaucoma. High risk individuals could access treatment early to help stop vision loss.

We are continuing to test additional patients and families to find other glaucoma gene changes and improve the accuracy of the PRS. We are also retesting the original families we studied in the 1990s. We will continue to analyse all the glaucoma patients who were enrolled in the GIST in the last 25 years. The opportunity to have this testing performed by a US-based laboratory owned by the company Regeneron has arisen. As part of ongoing research, these results will be combined with that of other international research groups to better understand genetic risk factors for glaucoma. The ultimate aim is to identify potential new treatments for glaucoma. If you have any questions about this testing contact us at the details below.

We will be recontacting family members who were unaffected by glaucoma when they were seen as part of our research in the 1990s to find out whether they have since developed glaucoma. For the first time anywhere in the world, this will help us determine how useful the PRS can be in screening for glaucoma. If we check the accuracy of the PRS, then this offers the possibility of widespread genetic testing for glaucoma, not only for relatives of people with glaucoma, but also for the general population.

One impact of the GIST is that visual field testing for glaucoma has increased in Tasmania.2 The PRS will allow us to ensure that those at highest risk for glaucoma continue to undergo regular eye examinations, while individuals at lower risk are screened less often, conserving healthcare resources and saving clinician and patient time.

People who wish to learn more about the outcomes of the last 25 years of the GIST can read the attached articles.

We will be contacting many GIST participants again over the next 2 years and hope to be able to provide everyone with updates on their genetic test results. For further information or any specific questions, contact us (03) 6226 4731 or by email at alex.hewitt@utas.edu.au or david.mackey@utas.edu.au

1. Craig JE, Han X, Qassim A, et al. Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression. Nat Genet 2020; https://doi.org/10/1038.s41588-019-0556-y.

2. Mackey DM, Craig JE, Hewitt AW. Seeing the impact of the Glaucoma Tasmania after 25 years (letter). Clin Experiment Ophthalmol 2019;47:677-9.

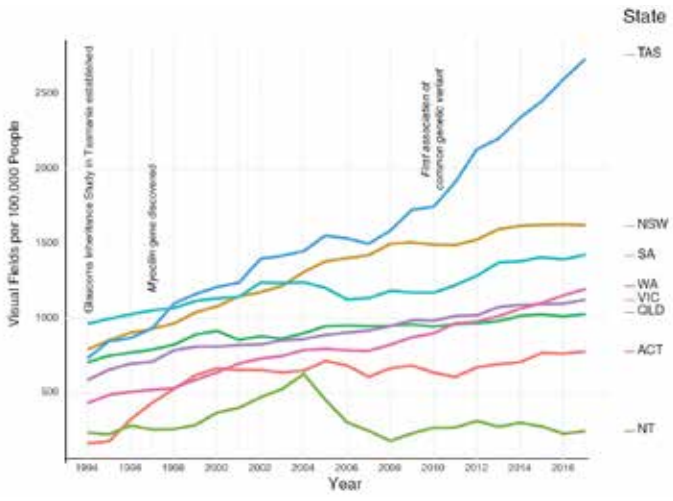


FIGURE 1 Visual field testing (which is predominantly performed for glaucoma) in procedures per 100,000 population from 1994 (the year the glaucoma inheritance study in Tasmania [GIST] started) to 2017, by state/territory. The GIST recruitment ran from 1994 to 1999, while the telemedicine familial glaucoma project ran from 2008 to 2010.

Vaccine **Research**

Heterologous effect of diphtheria, tetanus, acellular pertussis vaccination on influenza vaccine challenge in the elderly

Professor Katie Flanagan – Infectious Diseases Specialist

Extension Grant - $200,000

This study commenced in 2016 and involved the establishment of the Clifford Craig Foundation 'Tasmanian Vaccine Trial Centre' at the LGH, plus a research laboratory at UTAS (Newnham).

This global-scale vaccine research is a multi-year project that involves a number of collaborating institutions including Clifford Craig Foundation, LGH, UTAS, Monash University, RMIT University, Doherty Institute, Hudson Institute of Medical Research and the Wellcome Sanger Institute in the UK.

The Clifford Craig Foundation has provided funding to enable Northern Tasmania to be the recruitment location for the research study. This funding covers the cost of the recruitment, vaccination, biospecimen collection & processing and shipment to Melbourne and other laboratory centres related to the project. To highlight the significance of the research being undertaken by Professor Flanagan and her team, the project has successfully attained NHMRC funding of $795,000 to pay for the costly immunology assays.

Chief Investigator Professor Katie Flanagan, the first specialist in infectious diseases at the LGH, explains it is vital to assist Tasmania's large elderly population to age healthily. "Our studies in African children demonstrate that the diphtheria-tetanus-whole cell pertussis (DTwP) vaccination can lead to impaired immunity but it is not known if the diphtheria-tetanus-acellular pertussis (DTaP) vaccination used in Australia has the same effect,"' Dr Flanagan said.

The study is investigating the effects of DTaP and influenza vaccination on the immune systems of elderly Tasmanians. "I think answering the question of why the elderly respond less well to vaccines is a major public health priority. We are trying to understand in great detail what these vaccines do to the immune system and how they affect one another in order to identify mechanisms to improve vaccine responses in the elderly, and therefore improve the health of the elderly population. This study will provide the much-needed evidence to optimise vaccine responses in older age groups, with future global health implications."

To date, the research team has recruited 241 people into the study (allowing for dropouts) and thousands of biospecimens have been collected and stored. Recruitment to the younger female group has been excellent (n=118), but recruitment to the other age groups has been lower (young men n=50, older men n=50, older women n=40). Many immunological assays have been conducted and the data are providing novel insights into the effects of vaccination in aging Tasmanians.

The extension funding commitment by the Clifford Craig Foundation will enable the recruitment phase to continue until the end of 2021, and into 2022 if necessary. It is anticipated that in excess of 400 participants would have been recruited by then which will be sufficient to answer all of the study questions. The focus will now be on recruiting into the older cohort and younger men.