Researching our research

Research case studies
2006 - 2011

Arthritis AUSTRALIA

About arthritis

Arthritis is an umbrella term for a range of conditions that affects the joints. There are over 100 different types of arthritis affecting people of all ages, including children. The most common types are osteoarthritis and rheumatoid arthritis.

Arthritis is one of the most common, disabling and costly chronic diseases in Australia. It affects more than three million Australians and costs the health and welfare systems well over $5.6 billion a year.

The total cost to the economy of arthritis alone, including the cost of lost productivity and wellbeing, was estimated to be $24 billion in 2007.

By 2050 it is projected there will be 7 million Australians with arthritis, taking into account our ageing population and the impact of increasing levels of obesity.

About Arthritis Australia

Arthritis Australia is the peak arthritis organisation in Australia and is supported by affiliate offices in ACT, New South Wales, Northern Territory, Queensland, South Australia, Tasmania and Western Australia.

Arthritis Australia provides support and information to people with arthritis as well as their family and friends. It promotes awareness of the challenges facing people with arthritis across the community, and advocates on behalf of consumers to leaders in business, industry and government.

In addition, Arthritis Australia is the leading non-government provider of arthritis research funding in Australia, supporting research into potential causes and possible cures as well as better ways to live with the disease.

Introduction

> Our seed-funding approach has initiated many important projects and established the careers of some highly creative and visionary researchers.

Arthritis Australia has been a proud supporter of musculoskeletal research for 30 years. The Arthritis Australia Retrospective Research Survey, launched in 2013, has brought us valuable insights into the quality and importance of our research, and a new appreciation of the high calibre of our research community.

The commitment and innovative spirit of Arthritis Australia's researchers was a stand-out finding of the survey. Our seed-funding approach has initiated many important projects and established the careers of some highly creative and visionary researchers. Projects as diverse as the trial of a drug to halt the development of osteoarthritis, an analysis of the burdens of arthritis on Australian women, and the establishment of a 'biobank' to help find the causes of childhood arthritis have all been kick-started with funding from Arthritis Australia.

The following case studies serve to put faces to some of Arthritis Australia's most successful research stories over recent years. These projects and many more continue to develop and move closer to their goal of improving the lives of people with arthritic disease.

Arthritis Australia congratulates all of our researchers on their achievements, and looks forward to supporting more world-class research and a new generation of talented researchers into the future.

Ainslie Cahill
Chief Executive Officer
Arthritis Australia

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Searching for the genetic trigger of a mysterious childhood illness

Our strategy is to use the most powerful techniques currently available to us to search for the genetic 'needle in a haystack' behind Kawasaki Disease.

Professor David Burgner is a paediatrician and scientist, currently based at the Murdoch Childrens Research Institute, Monash Children's Hospital, and The University of Melbourne. His research covers a broad range of childhood infectious and inflammatory diseases, and he is a leading authority on Kawasaki Disease. After a post-graduate training that included stints at the University of Oxford, Great Ormond Street Hospital and St Mary's Hospital, London, he established and led the first clinical paediatric infectious diseases unit in Western Australia, also developing and leading the state's paediatric refugee health service and paediatric tuberculosis service. He has authored numerous clinical guidelines and policies, including for the Federal Government and the Royal Australian College of Physicians.

Professor Burgner was awarded an Arthritis Australia and State and Territory Affiliates Project Grant in 2006 for his research on Kawasaki disease.

Kawasaki disease is a mysterious and life-threatening illness that strikes young children seemingly 'out of the blue'. First described in Japan in 1967, the disease is now recognised worldwide, and its incidence is growing steadily. There are about 200 cases diagnosed in Australia every year, but many more cases may be missed. Kawasaki disease causes a range of unusual and worrying symptoms. A very high fever, together with a skin rash, swelling of the hands and feet and inflammation of the eyes and mouth are all hallmarks of Kawasaki disease. Rarely, a potentially fatal enlargement of the coronary arteries occurs, sometimes requiring surgery. The majority of children with Kawasaki disease are diagnosed and treated quickly and recover fully, but a small number develop long-term effects. Arthritis is one manifestation of the disease.

Professor Burgner's research interests focus on the origins of Kawasaki Disease. "The cause is unknown, and there is still no cure. Common infection(s) may be the trigger, but we know that a child's genetic make-up plays a large part. Our strategy is to use the most powerful techniques currently available to us to search for the genetic 'needle in a haystack' behind Kawasaki Disease."

First used successfully in 2005 to search for the genes responsible for the eye condition age-related macular degeneration, Genome-Wide Association Studies (GWAS) analyse the DNA of thousands of individuals with a disease, comparing the results with those of a similar number of unaffected individuals. Differences in the frequencies of certain variant genes between the two groups can lead researchers to pinpoint a genetic region, or even a particular gene associated with causing or increasing susceptibility to a disease. A GWAS is only possible if a co-ordinated effort is made to recruit the large number of individuals required for genetic analysis – a challenge with relatively uncommon conditions such as Kawasaki Disease.

Determination to understand the genetic basis of Kawasaki Disease led Professor Burgner to establish the International Kawasaki Disease Genetics Consortium. One of the largest international collaborative studies of Kawasaki Disease in the world, the consortium places Australian researchers at the centre of important and innovative Kawasaki disease research, collecting data and biological material from sufferers and their families across 12 countries. With over 2100 cases recruited to date, the consortium is providing biological material and data for Kawasaki Disease projects worldwide.

This research led to publications in PLOS Genetics – the first GWAS of any infection-related disease – and in Nature Genetics.

Women and the burden of arthritis

> The Arthritis Australia grant was a turning point in my career.

Professor Lynne Parkinson is Professorial Research Fellow at CQ University, Australia, and Conjoint Associate Professor within the School of Medicine and Public Health at the University of Newcastle, NSW. As a population health gerontologist over the past five years, Professor Parkinson has developed an independent program of research in chronic conditions of older age, with a focus on the impact of arthritis in ageing women. Her expanding and internationally collaborative program explores the complex interactions between the individual, the environment and health in older people, and has helped to place Australia as a leader in ageing and chronic disease.

Professor Parkinson was awarded an Arthritis Australia and State & Territory Affiliates Project Grant in 2006.

In common with many industrialised nations, Australia's population is ageing. Increased longevity brings a range of age-related health problems, with significant impacts on the physical and mental health of individuals and their families, and an increasing burden on healthcare systems. As mothers, carers and members of the paid workforce, women are particularly affected by the pain and disability of chronic, age-related diseases.

The impact of arthritis on the lives of Australian women as they age is the major focus of the research of Professor Parkinson. Her Arthritis Australia grant supported the groundwork for an extensive program of research, which now draws on data collected as part of the Australian Longitudinal Study on Women's Health (ALSWH). Established in 1996 with the recruitment of 40,000 women of all ages, ALSWH explores the factors contributing to the physical and emotional health of individual women in Australia as they age, and assesses the effects of changes in health policy and practice.

Professor Parkinson's Arthritis Australia grant helped her to secure significant further funding from, among others, the National Health and Medical Research Council, Victoria Health, and the Australian Academy of Science. Her research now encompasses a wide range of topics; understanding the impacts of other medical conditions on the experience of arthritis, pain and depression, women's use of healthcare resources, and the prevention of arthritis. "This has helped us to establish some important realities about women and arthritis," says Professor Parkinson. "For example, we know that arthritis is very common in older Australian women, and that it has significant impacts on health and quality of life over time. Women with arthritis are more likely to have poor general health and suffer from depression and anxiety. Arthritis is also associated with significant medicine use - 60% of women use arthritis-related medicine."

The wide-ranging research program has also answered some very specific questions about the lives of women with arthritis. For example, it was found that a large proportion of women with arthritis – an estimated 46% – consult complementary and alternative medicines (CAMs) practitioners, with 79% using at least one self-prescribed CAM. It was also found that women based in rural areas often have difficulty accessing Medicare-funded doctor services and are more likely to be admitted to hospital than women without arthritis.

Importantly, Professor Parkinson's work has influenced the formulation of health policy in Australia. The Federal Government's 2010 review of the National Women's Health Policy referenced her research, and she has co-authored a report on the use and costs of medications and other health resources by women participating in the ALSWH study, prepared for the Australian Government's Department of Health and Ageing in 2008. Her work for Victoria Health Promotion, detailing effective prevention and health promotion strategies for musculoskeletal conditions, has been adopted as the basis for Victorian health promotion policy and practice.

"The Arthritis Australia grant was a turning point in my career – it was the first grant I obtained in this area of research, and seeded my extensive program of work in arthritis. The significant public health issue of women with arthritis continues to be an important focus of my research."

The power of genetic research – new therapies and diagnostic tools for complex diseases

> We hope to discover the causes of these diseases, and use the genetic information we find to help us diagnose them earlier and more accurately.

Professor Matthew Brown is currently Professor of Immunogenetics at the University of Queensland and Director of the University's Diamantina Institute. From 1994 until 2005, he was based at The University of Oxford where he became Professor of Musculoskeletal Sciences. Trained in Australia as a clinical rheumatologist, Professor Brown's major research focus remains musculoskeletal disease, with a special interest in the genetics of the painful and disabling disease of the spine, ankylosing spondylitis (AS).

Professor Brown has held four Arthritis Australia grants; The Phyllis MacDonnell grant, awarded in 2006, an Arthritis Australia and State and Territory Affiliates Grant in 2008, The Clitheroe Foundation Grant in 2010, and The Ray and Pam Robinson Grant, awarded in 2011.

Support from Arthritis Australia has played a key role in re-establishing Professor Brown's career in his native country, after a decade spent working in the UK. Whilst at the University of Oxford and as a principal investigator with the UK's Wellcome Trust Case-Control Consortium, Professor Brown was a key player in the development of the genome-wide association study (GWAS), a breakthrough approach to genetics research. Now at the University of Queensland's Diamantina Institute, Professor Brown leads an international group continuing investigations into the genetics of several arthritic diseases, along with a range of other diseases that have a significant impact on public health.

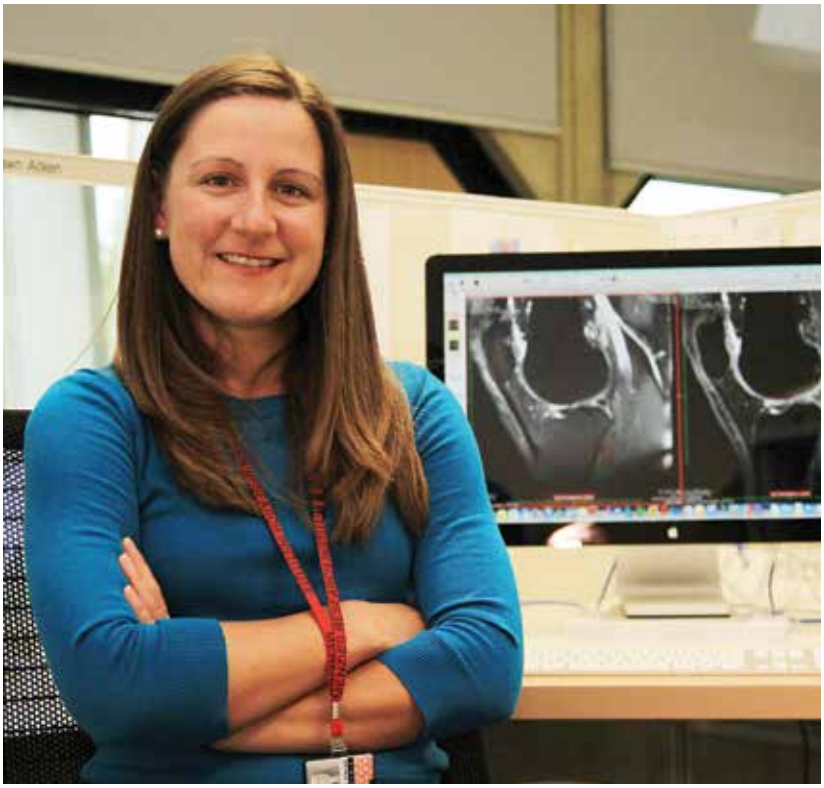
Professor Brown's first Arthritis Australia award in 2006 contributed to the discovery of variants of a gene that influences the immune system and is associated with the development of rheumatoid arthritis (RA). The protein encoded by this gene is found in large amounts in the joints of people with RA, making it a prime suspect in the development of the disease. "The causes of RA are not yet fully understood, but we know that genetic factors are important contributors - about 60% of the risk of developing RA is determined by an individual's genetic makeup," says Professor Brown. "The identities of most of those genes remain a mystery, but findings such as this bring us closer to understanding why certain individuals are far more likely to develop the disease than others." These results suggested the existence – since proven – of several other genes associations with RA. Continued support from Arthritis Australia and other funders, including NHMRC and the Queensland State Government, has since aided the establishment of a large RA and tuberculosis genetics research program in partnership with China and Norway, and a major program of research into the genetics of diseases including motor neurone disease, epilepsy, schizophrenia and ankylosing spondylitis.
The research has identified several molecular targets for the development of new diagnostic tests and vaccine-based therapies for RA and AS, some of which have attracted the interest of pharmaceutical companies and are undergoing clinical trials.

In 2011, Professor Brown was awarded an Arthritis Australia scholarship to establish a recruitment initiative for the collection of samples from people with common rheumatic diseases. Utilising the powerful GWAS research approach, The Arthritis Genomics Recruitment Initiative in Australasia (AGRIA), aims to close knowledge gaps in the causes of three of the most common arthritic diseases affecting Australasians – AS, gout and giant cell arteritis, a condition that affects around 1 in 500 people, causing inflammation of the arteries and leading to potential blindness. AGRIA researchers are building a resource of well-characterised cases with these conditions for genetic studies to identify the underlying genetic risk factors involved. Detecting variations in certain genes between people who have these diseases and those who don't can help researchers to understand more about their causes in the Australasian population – knowledge that is needed to design better targeted, more effective drugs and diagnostic tests. "This resource will enable many future genetic studies, both in Australia and internationally," says Professor Brown. "We hope to discover the causes of these diseases, and use the genetic information we find to help us diagnose them earlier and more accurately."

Professor Brown's work has led to the awarding of several prestigious research prizes, including the Australian Rheumatology Association's Parr Prize in 2010, and the 2013 Queensland Premier's Science Fellowship, in recognition of his global contribution to disease research. The $2.5 million Fellowship will advance the team's efforts in understanding the genetics of RA and multidrug-resistant tuberculosis, a growing problem in Australia, and acknowledges not only the excellence of the research, but its commercial and healthcare potential. In 2013 Professor Brown was also made Fellow of the Australian Academy of Sciences in recognition of his research contribution, the first Australian rheumatologist to receive this accolade. "We are on course to developing affordable diagnostic tests within the next five years, with new treatments that target the fundamental causes of these common but debilitating diseases not far behind," says Professor Brown.

Bone marrow lesions and osteoarthritis – a new therapeutic target

> We have found a treatment that can not only reduce the symptoms of osteoarthritis, but also change the structure of the knee.



Dr Dawn Aitken is a post-doctoral research fellow at The Menzies Research Institute, Tasmania. Her research is focused on risk factors for the onset and progression of osteoarthritis. Through improved understanding of the disease process, she aims to contribute towards the development of safer, more effective treatments and preventative strategies for osteoarthritis.

Dr Aitken was awarded an Arthritis Foundation of Australia – Australian Rheumatology Association Heald Fellowship in 2011.

Osteoarthritis (OA) is a slowly progressing disease with few obvious early warning signs. For many, the first indication of trouble is pain and stiffness in the joint. By that stage, cartilage destruction and joint deformity can be advanced, and there is little that can be done to slow or halt the damage. The challenge for researchers is to find 'biological markers' – changing physical or biochemical characteristics that can be detected and measured – to predict the development of osteoarthritis and intervene before the slow but often-unstoppable process of cartilage destruction takes hold.

Bone plays an important role in the development of OA. Bone marrow lesions (BMLs), abnormal areas of bone marrow around the knee joint, are strongly associated with some important features of OA. The larger the BML, the more rapid cartilage loss is and the more severe the pain. Unlike cartilage, BMLs can adapt rapidly, changing shape and volume over a period of months. The potential of BMLs as markers of response in short term trials of drugs for osteoarthritis has been explored, but Dr Aitken's research initially focused on the utility of BMLs for another purpose – their power to predict the likelihood of joint replacement surgery in people with knee OA. "This is a very important outcome measure – a large part of the economic burden of osteoarthritis is related to joint replacement surgery," says Dr Aitken.

The research was conducted as part of the Tasmanian Older Adult Cohort (TASOAC) study, aimed at identifying the environmental, genetic, and biochemical factors associated with the development and progression of osteoarthritis. The findings confirmed that BMLs are associated with the risk of cartilage loss, and are also strongly predictive of knee joint replacement surgery occurring in the years following their detection. This 'marker' showed impressive predictive power, independent of other indicators such as knee pain. Dr Aitken's research also found that dietary factors such as carbohydrate and sugar intake are associated with increasing size of BMLs, whilst HDL cholesterol is protective against BMLs enlarging over time.

"BMLs are not only early markers of OA disease that can be modified by environmental factors such as diet, but may also be reliable, independent indicators of the risk of future surgical intervention. Altogether, this suggests that BMLs are an important therapeutic target for OA," says Dr Aitken.

The next logical step for the team was to test the response of BMLs to a new therapeutic strategy. With leader Professor Graeme Jones, Dr Aitken and colleagues conducted a small 'proof of principle' trial of the commonly used osteoporosis drug, zoledronic acid, in people with knee osteoarthritis. A single infusion of zoledronic acid was found to significantly decrease both the size of BMLs and the severity of knee pain in the trial participants.

These exciting findings led to the recent award of a substantial NHMRC project grant to the team to conduct a large, multi-centre randomised clinical trial of zoledronic acid. The aim is to determine whether decreases in BML size seen in the first proof of principle trial will translate to reductions in cartilage loss and functional impairment of the knee joint over a longer period of time. The trial is now underway, and is due to finish in 2016.

"By slowing disease progression in knee osteoarthritis by targeting BMLs, it may be possible to delay knee replacement surgery," says Dr Aitken. "We have found a treatment that can not only reduce the symptoms of osteoarthritis, but also change the structure of the knee. This is important, because there are currently no treatments to slow or stop osteoarthritis from progressing."

Insights into childhood arthritis

> Our hope is that our research will pave the way towards better treatments that address the root cause of the disease. We can then do a better job at limiting the long-term damage that JIA can do.

Dr Justine Ellis trained as a complex disease geneticist at the University of Melbourne, with early work focusing on adult diseases. As group leader for Genes, Environment & Complex Disease Research at Melbourne's Murdoch Childrens Research Institute (MCRI), Dr Ellis and colleague Dr Jane Munro have led an important multi-disciplinary program of research known as CLARITY - ChiLdhood Arthritis Risk factor Identification sTudY, established with substantial support from Arthritis Australia. Dr Ellis was awarded a prestigious Australian Research Council Future Fellowship in 2012.

Dr Ellis was the recipient of three Arthritis Australia grants: the Arthritis Australia Kilimanjaro – Ascent for Arthritis Grant-in-Aid in 2008, an Arthritis South Australia-Juvenile Idiopathic Arthritis Grant in 2009 and an Arthritis Australia Project Grant in 2010. Dr Jane Munro was joint chief investigator on all three grants.

Juvenile Idiopathic Arthritis (JIA) is a relatively poorly understood disease. Although it has similarities to adult rheumatoid arthritis, JIA has its own distinct causes, symptoms and features. Up to 4 in every 1000 Australian children between the ages of 6 months and 16 years develop JIA. Most have only one or a few joints involved, but some develop very severe and disabling disease, affecting several joints as well as the eyes, skin or muscles. Many children with JIA 'grow out' of the disease and go on to lead arthritis-free adult lives. But for a significant minority, JIA will result in permanent joint damage and disability. The broader effects of JIA on the children who live daily with this disease can be profound, impacting on general physical and mental health, social relationships, body image, self-esteem and educational achievement.

Dr Ellis and co-investigator Dr Jane Munro have dedicated the past five years to understanding the causes of this complex disease. "Very little is known about the causes of JIA, but we do know that genes and the environment, play important roles," says Dr Ellis. "There are many studies looking at the genetics of immune disorders such as arthritis, but the rise in incidence over the last two decades tells us that something else, some change in the environment, must also be at work. My research aims to uncover the interactions between genes and environment that lead to JIA." In 2008, with support from Arthritis Australia, Dr Ellis and Dr Munro with colleagues at Melbourne's now Royal Children's Hospital, and MCRI established the JIA Case-Control Biobank, a collection of biological samples and clinical and environmental data from both children with JIA and healthy children. The Biobank underpins the CLARITY program. With the support of Arthritis Australia and other philanthropic and specialist organisations, the Biobank now houses samples and data from hundreds of children with JIA, as well as healthy controls. The team's goal is to recruit 1000 children from each group.

Each child participating in the CLARITY program donates a blood sample, which is carefully stored to enable a range of analyses for genes, immune system molecules and other substances that are suspected to play a role in the development of JIA. Participating families also complete an extensive questionnaire, which gathers information about events during pregnancy, in the early life of the child, and around the time of diagnosis. By comparing genetic sequences and environmental exposures between children with JIA and healthy controls, key elements that differ between the two groups can be identified, helping the researchers to close in on the combinations of genes and environmental factors that increase a child's risk of developing JIA.

"Our work has uncovered new risk factors for this debilitating disease," says Dr Ellis.
"Via international collaborations, we have identified a new gene for JIA. Our early preliminary data might also suggest that levels of vitamin D, in combination with certain genes, may increase the risk of developing JIA." This early lead, along with other interesting genetic findings, is now being followed up with a substantial three-year grant from the National Health and Medical Research Council.

CLARITY is already assisting with a number of other research projects, both nationally and internationally. Through the sharing of CLARITY's control samples, this important resource may contribute to new understanding of other autoimmune diseases, such as type 1 diabetes and inflammatory bowel disease. CLARITY is participating in a new project to understand the link between cardiovascular disease and inflammatory diseases such as JIA, and discussions are underway to explore possibilities for CLARITY's involvement in other projects.

"We are the only research group in the world collecting such detailed information on children with JIA," says Dr Ellis. "Our hope is that our research will pave the way towards better treatments that address the root cause of the disease. We can then do a better job at limiting the long-term damage that JIA can do."

Getting the best from e-health systems

> Freeing up nurse time for discussion with patients can go a long way towards improving patient education and compliance with treatment.

Associate Professor Kathryn Gibson is a conjoint Associate Professor at the University of New South Wales, Sydney. A graduate of Oxford University, she undertook physician training in Australia and is now a senior rheumatologist at Liverpool Hospital, Sydney. She chairs the South Western Sydney electronic medical record clinical governance and practice committee, is past chair of the NSW Department of Health e-health clinical advisory group and is a clinical lead for Health Share NSW on its electronic medication management project. She is also a member of the Musculoskeletal Network of the Agency of Clinical Innovation.

Professor Gibson was awarded an Australian Rheumatology Association Practitioner Fellowship in 2009.

The Australian government has invested heavily in 'e-health' computer systems to improve the productivity, efficiency and safety of healthcare services in the face of escalating costs and limited resources. Some organisations are able to utilise these systems to best effect; others don't manage to improve their practices significantly. Professor Kathryn Gibson has used her own clinical practice to explore the problematic issues around e-health systems. "It's clear that there is more to the successful utilisation of e-health systems in hospitals than simply installing them where there seems to be a need. There is a gap in our understanding of how to design and implement these systems to best support patient care and create more efficient, sustainable ways of working," says Professor Gibson.

In November 2009, an electronic Drug Monitoring System (eDMS) was introduced into the Rheumatology Department at Liverpool Hospital, replacing an informal paper-based and verbal system of communication. The previous system had evolved over several years to ensure the appropriate monitoring of patients taking DMARDS (Disease Modifying Anti-Rheumatic Drugs). It was complex, inconsistent and time consuming; it was also difficult to audit. The new eDMS allowed doctors to trigger a reminder to nurses to check pathology results at an appropriate time point, so that treatment could be instigated or adjusted according to a pre-determined protocol, whilst also alerting nurses to those patients who had not yet had their pathology tests done as advised.

Professor Gibson's study found that when the eDMS was introduced, no significant change was seen in the overall rate of patient monitoring. 'This was an interesting finding in itself - it seems that doctors have different attitudes towards monitoring generally, regardless of the type of system available to them', says Professor Gibson. When doctors did monitor their patient's drug use, the eDMS was used in over 99% of cases. Those that used it found that it made their practice more consistent, transparent and easier for others to access and understand. 'Monitoring rates didn't fall after introduction of the eDMS – this is important, because any new system must be acceptable to the majority of clinicians to be a worthwhile investment'. Nurses also reported that their time was freed up to run clinics more efficiently, seeing more patients and talking with them about various aspects of their treatment. "In busy clinics, doctors don't always have the time to answer all of a patient's questions or address their anxieties about treatment," says Professor Gibson. "Freeing up nurse time for discussion with patients can go a long way towards improving patient education and compliance with treatment."

Professor Gibson's exploratory Arthritis Australia grant contributed to a larger collaboration with a team headed by Professor Johanna Westbrook at the Centre for Health Systems and Safety Research, University of New South Wales. The team set out to accurately measure nurse time management, and found that the time spent monitoring medication almost halved with an eDMS. The downstream impacts of this were also measurable; the number of nurse-led clinics increased, as did the number of patients seen in each clinic. Nurses also spent significantly more time with patients and their relatives, and felt that the new system was safer and simpler.

The eDMS is now well established in the Rheumatology Department at Liverpool Hospital.
"It's clear from our research that electronic drug monitoring systems can have a measurable impact on the working practices of health professionals – the result is more efficient and effective patient care," says Professor Gibson. "In an ideal world, every e-health system would have such an impact, but we know that this isn't always the case. Our next challenge is to increase our understanding of the factors, both human and technological, that can either facilitate or hinder the successful implementation of e-health systems in clinical practice. We aim to use these findings to improve the outcomes of e-health implementations for patients, carers and clinicians."

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Arthritis Australia grant recipients and their research teams

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