



# PICTURE OF HEALTH

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A snapshot of HRB-funded research

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# 2012





# **PICTURE OF HEALTH**

A SNAPSHOT  
OF HRB-FUNDED  
RESEARCH 2012

**Published by:**

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ISSN: 1649-8844

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## FOREWORD

When we are sick, or someone we know is ill, we want and expect the best possible care. The best type of care is only available because of health research. Not only does it help pinpoint what the health problems are, research provides the evidence to improve our health, enhance patient care and transform approaches in the health care system.



During the past three years, the Health Research Board has been taking a strategic approach to fund health research that will translate research discoveries into real benefits for people and the health service. The Picture of Health 2012 demonstrates just some of the outcomes and achievements that are emerging from our funded work in this area.

During 2012, the outcomes from 92 HRB grants completed included:

- 17 new products and interventions in development
- 58 influences on policy and practice
- 1317 patients able to participate in cancer clinical studies
- 256 new national or international collaborations
- 113 research-related jobs across the health services and academia
- More than €14million leveraged in additional research funding for Ireland
- 38 PhD students trained across a variety of health disciplines

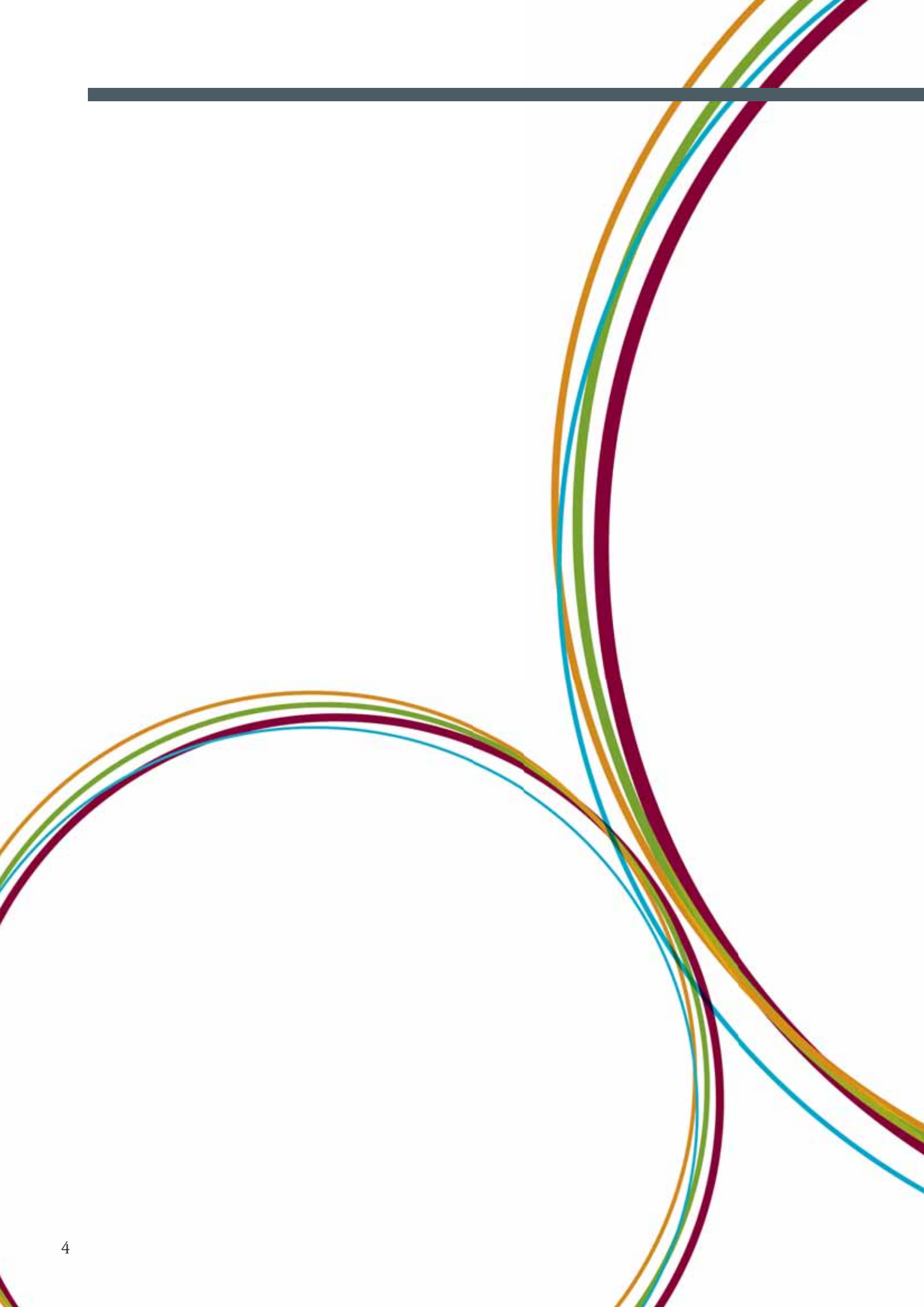
This edition features a broad range of health research projects, which capture the outcomes of a wide variety of health professionals as well as academics, who are not only delivering better treatments, but providing solid evidence for changes in approach to practice or policy.

It highlights the importance of engaging with the patient and the practitioner to get the best possible result. And it illustrates that working collaboratively across different health disciplines and drawing experience from different Institutions can yield positive results, both for the individual and health system.

It is evident from this report that the building blocks of our strategic plan are coming into place. We have a strong foundation on which we can build in order to deliver new treatments, better care, improvements to services and innovative changes to policy and practice.

A handwritten signature in black ink that reads "Enda Connolly". The signature is fluid and cursive, with a long horizontal stroke at the end.

Enda Connolly  
Chief Executive



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# IMPROVING PATIENT CARE THROUGH RESEARCH

## DEFIBRILLATORS IN GENERAL PRACTICE SAVE LIVES

In Ireland, an estimated 3-5,000 people die each year from sudden cardiac events some of which might not be fatal if they were treated in time. But many more of those lives could be saved if all GPs are equipped and trained to intervene rapidly, according to a study supported by the HRB.

The research was based on the five-year MERIT project, funded by the Health Services Executive, Pre-Hospital Emergency Council and the Department of Health and Children. That project equipped 500 GPs around Ireland with defibrillators and provided appropriate training to deal with a sudden cardiac arrest due to a heart complication called ventricular fibrillation.

“We know how to fix ventricular fibrillation, but fixing it is completely and utterly time dependent,” explains Gerard Bury, Professor of General Practice at University College Dublin.

“Nationally, only one in 20 people, at best, will survive a sudden cardiac arrest if it happens out of hospital. But this research, on the data from approximately 300 sudden cardiac events recorded in MERIT shows that the availability and proper use of

defibrillators by GPs, meant patients were three-four times more likely to survive the incident outside the hospital,” says Professor Bury. “And predominantly the events that we have recorded have been in small towns and rural Ireland, where traditionally outcomes have been worse.”

“The cost of around €4,000 per GP for equipment and training must be seen as a positive investment in terms of saving lives,” notes Professor Bury.

“This sort of structured intervention and support, allied with the strength of general practice can make a huge difference at local level,” he says. “Every GP in the country needs a defibrillator.”

### OUTCOME

- » Evidence that putting defibrillators in general practice can save lives.

## IMPROVING OUTCOMES OF DIABETES IN PREGNANCY – AN IRISH PERSPECTIVE

Having poorly controlled diabetes when you are pregnant is not ideal, for many reasons. If blood sugar levels are not kept in check, it can push up the risk of short and long-term health problems for both mother and baby.

Under a HRB programme grant, Professor Fidelma Dunne and Dr Geraldine Gaffney at NUI Galway headed a major study called Atlantic Diabetes in Pregnancy (DIP) to measure the incidence and outcomes of diabetes in pregnancy in the west and north-west of Ireland. And the results were arresting.

### **Education and process of care can change pregnancy outcome**

During the early weeks of pregnancy, it's important that blood sugar levels are controlled. One part of the Atlantic DIP study involved 104 women across five antenatal centres from Galway to Letterkenny who had diabetes before their pregnancies started.

“We were shocked by the outcomes of the pregnancies,” says Professor Dunne, a consultant endocrinologist at Galway University Hospital. “The stillbirth rate for women with diabetes was five times greater than the background population, the perinatal mortality rate was 3.5 times greater and the congenital malformation rate was twice that of the background population.”

Underlying the outcomes was that many pregnancies had started without the mothers receiving adequate support, notes Professor Dunne.

“Only 28 per cent of the women received pre-pregnancy care, 43 per cent received folic acid and just 51 per cent of the women had glucose control that would be deemed acceptable on international standards,” she says.

To help address the situation, Professor Dunne and colleagues looked to educate healthcare professionals and expectant mothers about the need to control blood sugars, and they ran pre-pregnancy clinics in four of the antenatal centres.

Did it work? Yes, according to an analysis of the pregnancies that were under the care of the new setup.

The number of women with diabetes attending pre-pregnancy care went up, as did the number taking folic acid. The live birth rate increased from 74 per cent to 92 per cent and perinatal mortality rate reduced. Miscarriage rates fell from 22 per cent to eight per cent and stillbirths from four per cent to one per cent.

“We achieved this because we had a significant uptake of folic acid and we had a significant improvement in sugar control,” says Professor Dunne. “It shows that changing the process of care for women with pre-gestational diabetes really improves the outcome of pregnancy.”

### **Gestational diabetes – an argument for universal screening**

Some women start a pregnancy without diabetes, but develop it about half-way through, and this ‘gestational diabetes’ can affect both the mother and the baby.

The HRB-funded study screened around 5,500 women at the five antenatal centres and found that more than 12 per cent developed gestational diabetes. These women more commonly had pre-eclampsia (a potentially life-threatening condition in late pregnancy) or chronic high blood pressure, more had delivery by C-section, the babies tended to be large and 26 per cent were admitted to the neonatal unit, compared with just over nine per cent of babies for women who did not develop gestational diabetes.

“Clearly gestational diabetes is common in the Irish population and clearly it can have significant impacts for the outcome of the pregnancy for the mother and for the baby,” says Professor Dunne, who explains the study showed that, even after pregnancy, the legacy of gestational diabetes continues.

“Within the first year of a woman’s first pregnancy, 18 per cent of those women continued to have a problem with glucose even though the pregnancy was completed, compared with only two per cent in the background who didn’t have gestational diabetes.”

Professor Dunne describes the outcomes as a signal that Ireland needs to introduce universal screening of women in pregnancy for gestational diabetes, rather than the current approach of screening pregnant women above a certain body mass index.

The HRB-funded study also showed that living far from an antenatal clinic was a barrier to attending gestational diabetes screening. “That is why glucose tolerance testing needs to be done in primary care rather than secondary care,” says Professor Dunne.

#### **OUTCOMES**

- » Measured regional levels and impacts of diabetes in pregnancy.
- » Improved pregnancy outcome for women with diabetes in the west of Ireland.

## SWITCHING ON TO ASSISTIVE TECHNOLOGY

For people with high-level spinal cord injuries and paralysis, seemingly everyday tasks like turning on a light, changing the TV channel or making a phone call become a challenge.

Assistive technologies can help people with limited movement to control appliances in their environment. But which technologies do people really need, what is it like to use them and what kind of impact can they have?

With the support of the HRB, Dr Michèle Verdonck looked at the issues with users in Ireland. For her PhD at University College Cork she worked with focus groups of people with high-level spinal injuries and developed a 'generic electronic assistive technology pack' (GrEAT). It contained commercially available equipment such as switches and mounts as well as instructions for users and their carers. "People wanted it to be simple and reliable, no bells and whistles," says Dr Verdonck, who is a senior occupational therapist at the National Rehabilitation Hospital in Dublin.

Six people with spinal injury used the GrEAT pack over the course of eight weeks and Dr Verdonck interviewed them and documented their experiences.

"Getting used to using environmental controls was a major issue but once they got used to it, they found the technology let them take back a little of what was lost," she says. "They start to become engaged with the technology and they talked about getting back to doing the everyday things we take for granted, like watching a DVD or making a phone call. They also talked about fun, like turning on a light when your parent didn't know you could do it. They were surprised that the technology worked, that it suited them and they were surprised that they got used to it, and they all found it was better to have had the experience than not to."

### OUTCOMES

- » Developed a cost-efficient generic environmental control technology pack to suit people with limited physical movement.
- » Demonstrated that relatively small starter packs for environmental control improve lives of people with spinal injury in an Irish setting.

## GETTING HIP TO PET SCANS FOR BONE HEALTH

You might think that bone is inert, just there to hold you up. But bone is living tissue and our bodies turn it over, reabsorbing and renewing it over time. As we get older, or in some medical conditions like osteoporosis, our ability to renew bone is impaired, and that can increase the risk of damage, such as fractures.

A HRB-funded study has been looking at an innovative way to measure that turnover using positron emission tomography, or PET imaging.

“The research looked specifically at the hip, which can be a vulnerable site for damage as we age,” says Dr Kathleen Curran, a lecturer at University College Dublin.

“The gold standard to assess hip bone health would be a hip biopsy, but that is invasive and painful,” she explains. “What’s more typically used is a less invasive approach – the patient gives a blood sample and some biochemical markers are measured. But those markers only give a global picture of bone health, they can’t tell you about a specific site like the hip.”

Dr Curran turned to PET imaging because it is both minimally invasive and it can offer a measure of bone turnover at the scanned site. Dr Michelle Frost at King’s College London took hip-bone scans of 12 healthy, post-menopausal female volunteers over the course of an hour and compared them to measurements taken from the lumbar spine.

PhD student Dr Tanuj Puri then carried out the analysis, and the data showed differences in bone turnover rates at the hip and lumbar spine. “It highlights the need for more location-specific rather than global measurements,” says Dr Curran.

“The PET approach could now be of interest for clinical trials to assess the impact of treatments on bone metabolism, and in the longer term might be useful for more general bone health screening,” she adds.

### OUTCOMES

- » Tested PET imaging for measuring bone turnover in the hip.
- » Clear evidence for the need to localise clinical measurements of bone health.

## POWER TO THE PEOPLE – AUTONOMY IN OLDER RESIDENTIAL CARE

Do older people in residential care have autonomy? It's a difficult question to answer, but a HRB-funded study did the groundwork. And the findings could enable autonomy for residents and thereby improve person-centred care.

“The whole process of engaging with residents, negotiating with them, knowing who they are as human beings, can influence the decisions that are made every day in a residential care home,” explains researcher Dr Claire Welford.

But the first task was to nail down what autonomy meant for older residents in care, because it was surprisingly poorly articulated in the literature. So Dr Welford undertook a concept analysis in her study at NUI Galway that revealed six attributes or ingredients for resident autonomy:

- that their capacity is encouraged and maintained
- they are involved in making decisions
- they delegate care needs based on their rights
- that care plans are negotiated through open and respectful communication

- that the unit has a culture of flexibility while maintaining resident dignity
- that family or significant others are included if a resident is cognitively impaired

But are those ingredients present in older care in Ireland? Dr Welford carried out a detailed assessment at one residential facility, which was selected as it would be considered typical. Her analysis found that autonomy was lacking for residents, so she worked with staff, residents and their families to facilitate more autonomy-focused care planning.

“Residents are now included in daily decisions about their daily lives and they are engaged in activities which are meaningful to them. Staff and families also engage with each other about the residents likes and dislikes,” she says.

### OUTCOME

- » Information for a resource pack and tool kit for all nursing homes in Ireland.

## IRISH PATIENTS HELP UNRAVEL GENETIC CLUES TO MOTOR NEURONE DISEASE

Every few days, a person in Ireland is diagnosed with motor neurone disease. The condition, where nerves that carry communications between the brain and muscles progressively stop working, is fatal and is not currently curable. But a HRB-funded project has characterised genes from hundreds of MND patients in Ireland, and the information is already helping to identify potentially important genes involved.

The project collected blood samples from around 500 people with MND and a similar number of ‘controls’ who don’t have the condition. By working out the ‘letters’ of DNA in the samples, the approach has already identified around 1500 genes that might be important in MND, explains consultant neurologist Professor Orla Hardiman, a HRB Clinician Scientist in Trinity College Dublin and Beaumont Hospital.

Using this DNA bank from Irish patients, Professor Hardiman’s group was able to confirm the presence of a key genetic variant on chromosome 9 in around half of the Irish population with inherited MND, and they are now seeing emerging genetic patterns of interest among people who are related. This work is being undertaken in TCD in collaboration with Professor Dan Bradley.

“Our graduate students Dr Russell McLaughlin and Kevin Kenna have found a number of intriguing variants that look like they are clustering around the disease,” she explains. Teasing out the genetic roots of MND will generally help to identify potential ways to target the condition, and the DNA bank from Ireland localises the picture for patients here.

“The genetics can help us to understand the mechanisms of the disease and identify the pathways that can contribute,” says Professor Hardiman. “And looking at ways to interrupt the abnormal gene function is one possible therapeutic intervention that could take place in the future.”

### OUTCOMES

- » Built a database of genetic information from patients in Ireland with motor neurone disease.
- » Identified numerous genes that could be involved in the disease.



## PEOPLE WITH CYSTIC FIBROSIS IN IRELAND ARE LIVING LONGER

Ireland has one of the highest incidences of cystic fibrosis in the world and around 1,200 people are thought to be living with the condition here. But are their life expectancies increasing in line with people the UK and US?

A HRB-funded project at University College Dublin has been coming up with some answers by analysing data from the CF Registry of Ireland. Since 2002 the database has been gathering valuable clinical data from around 1,100 people in Ireland with CF, explains Dr Abi Jackson, a post-doctoral researcher at UCD School of Public Health, Physiotherapy & Population Science.

“We wanted to find out more about the CF population in Ireland using this fantastic resource, the Registry, which collected data about demographics and clinical information on an ongoing basis,” she says. “It covers 90 per cent of the CF population, which will give you a very good idea of what is happening with the population.”

Dr Jackson worked with Professor Cecily Kelleher to analyse the CF Registry of Ireland data, and in conjunction with the CF Trust in the UK and the CF Foundation in the US they developed a new method to analyse life expectancy.

The results showed that life expectancy has been increasing in Ireland and that the Irish figures are slightly lower than in the US but still compare well. “One of the findings was that people in Ireland with CF who were born between 1985 and 1994 are living a similar length of time as those individuals in the US,” says Dr Jackson.

The project has also generated an understanding of CF survival in Ireland prior to the introduction of mandatory newborn screening in 2011. “Early intervention is important for survival and health,” says Dr Jackson. “This project means we have an analysis of the data before July 2011, and so we will be able to see if newborn screening makes a difference in Ireland.”

### OUTCOMES

- » Found that life expectancies of people with cystic fibrosis in Ireland are increasing and are similar to those seen in the UK and US.
- » Provided a baseline analysis of health and survival rates before the introduction of mandatory newborn screening in 2011.

## GIVING MIGRANTS A VOICE IN GP CONSULTATIONS

When you go to the doctor, it's important to be able to talk about the issue that brought you there. And then to understand the treatment the doctor recommends.

But what happens when the doctor doesn't speak your language? That can be a concern for migrant health service users in Ireland. And that's why a project at NUI Galway set out to ask migrants and health professionals about the ideal ways to break down communication barriers in consultation.

The Health Services Executive National Intercultural Health Strategy 2007-2012 clearly identified language, communication and support as priority areas for further research, explains Dr Anne MacFarlane, who is now Professor of Primary Healthcare Research at the University of Limerick's Graduate Entry Medical School.

So she, Mary O'Reilly-de Brún from NUI Galway and the Centre for Participatory Strategies, Galway, Diane Nurse from the HSE National Social Inclusion Unit and several peer researchers from migrant communities carried out participatory action research to seek the opinions of 51 migrants, five interpreters and 17 health service providers/planners.

We gave migrants an opportunity to have a voice in determining what they saw as best practice and generate a dialogue between stakeholders," says Dr MacFarlane.

The ideal strategy they found involved formal and trained professionals for either telephone or face-to-face interpreting, who would be monitored in practice to ensure they met a code of professional conduct. Participants also saw the benefit of bilingual GPs.

And while participants felt that it could sometimes be pragmatic to use a family member or friend to interpret, or to use a dictionary or online translation tools, these approaches were not seen as best practice.

### OUTCOMES

- » Informed guidelines on interpreting needs of migrants in GP consultations.
- » Led to Irish co-ordination of the €2.9 million EU FP7 RESTORE project on implementing guidelines and training initiatives to optimise primary care for migrants in Europe.

## READY FOR HOME?

When older patients are discharged from hospital by a doctor, they will most likely say that they are ready to go home. But are they? Discharge can be a vulnerable time. A HRB-funded study at University College Cork suggests that many older patients have concerns about how they will manage after discharge, and has also identified a need for more patient knowledge about the services they can access.

In the first study of its kind in Europe, researcher Dr Alice Coffey interviewed 335 older patients just before they left hospital. Using a series of questionnaires, she asked the patients themselves how they were feeling about their transition to home and what kind of support they expected to get at home. The interview also explored their levels of independent living, pain, comfort, knowledge about their condition and their medications.

“I conducted this research using a scale to measure the older person’s perspective on their readiness for discharge, as this may differ from the perspective of health care professionals and family,” explains Dr Coffey, who is a College Lecturer at UCC.

“The majority of older people I interviewed felt physically ready to go home at the time of discharge, but felt less ready with regard to their knowledge about medical follow up, their medication and services available to them.”

In follow-up interviews with 227 of these patients six weeks later, Dr Coffey found that a quarter of respondents had been readmitted to hospital. “The people who felt less ready for discharge were much more likely to be readmitted, more likely to be over 80 and were more reliant on family support,” she says.

The findings of the study will further inform health care professionals about the multi-dimensional nature of patient discharge.

### OUTCOMES

- » Informs discharge practices relating to older people.
- » Highlights the need for more person-centred education and information about available services.

## HOW WAS YOUR STAY? ASSESSING INPATIENT EXPERIENCE IN IRELAND

Most patients feel they are treated with dignity and respect in acute hospitals – but there's room to improve, according to a HRB-funded study that analysed responses from more than 5,000 inpatients in acute hospitals around Ireland.

The surveys, carried out in 2010 by the Irish Society for Quality and Safety in Healthcare (ISQSH) asked patients to rate their experiences through 142 questions, and also gave them an opportunity to write their comments.

“There were plenty of encouraging results – 92 per cent of patients were satisfied with the service overall and the safety precaution of checking patients identity prior to provision of medication seems to be on the increase since a survey in 2004,” says Dr Hilary Dunne, CEO of ISQSH.

But the analysis highlighted that in 2010 around 62 per cent of patients were not aware of complaints procedures and that 39 per cent did not feel encouraged to speak up about their hospital experience.

“Patients are afraid to complain while they are in the service because they are afraid of the impact it might have on their care,” says Dr Dunne.

The study, carried out in conjunction with the University of Ulster, also highlighted issues that could be addressed

relatively easily, such as clinical staff introducing themselves to patients by name rather than by their position.

“We want to deliver patient-centred care so we have to think; if it were me lying in that bed, or my mother or father or sister or brother, what care would I expect and want?” says Dr Dunne. The study validated the survey tool, which means it can now be used with confidence to assess more datasets about patient experience, and the team also worked with a software company to develop an easy-to-use ‘dashboard’ that makes it easier to filter and work with the data. The project also produced a shorter, 10-question survey tool that could be used to more rapidly assess patient experience in smaller-scale studies.

### OUTCOMES

- » Validated survey tools to measure patient experience in hospitals.
- » Developed software to filter and view the data.
- » Highlighted a need for greater awareness among patients of complaints procedures.

## A SILENT TOPIC: MANAGING AFTER RECTAL SURGERY

Colorectal cancer is one of the most common forms of cancer in Ireland. Surgery is the primary treatment for rectal cancer, but patients can experience temporary problems after surgery such as bowel incontinence.

So how do they manage? With the support of the HRB, Dr Margaret Landers at University College Cork surveyed 143 patients across 10 clinical sites in Ireland who had undergone a procedure called a rectal resection. The patients had retained the sphincter or muscle after surgery and so did not need to get a permanent alternative opening called a stoma.

The survey asked patients about how they experience and manage symptoms and the impact on everyday life. In their responses, they frequently reported bowel problems including frequency, irregular patterns, urgency and incontinence.

“If patients had radiotherapy or required a temporary stoma, it compounded their symptoms,” says Dr Landers. “One of the

main strategies was to always know where the nearest toilet was when they were out and about. Men tended to use bowel related medication to manage symptoms while women used a wider variety of strategies, including incontinence pads and bringing a change of clothing with them.”

Dr Landers says the study highlights the need to talk to patients about symptoms following rectal surgery, to reassure that many of the symptoms are a temporary consequence of surgery rather than a sign that the cancer has returned and to suggest self-management strategies that are both practical and realistic.

She now aims to develop a website that will provide additional information and support for patients following sphincter-saving rectal surgery.

### OUTCOMES

- » Identified patient symptoms and self-management strategies following rectal surgery.
- » Findings will inform and augment the current support available for patients.





**SEARCHING FOR  
BETTER  
TREATMENTS**

## HOW TO HIT A TUMOUR SPOT ON – WITH ENGINEERED ADULT STEM CELLS

Wouldn't it be great if there was a delivery system that could find tumours in the body and smuggle agents in to kill them? Such Trojan horses might be right under our noses – could we use adult stem cells to deliver anti-cancer therapies in a targeted way to tumours?

Mesenchymal stem cells in your bone marrow normally play roles in healing wounds, and they appear to have a knack for finding tumours.

A study at NUI Galway engineered human mesenchymal stem cells so they also had another trick – they had an extra protein which meant they could take up radioactive tracers. The researchers then put the engineered stem cells into the bloodstream of mice with induced cancer and put tracers in too.

“The stem cells took up the radioactive tracers, so we could watch them as they travelled through the bloodstream and we could see where they went,” explains researcher Dr Róisín Dwyer,

who collaborated with the Regenerative Medicine Institute at Galway and the Mayo Clinic in the US on the project.

Two weeks later, the adult stem cells had concentrated at tumour sites rather than healthy tissues, showing they had hit the target. Then, when the researchers gave a therapeutic dose of the radioactive molecule, the stem cells at the cancer sites were able to take it up, and the tumours shrank.

While work remains to be done on the system to bring it closer to the clinic, the fundamental tracer and therapy system used in the study have previously been used in patients, explains Dr Dwyer, who won an award from the Irish Cancer Society for the work.

### OUTCOMES

- » Showed that adult stem cells can target tumours and deliver therapy in a preclinical model.
- » Potential for developing a new therapeutic delivery system.



## KEEPING A STEP AHEAD OF DIABETIC FOOT DISEASE

If you have a stone in your shoe or your footwear is pinching, nerves in your feet will soon tell you. But over time in diabetes, those nerves can become damaged and you don't get the pain signal to protect yourself.

As a double-whammy, poor vascular function in diabetes can also make lesions slower to heal. The eventual upshot could be severe foot ulcers and even the need for amputation.

Now a new study has measured, for the first time, the levels of risk of diabetic foot disease among patients in a community setting in Ireland. The research saw practice nurses, with the help of a podiatrist, assessing nearly 600 patients with diabetes at 12 GP practices in the west of Ireland. It found that 64 per cent of patients were at low risk, 25 per cent had moderate risk and 11 per cent were at high risk of the serious foot complication.

The study also found that simple screening methods were effective, like using a monofilament to check for light touch sensation and feeling for a foot pulse

to assess vascular function. Taking an imprint of the foot on carbon paper was a useful tool to help patients understand where the pressure points were. And the researchers observed a potentially useful link between a standard blood test for impaired kidney function and the risk of developing diabetes-related foot problems.

"We now have real data from Ireland on the percentage of people who fall into the low, moderate and high risk categories for diabetic foot disease," says researcher, Dr Sean Dinneen, a senior lecturer in the discipline of medicine at NUI Galway. "And this is going to be helpful for planning how to identify patients in the community setting who are at risk of developing diabetic foot complications and how best to direct services into the future."

### OUTCOMES

- » First assessment of the risk of diabetic foot disease among patients in a community setting in Ireland.
- » Evaluation of tools to measure diabetic foot risk in general practice.
- » Identified a potential link between a standard blood test and diabetic foot risk.

## TOWARDS A UNIVERSAL FLU VACCINE

Every flu season, we get a new flu vaccine. Why? Because the predominant flu virus that circulates is likely to have 'changed its coat', and vaccines from previous years won't give us enough protection. And if a pandemic flu breaks out, there's a global scramble to develop and distribute vaccines in time.

That's why a 'universal' flu vaccine that protects against many strains, including potential pandemic flu, is something of a holy grail in research, and a HRB-funded team at Cork has been making strides in the area.

"Instead of targeting the outer surface of the flu virus, which is the part that changes the most, we want to develop a vaccine that targets more hidden parts of the virus, which tend to change less," explains Dr Anne Moore, a Lecturer in the School of Pharmacy and the Department of Pharmacology and Therapeutics at University College Cork.

Her team has been looking at a 'recombinant' vaccine, which puts small amounts of genetic

material from a flu virus into a harmless carrier virus. When this is injected into a host, the vaccine starts making the proteins from the flu virus and the host immune system hopefully starts building up a 'memory' of it.

The Cork study used two such vaccines that were designed to elicit particular immune responses. And it found that the universal vaccines provided some protection against very divergent strains of flu virus in mice.

The study worked out important elements of how the immune system responds to the two vaccines and has established expertise in universal flu virus development at UCC, explains Dr Moore.

### OUTCOMES

- » Worked out response mechanisms to two potential universal flu vaccines.
- » Built a network of virology and vaccine collaborators.
- » Led to an EU-funded study on flu vaccines in large animals using a novel vaccine delivery platform.

## LOOKING AFTER SMILES IN OLDER PEOPLE

In the space of a generation, people in Ireland have come to expect they will have healthy teeth in older age. In response, dentists need to be able to offer effective treatments to keep older patients' teeth working and looking well without breaking the bank.

So with support from the HRB, a study at University College Cork sought to evaluate an approach that replaces some, but not all, lost teeth in older patients.

The study involved 130 older people. Half of the participants underwent a conventional course of treatment to replace all of the missing teeth. Meanwhile the other 65 underwent a "functionally-oriented" treatment strategy that replaced only some of the teeth that were missing yet still provided the person with adequate biting contact and appearance.

Initially both treatments scored well in the trial, and after a month the measured outcomes were similar for function and for the patient's quality of life, explains Professor Finbarr Allen, who is Dean of Dentistry and Head of the Cork University Dental School and Hospital at UCC.

But over the course of six to 12 months a gap started to emerge between the conventional treatments and the new functionally-oriented treatment, he notes.

"The quality-of-life scores for the patients who received the functionally-oriented treatment was better at the one-year mark," says Professor Allen. "Another factor in favour of the functionally-oriented treatment is that it is twice as cost-effective as the conventional approach of replacing all missing teeth," he adds.

Dr Gerry McKenna won a major international award for his PhD work on the study, and with proof of concept now established through the trial in Ireland, Professor Allen is seeking to carry out a multi-centre trial across Europe to inform and influence dental health policy on a wider scale.

### OUTCOMES

- » Evidence that a more functional approach to tooth replacement in the elderly is both clinically and cost-effective.
- » Proof-of-concept results to influence dental health policy for older patients.

## DIGGING INTO THE GENES BEHIND RARE DISEASES

Ireland has a relatively high level of rare diseases, and sometimes the genetic variations that underlie them are not found anywhere else in the world. But by analysing genes from Irish families with rare diseases, a HRB-funded study has been identifying new genes responsible for rare disorders, and developing easier ways to diagnose conditions, screen for carriers and help genetic counselling.

“If you want to have a direct impact on health in the Irish population, you need to be doing the research on the Irish families,” says Dr Jillian Casey, a post-doc at the National Children’s Research Centre in Crumlin.

Working within families that have a history of a rare condition, the researchers have been looking for regions of DNA that are common to all of the affected individuals but that are not shared by their healthy relatives.

Their search has led them to identify a key eye development gene associated with a micro-anophthalmia where eyes fail to form normally. “We showed for the first time that changes in this gene can cause an isolated eye disorder,” says Dr Casey.

The team, co-led by Dr Sean Ennis, UCD, and Dr Sally Ann Lynch, National Centre for Medical Genetics, also identified another gene linked with familial glucocorticoid deficiency, which can result in poor growth and a high susceptibility to viral infections.

The findings have led to the development of genetic tests for use in the clinical setting to help with earlier diagnosis and to identify carriers in affected families. Further research is also helping to develop a single screening test to diagnose an array of rare diseases present in the Irish population.

### OUTCOMES

- » Identified genes linked with rare disorders in Irish families.
- » Pinpointed a key gene in eye development.
- » Developed genetic tests for rare conditions.

## A HELPING HAND FOR HEPATITIS C TREATMENT

Hepatitis C (HCV) is a major global health problem: around three per cent of the world's population is infected with the virus, which can cause liver damage over time. In Ireland, hundreds of women were infected with HCV through blood-related products in the 1970s and 1990s.

The main drug to treat HCV is interferon, which activates the body's own anti-viral immune defenses. Yet it doesn't help everyone to clear the virus – many will have treatment, but the virus avoids elimination.

A HRB-funded study has shed light on why interferon doesn't work in some people, and is enabling the development of potential new therapies to help clear the virus. The problem lies with a version of the virus called genotype 1, which is the version that affected the women in Ireland who received contaminated blood product called anti-D.

Around half of people infected with genotype 1 will not respond to interferon therapy. By analysing immune and liver cells from these women, Dr Nigel Stevenson and his team at Trinity College Dublin identified gaps in the normal signalling process that interferon uses to tell the cell to clear the virus.

And they discovered that HCV literally hijacks the cell's own machinery, making it degrade these specific proteins involved in passing along the message from interferon that tells the cell to kill the virus.

"We worked out a mechanism by which HCV avoids being destroyed," says Dr Stevenson. "We now know the specific regions within HCV that hijack the cell's own machinery to degrade essential proteins within the anti-viral interferon pathway – therefore, these HRB investigations have pointed the way to developing potentially novel therapeutics, designed to cure HCV."

Armed with this knowledge, his group is now developing molecules designed to block HCV from interfering with anti-viral responses to interferon. The ultimate aim is a therapy that can be given along with interferon to enhance its role in clearing the virus.

### OUTCOMES

- » Identified how hepatitis C blocks interferon treatment in patients.
- » Potential for new therapies to tackle the hepatitis C virus.

## DOES THE IMMUNE SYSTEM WISE UP TO FOREIGN STEM CELLS?

Adult stem cells can deliver powerful therapies. Already they are used in the clinic to help people being treated for leukaemia. Meanwhile, adult stem cells have applications, or are being trialled, for various other conditions too, such as helping heart tissue to repair after a heart attack.

But a HRB-funded study has sounded a note of caution for treatments that require many infusions of stem cells in the same patient. The research highlights that the immune system could get wise to 'foreign' stem cells over time and potentially eliminate them.

"Stem cells are going into thousands of patients in clinical trials," says Dr Thomas Ritter, a Senior Lecturer in Medicine (Gene Therapy) at NUI Galway. "I have no doubt that these stem cells are efficacious, but no-one really analyses immune responses that are being mounted against these cells."

Working with a pre-clinical model, Dr Ritter watched what happened when stem cells from one animal were transplanted into another (genetically distinct animals which mimics the human situation). "When you inject these adult stem cells suddenly there is the formation of antibodies, so the immune system is mounting a response," he says.

But if the treatment works, why should it matter what the immune system does? A problem could arise if the same host gets another transplant of stem cells, according to Dr Ritter. "After 14 days we injected another batch of adult stem cells into the animals," he says. "If there was no immune response then these cells would have survived for a long period of time. But we have shown that these cells are being quickly removed the second time around."

If the same holds true for humans, it could mean that while initial adult stem cell therapies could work, repeated doses might not be effective unless the immune system response is also dealt with, says Dr Ritter.

"We are giving a note of caution to researchers in the field that when they do adult stem cell therapy, they also have to investigate thoroughly immune problems that may arise."

### OUTCOME

- » Warns that the immune system could stop repeated transplants of adult stem cells from working.

## A STIFF WARNING FOR HEART FAILURE

Heart failure, where the heart isn't doing its job well, is one of the leading causes of hospitalisation among the elderly in Ireland. Yet despite being a common and costly medical condition, we still have a way to go to diagnose it and to predict in advance who is at high risk. But a HRB-funded project has identified potential biochemical markers that could help.

The better known type of heart failure is 'systolic', where the pump is weak, and that can be treated to some extent. But there's another type of problem – diastolic heart failure – where the heart tissue grows stiff and cannot expand to fill the organ with a large enough volume of blood before pumping.

“What has emerged over the past five years is that maybe 40 per cent of the patients with heart failure in hospital have got diastolic heart failure,” explains Dr John Baugh, a lecturer at University College Dublin. “And the big problem with that is that there are currently no treatments.”

Being able to more easily diagnose diastolic heart failure could help in clinical management. And being able to detect when someone is at high risk could possibly aid in prevention or the delay of symptoms.

So Dr Baugh and colleagues analysed proteins from the blood of patients at risk of diastolic heart failure and identified several potential biomarkers.

The findings have led to a patent and have paved the way for more in-depth studies on a suite of biomarkers that could help doctors to identify with just a simple blood test whether someone is at risk of a stiff heart or has already developed the condition. The results could also ultimately inform new approaches to prevention and treatment.

### OUTCOMES

- » Patented several potential markers for diastolic heart failure.
- » Paved the way for ongoing validation of technology to easily identify patients with, or at risk of, diastolic heart failure.

## A CANDID LOOK AT FUNGAL INFECTIONS

Most of the time, fungal infections are irritating. But in some cases they can be life-threatening, and the arsenal of drugs we have to fight them is limited.

That's why Dr David Fitzpatrick has been taking a gene's-eye view of a clinically important type of fungus, and from this perspective has been pointing out potential chinks in the armour that could be targets for future anti-fungal therapies.

With support from the HRB he looked at *Candida* fungi, which are single-celled yeasts. The most notorious among them is *Candida albicans*, which causes thrush but can also have more serious consequences if it gets into the bloodstream and causes a potentially fatal systemic infection.

"By comparing the genetic material of the more virulent *C. albicans* with less clinically troublesome *Candida* species we were able to identify where *C. albicans* had genetic expansions for features such as cell wall structures and protein pumps, which might make it more aggressive in the body," explains Dr Fitzpatrick, who is now a lecturer at NUI Maynooth but carried out the HRB-funded project at University College Dublin.

He also discovered bacterial genes in the emerging pathogen *C. parapsilosis*. The findings suggest that the genes may have been transferred into the fungal genome and could give the fungus a competitive advantage.

Because fungi are genetically more similar to humans than bacteria are, it can be difficult to find therapies that kill off the fungus without affecting the patient's own cells, but Dr Fitzpatrick explains that identifying key virulence genes in fungi that are not present in humans could offer avenues for new drug therapies to be developed: "We are coming up with potential targets in a clinically important group of fungi."

During the project, he and colleagues also built up a *Candida* Gene Order Browser tool, which is now online and is available for the research community to help them analyse and compare *Candida* genes.

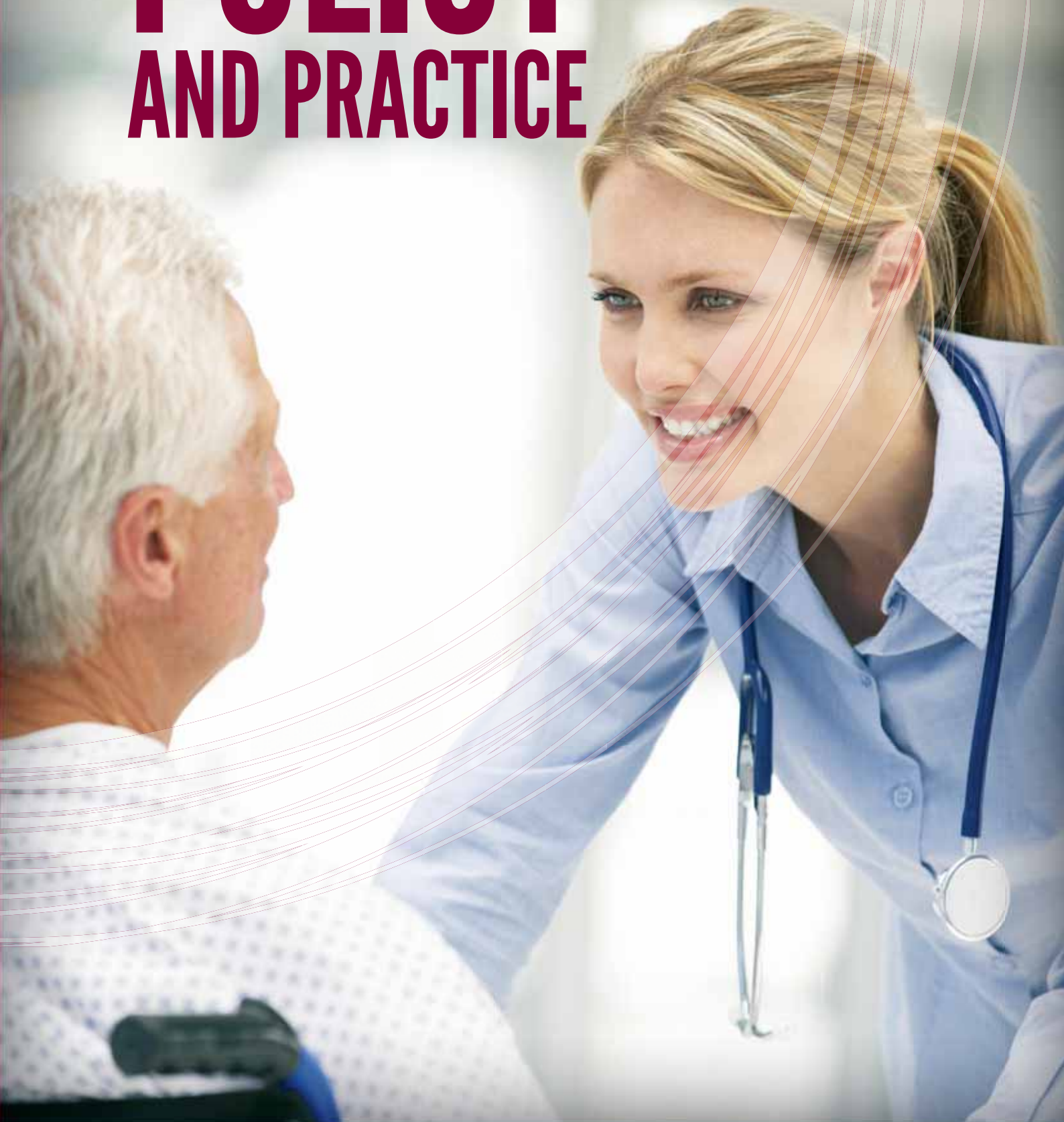
### OUTCOMES

- » Identified new potential drug targets against clinically important fungal pathogens.
- » Built up an online tool for researchers analysing fungal genes.



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# INNOVATING HEALTH POLICY AND PRACTICE



## ESTABLISHING STANDARDS FOR THE QUALITY OF PRIMARY CARE

Primary care is the first port of call for many people who are concerned about their symptoms. And offering effective medical and nursing care in the community setting helps to ease the burden on hospital services.

That's why the HRB Centre for Primary Care Research – a collaboration between the Royal College of Surgeons in Ireland, Trinity College Dublin and Queen's University Belfast – is seeking to further improve the standard of primary care in Ireland.

### The right medicine

Medication – both prescription and over-the-counter – forms a cornerstone of primary care, so the Centre is analysing medicines management in vulnerable groups in Ireland and it is also developing supports to help primary care physicians diagnose and prescribe for conditions appropriately.

Part of the underlying issue is that we now have an enormous diversity of medications on offer, and people are living longer, explains Professor Tom Fahey, Principal Investigator at the strategic centre, which was launched in 2008.

“Over the last 25 years, the number and volume of drugs that people are taking, particularly in middle and older age, has substantially increased,” he says. “This has presented a challenge for doctors to make sure patients are on the right medicines for the conditions they suffer from.”

Work at the HRB Centre for Primary Care Research has been assessing the medicines that various groups in Ireland take. The results show that among the people assessed, around one-third of elderly people are on potentially inappropriate medication (where risks of taking a drug may exceed its benefits) and that they appear likely to have poor health-related quality of life. Meanwhile, children in Ireland are frequently being prescribed expensive, second-line antibiotics. And around 40 per cent of women take medication while they are pregnant – most are considered safe to take during pregnancy but around two to three percent take drugs that could potentially be harmful to the developing foetus.

System-wide changes are needed to improve medicines management in primary care in Ireland, according to Professor Fahey. “We have shown that the prevalence of prescribing potentially inappropriate drugs doesn't really alter significantly among practices,” he says. “So any strategy for change has to be global rather than targeted at individual practices. Ireland is not unique and other European countries face similar challenges.”

## Supporting clinical decision-making

One strategy being developed by the HRB Centre for Primary Care Research is a suite of decision-support tools that could ultimately be rolled out to physicians across Ireland and internationally. Already the Centre has developed clinical management pathways, supported by a pharmacist, that enable GPs to find alternative treatments to a potentially inappropriate drug, and the Centre is testing its impact in a clinical trial.

Another area of research is to help diagnoses in the clinic that use validated 'clinical prediction rules', which use focused questions that allow health professionals to rule in or rule out a particular condition," he says.

There are many such clinical-prediction rules, but they have not all been validated through clinical studies, explains Professor Fahey. So research at the Centre is systematically reviewing rules and building an online resource that doctors can use: not only does it provide the rule, but it also indicates whether the rule has been validated.

## A wider view on primary care

Raising the standard of primary care in Ireland needs a concerted infrastructure to gather data, trial new approaches and disseminate up-to-date information about practices that are supported by evidence.

The Irish Primary Care Research Network, a collaboration between the HRB Centre for Primary Care Research, the Irish College of General Practitioners and the WestRen Research network led by the Department of General Practice at NUI Galway, seeks to assess and provide comparative clinical data that enable health professionals to enhance the quality of care they provide to their patients.

At present, the Network is looking at practices in relation to care of diabetes, heart failure, pregnancy and childbirth drugs. "This offers a way in which we can generate comparative clinical data from practices in Ireland," says Professor Fahey. "It should raise the quality of care and general medicines management across the different domains," he says. "We are particularly interested in multi-morbidity, where people have a number of different medical conditions at the same time. People tend to present with clusters of conditions and the challenge is to manage those different conditions simultaneously."

The Centre is also working as part of a European Commission-funded FP7 consortium on the TRANSFoRM Project to integrate decision support directly into primary care electronic records systems.

## OUTCOMES

- » Analysis of potentially inappropriate medication in vulnerable groups.
- » Decision-support tools to help diagnosis and prescribing in primary care.
- » Established a network of practices for clinical studies to benefit patient.

## THE INFORMATION DIET – PROMOTING HEALTH AND WELLBEING WITH HIGH-QUALITY DATA

Diet-related health problems are a big issue in Ireland, literally. Overweight and obesity are now a firm fixture in the population here, and diet can also drive up levels of diabetes, high blood pressure and cardiovascular disease.

Big problems need big strategies and the HRB Centre for Diet and Health Research is bringing researchers and data together to get a handle on the size of the problem in Ireland and, importantly, to strengthen the evidence base for the prevention of diet-related illness.

Launched in 2008, the Centre spans University College Cork, University College Dublin and the University of Ulster. It is co-funded by the Department of Agriculture, Fisheries and Food and it works in partnership with other major agencies on the island of Ireland that have an interest in public health and nutrition.

“Diet is a critical determinant of health,” says the Centre’s director, Ivan Perry, Professor of Public Health at UCC. “The mission of the Centre is to contribute to the evidence base on diet and health and ultimately to promote the health and wellbeing of the Irish population.”

### Growing healthily

Childhood is a crucial time to build a healthy foundation and the Centre is working in conjunction with the Growing up in Ireland study to look at diet and health in children. Family influence is a focus, the Centre’s analysis of the Growing

up in Ireland data shows that 85 per cent of children aged nine have at least one overweight or obese parent in Ireland, and in general the greater the levels of parental overweight or obesity the more likely the child will be overweight or obese.

Meanwhile, intergenerational analysis by the Centre of the Lifeways Cohort data has shown that grandmothers and mothers have a strong influence on childhood weight. “These associations make a strong argument for interventions and policies that consider the whole family,” says Professor Perry.

The Centre has been involved in a major study on diet in pregnancy, which shows that expectant mums who have a low GI diet can reduce weight gain by up to 20 per cent. And it is now preparing to collect information about diet and physical activity among 1,000 children in Cork, which will align with and add depth to the Growing up in Ireland data.

### Healthy diets in adults – routes for improvement

What are the ingredients of a healthy lifestyle? The HRB Centre for Diet and Health Research is analysing data from surveys to build a better understanding of health in adults in Ireland. As an example the Centre

has looked at information from the Survey of Lifestyle, Attitudes and Nutrition (SLÁN) to analyse the impact of salt levels in the diet and how living far from a supermarket is linked to a poorer quality diet.

As well as analysing existing data, the Centre is now collecting new information through the Mitchelstown Cohort Study, which involves around 2000 middle-aged men and women.

“It’s one of the largest primary care-based studies to be carried out in Ireland to date and we are gathering high quality dietary and lifestyle data as well as blood samples,” says Professor Perry.

The Centre is also building a database of information about people in Ireland who are undergoing treatment for severe obesity, it is analysing consumer behaviours and media coverage of health and obesity in Ireland and it is working to enhance nutritional standards in catering and food labelling in general.

## Totting up the bigger picture

By analysing population data from Ireland, the Centre is helping to shed new light on health trends, costs and the potential for interventions. One encouraging development is that since the mid-1980s, death from cardiovascular disease has declined by about 50 per cent, says Professor Perry.

“What we are finding is that roughly 60 per cent in the fall in death rates can be explained by an improvement in risk factors – things like better diet and less smoking,” he says. “And roughly 40 per cent has been influenced by improvements in treatment such as better drugs and coronary artery bypass grafts.”

As well as looking at mortality trends, the Centre is modelling the potential for further improvements that could be achieved through public policy measures to reduce dietary salt and unhealthy fats and to boost fruit and vegetable intake.

Meanwhile, working with safefood, the Centre has been estimating the national cost of obesity on the island of Ireland, both the direct costs and the indirect impacts through premature deaths and lost productivity.

“Getting the numbers on those impacts will provide strong evidence to influence public policy,” says Professor Perry, though he notes that the shifts can happen gradually. “It is like the tide coming in or going out – you might look back over several years and only then realise there has been a fundamental shift in thinking about issues. We want to inform those shifts in thinking.”

## OUTCOMES

- » Mining large, existing health-related datasets in Ireland to inform policy on diet and health.
- » Collecting new high quality data from cohorts in Ireland.
- » Identifying major trends and costs associated with health in Ireland.

## A NEW VIEW OF ROAD TRAFFIC COLLISION ‘HOTSPOTS’

Every year in Ireland, hundreds of people die or are seriously injured in road-traffic collisions. Knowing the ‘hotspots’ where collisions are more probable means that measures such as speed limits or warnings can be put in place to hopefully bring about safer journeys. But are there better ways of working out where the hotspots lie?

In a project funded by the HRB, Dr Erica Donnelly-Swift and Professor Alan Kelly from Trinity College Dublin put the numbers through their paces. Their basis was information from around 8,000 collisions on national primary and secondary roads between 2005 and 2009, accounting for more than a quarter of all collisions nationwide.

By analysing the collision data along with information from electronic maps, they applied statistical methods that let them scan not only time, but stretches of road as well. Their approach allowed them to more precisely map out known or suspected hotspots and to also identify new hotspots on national primary and secondary roads.

“We developed a method to look at multiple hotspots along a network,” explains Dr Donnelly-Swift. “And by using a systematic approach to look at alternative secondary hotspots, we identified the location of many hotspots along a particular stretch of road.”

The research also highlighted that around half of collision events occurring at hotspots on national primary and secondary roads involved multiple vehicles, and that collisions are more frequent in darkness.

“Our findings and methods should inform policies and measures aimed at reducing the numbers of deaths and injuries from road-traffic collisions on national routes,” says Dr Donnelly-Swift. “Ultimately we hope this research will save lives by providing information on hotspots and a national perspective on road-traffic collisions.”

### OUTCOMES

- » Developed improved statistical methods for pinpointing hotspots for road-traffic collisions on national primary and secondary roads in Ireland.
- » Evidence to inform road safety policy and measures.

## RESISTANCE NEEDED FOR ANTIBIOTIC MISUSE

Do prescribing habits really have an effect on the rise of antibiotic resistance? A HRB-funded study in the west of Ireland shows that many antibiotics are prescribed inappropriately, and highlights a link between the prescription of antibiotics and an increased risk of antibiotic resistance.

“By using antibiotics we make them gradually less useful,” explains Dr Akke Vellinga, a senior lecturer in primary care and lecturer in bacteriology at NUI Galway. “The antibiotics end up in the environment and the bacterial community adapts by developing resistance.”

The study looked at databases on prescribing practices and antibiotic resistance.

“We found there was a very direct link – the more antibiotics a practice prescribed the higher the chance that an individual patient will be diagnosed with a resistant *E. coli*,” says Dr Vellinga.

The study also analysed urine samples from all patients who had suspected urinary tract infections at a selection of practices and examined what, if anything, had been prescribed for them.

“We saw that only 20 per cent of the urine samples had an organism identified, but 56 per cent of them had an antibiotic prescribed,” says Dr Vellinga. “And of those 56 per cent, only 37 per cent were prescribed according to the recommended treatment.”

In addition, the risks of being diagnosed with an antibiotic-resistant bacterial infection shot up if a patient had more than one course of antibiotics: having two or more rounds of the medication could increase the risk of resistance by more than six-fold.

The analysis also pointed to an area risk of antibiotic resistance, suggesting the possible spread of resistant bacteria in the community.

### OUTCOMES

- » Quantified the increased risk of antibiotic resistance due to inappropriate prescribing in general practice.
- » Findings are informing an education and awareness campaign about antibiotic prescription and use.

## PEER SUPPORT IN DIABETES – DOES IT REALLY WORK?

It seems intuitive that peer-support groups for people with Type 2 Diabetes would improve outcomes by helping participants manage their condition better. But a trial in Dublin funded by the HRB did not find that was the case.

Focus groups showed that people with diabetes wanted to hear about the condition in “lay” language, and peer support seemed to offer a route to do this, explains Professor Susan Smith, who worked on the project when she was based at the Trinity College Dublin Department of Public Health and Primary Care.

She and colleagues ran a randomised controlled trial involving almost 400 patients from 20 practices. Over the course of two years, 29 trained peer supporters ran meetings every three months where people diagnosed with Type 2 diabetes could come and talk about different aspects of their condition.

But while those who attended the meetings said they liked the experience, it did not have a significant clinical effect on their blood sugar control, blood pressure or cholesterol, explains Professor Smith.

“In addition, there was a non-attendance rate of about 30 per cent, which could be difficult for the volunteer peer supporters,” she adds.

The study, which was published in the British Medical Journal, was included in a major systematic review that also concluded there was limited evidence for peer support groups having a clinical impact in diabetes.

However the HRB-funded study also found that many of the participants had multiple other chronic conditions such as arthritis, heart disease and depression as well as diabetes, and this should be noted by clinicians, according to Professor Smith, who is now Associate Professor of General Practice at the Royal College of Surgeons in Ireland.

“We probably need to move away from disease-specific interventions and to consider managing multiple conditions at the same time,” she says. “It’s important to be aware of that broader spectrum.”

### OUTCOMES

- » Randomised controlled trial found that peer support in diabetes had limited impact on clinical symptoms.
- » Identified a need to tackle multiple chronic conditions in patients with diabetes.



## CHILDREN ARE NOT SMALL ADULTS – NEW PERSPECTIVES ON THE YOUNG IMMUNE SYSTEM

Ireland has one of the highest rates of asthma in the world, and it presents mainly in children. Yet we still have plenty to learn about what underlies childhood asthma and other immune-related conditions like eczema and potentially life-threatening allergic reactions that cause anaphylaxis.

In general, immune responses in children remain relatively under-explored. But a HRB-funded project has looked at differences between the young and adult immune system in the mouse, and has highlighted the involvement of a particular immune cell in allergies in the young.

Professor Padraic Fallon was inspired to investigate the young immune system when he observed that children in African countries where flatworm infections are endemic respond quite differently to infection compared to adults.

“From the perspective of the immune system, a child is not just a small adult,” he says. “Yet much of what we know about responses to allergies comes from studies of the adult immune system.”

Fallon, who is Professor of Translational Immunology at Trinity College Dublin, looked at mouse models of anaphylaxis and asthma to compare how young and old responded to triggers or ‘allergens’ such as eggs and peanuts.

“We saw that the response to certain allergens was different in juvenile animals, and we identified a specific mechanism,” says Professor Fallon “We saw that a type of immune cell called basophils were defective in the juvenile animals that had an allergic reaction.”

Until recently, basophils have not been a focus of attention in allergic diseases, but his study adds to a growing body of evidence that basophils need to be further examined in the context of childhood allergies.

### OUTCOMES

- » Found that cells called basophils are defective in allergic responses in a young immune system.
- » Identified need for a focus on basophils in childhood allergies.

## HOW CAN WE TELL IF YOUR HEART IS WORKING WELL?

For many people, heart failure is a problem that grows silently. One hint that the heart is coming under stress can be that it produces a hormone called BNP (B-type natriuretic peptide). Doctors monitor blood levels of BNP in patients with heart failure, but could GPs also use BNP to identify which of their patients also need a closer eye kept on their hearts?

A HRB-funded study has been building up our understanding of BNP in people who have not been diagnosed with heart failure but who may be at risk.

“BNP seems to be quite variable in those that are presumed well, and we wanted to look more at that variability,” says researcher Dr Carmel Conlon at University College Dublin. She looked at data from around 1500 patients attending 36 GP clinics in Dublin, who were participants in the STOP HF (St Vincent’s Screening TO Prevent Heart Failure) Study.

By measuring levels of BNP and other markers in their blood samples and analysing clinical data about their risk factors and medication, Dr Conlon was able to spot some interesting associations.

One was that if a person is taking ‘beta-blocker’ medication for high blood pressure, their levels of BNP could be as

much as doubled. “That means that if we were to observe BNP in a patient the community in the absence of knowing they are on beta-blockers they might be put in the wrong category of risk for heart failure,” explains Dr Conlon.

More generally, the findings that Dr Conlon and her supervisors Professor Cecily Kelleher, Professor Kenneth McDonald (principal investigator of the STOP HF Study) and Dr Mark Ledwidge saw in the study should help to define the BNP reference ranges for use in community-based patients who have simple risk factors for heart problems.

“Ultimately this should better inform how GPs can screen for patients who need to be brought forward for other investigations,” says Dr Conlon.

### OUTCOMES

- » Quantified how heart medication can increase the blood levels of BNP, a heart stress marker in patients.
- » Findings will inform a reference chart/tool to help identify patients who need to have further heart tests.

## SMOKING AND OBESITY – A DOUBLE WHAMMY FOR THE IMMUNE SYSTEM

If you smoke, you increase your risk of developing lung and other cancers. And if you are obese, that can also bump up the chances of certain types of cancer. But how? HRB-funded research has been shedding light on how smoking and obesity can each literally paralyse the body's immune defences against tumours.

The experiments, carried out by Professor Donal O'Shea's obesity and immunology research group at St Vincent's University Hospital, showed that people who smoke and people who are obese each had fewer numbers of natural killer cells (NKs) and natural killer T-cells (NKTs), which are involved in seeking out and destroying viruses and tumour cells in the body.

"We counted these cells in blood samples from obese and lean people, and we saw that the numbers of both NKs and NKTs were reduced," says senior scientist Dr Andy Hogan. "In addition, when the team challenged cancer-killing immune cells taken from obese people or smokers in the lab, the cells did not seem to function that well," he adds.

Next, the researchers pumped cigarette smoke into the environment of immune cells growing in the lab. Cells that came from non-obese people became less effective in an environment comparable to smoking 20 cigarettes per day. And cells from obese people were even less effective when exposed to the cigarettes.

The better news is that the researchers also found that gut hormones from the body could offer protection to the immune cells from the cigarette-laden environment, and they are now exploring the groundbreaking findings in new projects.

The findings stand to inform health awareness campaigns around smoking and obesity and could point the way to new protective strategies in the clinic.

### OUTCOME

- » Identified links between smoking, obesity and reduced immune protection against cancer.

## “CATCHING CHILDREN BEING GOOD” HELPS THEIR CONDUCT AND THEIR PARENTS

Conduct problems in children can have serious implications. Their behaviour can affect their schooling, social development and career potential and can place considerable strain on their families and teachers.

Research suggests that group-based behavioural parenting programmes can help to address child conduct issues, but how does the evidence really stack up?

Mairead Furlong at the Department of Psychology, NUI Maynooth, did the work to find out: with the support of the HRB and an international team, she carried out a comprehensive Cochrane Review, a meta-analysis that combined data from a large number of high-quality studies to get an accurate and richer insight into this issue.

An initial review of 16,000 studies was reduced to just 13 randomised controlled trials that involved around 1,100 children and which (according to stringent criteria) were eligible to be included in the review. The group-based parenting interventions they examined involved rewarding the child's positive behaviour with attention – “catching them being good” – and ignoring or limiting negative behaviour.

When the data from these key studies were combined, the results showed that group-based parenting interventions work well: children's conduct problems were reduced from being very severe and clinically significant to non-clinical levels and the mental health of parents also appeared to improve, at least in the short term.

“We also found that it is important that these programmes are delivered with fidelity in the way that they were intended,” says Ms Furlong. “Practitioners sometimes may wish to add or remove elements, but our research shows that they have to do what they are meant to do, otherwise the approach may not work.”

While data on cost-effectiveness were limited, the analysis suggested that an intervention would cost an average of €2,200 per family to reduce clinically significant conduct problems to non-clinical levels.

“This is modest when compared to the potential health, legal and social costs of continuing conduct problems, which can amount to hundreds of thousands of Euro,” says Ms Furlong.

### OUTCOMES

- » Cost-effective interventions to address child conduct issues.
- » Highlighted the need to deliver intervention programmes with fidelity, because changing them even slightly can reduce overall effectiveness.

## TACKLING A WEIGHTY WARNING SIGN FOR PATIENTS WITH HEART FAILURE

Could remote monitoring technology help people who have heart failure avoid having to go back into hospital? A trial supported by the HRB sought to find out.

“One of the major problems for a patient with heart failure is the likelihood of readmission into hospital because the condition deteriorates,” says consultant cardiologist Professor Kenneth McDonald, Director of the Heart Failure Unit at St Vincent’s University Hospital, who led the trial.

“We wanted to see if you monitor these individuals more closely than the normal standard of care, can you pick up the early signs of emerging deterioration and intervene, and would this reduce the rate of hospitalisation.”

One warning sign is a rapid gain in weight because as the heart fails the kidneys can’t eliminate fluid as efficiently. In the standard disease management programme, patients weigh themselves at home each day and if they see a rapid increase they call their GP or support team.

The trial looked to see if it was possible to use technology to pick up on the weight gain and report it more reliably: the weighing scales was able to ‘tell’ a mobile phone the reading, and this got sent to the team. And if there was a potential cause for concern, it alerted the team to look into it.

However, the study, which involved 87 patients, found that using the telemonitoring system did not reduce

hospital readmissions any more than the standard disease management programme.

“When compared to fairly sophisticated disease management care we would not advocate the use of the system as it was set out in this trial,” says Professor McDonald. “However it is an important study because even though it was negative it has highlighted that the approach does need to be altered before spending money and resources on implementing a telemonitoring system for heart failure patients who are at risk. So we are now looking at more sophisticated means of monitoring signs and symptoms.”

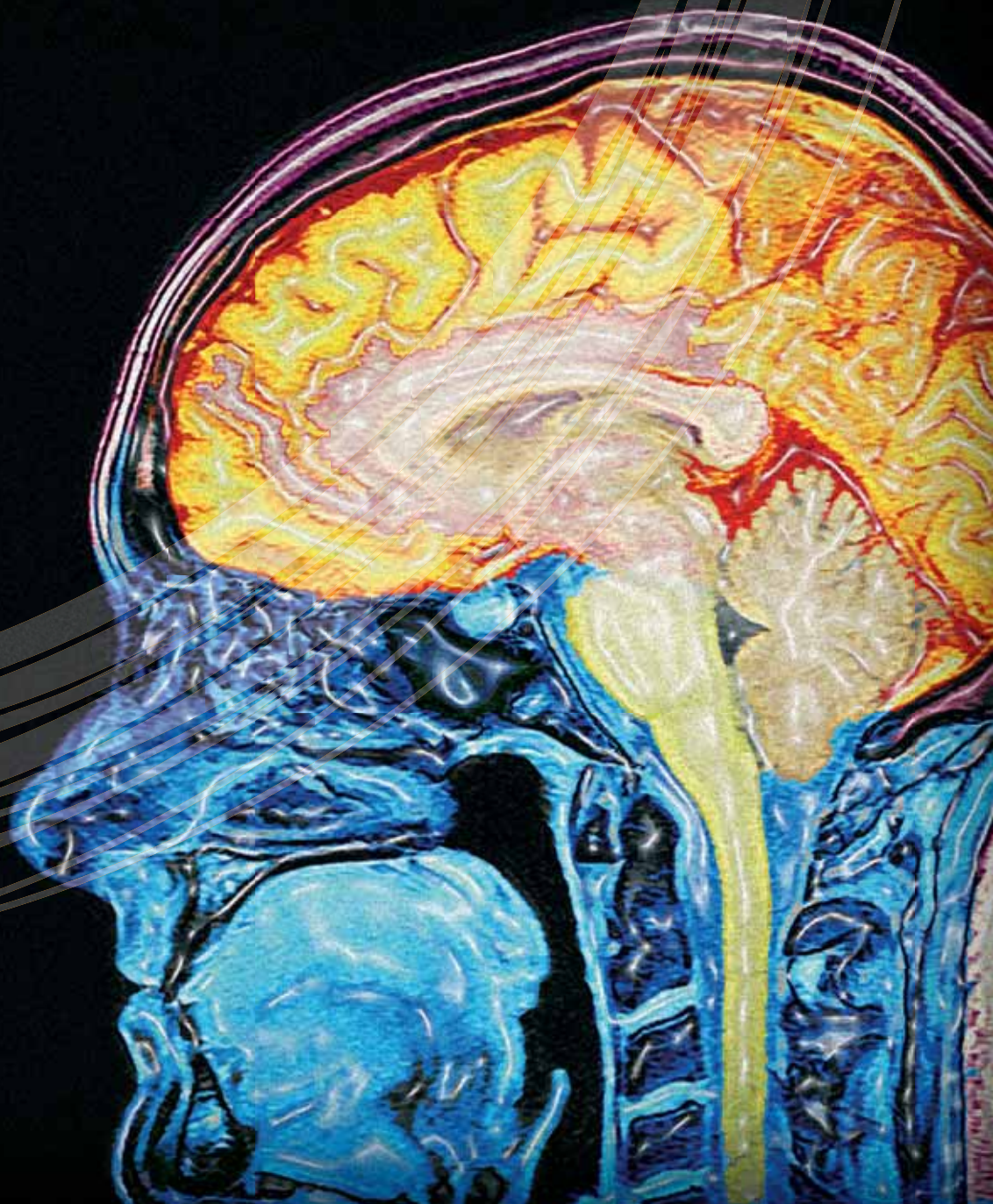
### OUTCOMES

- » Found that monitoring weight remotely did not reduce hospital readmission rates for at-risk patients with heart failure.



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**SPECIAL FOCUS:  
UNDERSTANDING THE  
BRAIN**



## TARGETING PARKINSON'S DISEASE FROM THE INSIDE OUT

Parkinson's disease occurs due to a loss of brain cells that control our movement and co-ordination. Many drugs have been made to control abnormal brain cell function that work by binding proteins called 'receptors' on the outside of cells.

A HRB-funded study has been looking at a different approach – researchers have been making a new type of drug, called iDrugs, that control receptor function from the inside of cells instead.

"In a juvenile type of Parkinson's disease, one reason for a loss of brain cells is due to toxic proteins that build up inside them," explains Professor Kumlesh Dev from the Trinity College Institute for Neuroscience. One of those proteins is called the PAEL receptor. Normally this receptor gets broken down within the cell by an enzyme called parkin, but in Parkinson's this enzyme is altered. "The PAEL receptor therefore builds up to toxic levels in brain cells," he says. "And that leads to one of the many mechanisms that cause Parkinson's."

Professor Dev and his group have been looking at ways to target the PAEL receptor within brain cells, in the hope of guiding them to a less damaging outcome.

By screening proteins that interact with PAEL receptor inside the cell they homed in on a protein called Pick-1, which seems to control PAEL receptor build-up in the cells. So they made an iDrug that enters the cell in the hope of blocking a tiny 'hotspot' site of interaction between the PAEL receptor and Pick-1.

As well as the Pick-1/PAEL receptor relationship, Dev's group also identified two other potential protein-protein interactions that could control PAEL receptor toxicity.

"We have identified, we believe, new proteins that regulate PAEL-receptor trafficking and these new proteins in theory could be new targets to regulate that receptor function and for possible therapy," he says.

### OUTCOME

- » Discovered a potential target to stall development of early-onset Parkinson's disease.



## DO COMBINATIONS OF GENES INCREASE ADHD RISK?

The genetics behind psychiatric disorders can be complex – research has found many gene variants that can increase the risk of developing particular conditions. Attention Deficit Hyperactivity Disorder (ADHD) is no exception. Many individual gene variants have already been pinpointed that could each increase the risk of developing ADHD, which can result in symptoms such as hyperactivity, impulsivity, and inattention.

But how does having more than one of those gene variants affect risk? Dr Ricardo Segurado has been using software to investigate how various combinations of genes involved in brain cell communication might influence the likelihood of ADHD.

“People have found that one by one, these genes seem to be associated with ADHD – but I was looking at them in combination,” says Dr Segurado, who worked on the HRB-funded project with Professor Michael Gill in Trinity College Dublin. “I looked at 24 genes and there’s a huge number of possible combinations, so I developed a statistical algorithm and wrote a computer programme that could correct for the vast number of tests.”

Using the software, Dr Segurado identified two genes where a combination of variants could increase risk substantially – a gene involved in noradrenaline’s action in the brain and another gene linked to the function of the brain messenger chemical dopamine.

While more research would be needed to look at whether the functions of the genes could be linked to ADHD, the finding shows that the computer programme can be used to inform molecular studies. The software is now available for use by the wider research community.

### OUTCOMES

- » Identified that combinations of genetic variants could be linked with increased risk of ADHD.
- » Developed a software tool for assessing gene combination effects.

## DON'T FORGET – ASSESSING PATIENTS WITH TRAUMATIC BRAIN INJURY

In traumatic brain injury – whether from a road traffic accident, an assault, a fall or repeated concussion – the damage may happen quickly but the effects can be lasting. Many people need rehabilitation to help them adapt to long-term symptoms such as problems with decision making and memory.

But how can clinicians know in advance how intense that rehabilitation needs to be?

A HRB-funded project at Trinity College Dublin looked at symptoms that patients experience in the long term after traumatic brain injury, and is finding that gathering data early on about a patient's cognitive function and social support may be able to help tailor their rehabilitation.

The study recruited around 50 traumatic brain injury patients through the National Rehabilitation Hospital. The volunteers, who were at least six months out from the injury, took standard tests on psychology and cognition and they also carried out computer-based tests designed to measure reaction times and the ability to switch between tasks and inhibit information.

Some patients seemed to be better able to compensate for the effects of their injury by creating workarounds in the brain to allow them to carry out the required functions, explains researcher Professor Paul Dockree.

The study collected brain signal 'biomarkers' which illustrated how the higher performing patients were able to create workarounds

by literally using both sides of their brain while the low performing patients relied only on the left hemisphere.

"We are also seeing that if you have lower cognitive reserve there's a risk that after traumatic brain injury you will show decline over time in your memory function, whereas if you have a higher cognitive reserve, it's likely there will be more preservation of your memory ability in the longer term," says Dr Dockree. "That has implications for memory rehabilitation – it's important to undergo rehabilitation early to boost memory function. The study findings identify the need to collect more cognitive markers in patients with traumatic brain injury so clinicians can map out a more clinically useful treatment for them."

### OUTCOMES

- » Found link between cognitive reserve and long-term memory problems after traumatic brain injury.
- » Identified importance of psychological and cognitive assessment after traumatic brain injury to personalise and improve rehabilitation.

## CELL WASTE AND ALZHEIMER'S – A NEW PERSPECTIVE?

As cells in our bodies grow and function, they produce waste. For long-lived cells like neurons in the brain, managing that waste is important to avoid a build-up of molecules that could ultimately cause damage.

With funding from the HRB, Dr Barry Boland has been investigating the concept that when brain cells don't handle their waste well, a protein called amyloid could build up. Amyloid build-up is in turn linked to the impairment of brain cell function in Alzheimer's disease.

In particular, he has been looking in the lab at the role of lysosomes in the cell, which are like disposal units where molecules are brought to be broken down.

"When we reduced the ability of the lysosome to clear out waste products, amyloid was one part of the waste that built up," says Dr Boland, who worked on the project with Professor Dominic Walsh at University College Dublin.

The study also identified mechanisms by which amyloid precursor protein gets sent to lysosomes in the cells. Knowing these details could offer a potential future route for improving waste processing.

"We think a waste-management problem could precede the amyloid build-up problem," says Dr Boland. "A lot of drug approaches are based on removing amyloid in Alzheimer's but perhaps if you could maintain the flux of waste material moving through lysosomes you could prevent neurons from accumulating so much amyloid in the first place."

### OUTCOME

- » Identified a potential link between waste processing in cells and Alzheimer's disease.

## PAYING ATTENTION TO ATTENTION AFTER BRAIN INJURY

Suppose you are out at a café with a friend. You want to be sociable but you can't make out what they are saying against the background noise. Such a lack of 'auditory gating', or being able to selectively attend to one sound among many, can be an after-effect of traumatic brain injury (TBI).

Problems with this kind of attention might lead to social isolation, anxiety, depression and difficulties working in an office, and it may also reduce the impact of other forms of rehabilitation, according to Ms Suvi Dockree, Head of Psychological Services at Headway.

So, in conjunction with Trinity College Dublin and with input from the National Rehabilitation Hospital, Headway carried out a HRB-funded study to address the issue.

The project built up neuro-psychological profiles of patients who experienced problems with auditory gating months or years after the brain injury. It also trialled a four-week protocol that trained people with TBI to improve their ability to pick out sounds from a background din. During the twice-weekly training sessions, clients wore headphones and were asked to complete tasks against increasing levels of competing noise.

The 17 clients with TBI who underwent the training showed significant benefits in auditory comprehension and everyday

memory compared to the nine clients with TBI who did not do the training, and people who had initially reported more stress and distractibility appeared to do particularly well.

"The findings provide evidence for including such a training programme in post-acute rehabilitation settings for people who have suffered traumatic brain injury," says Ms Dockree.

*"My ability to read for longer increased. For example, 15 to 20 pages instead of 5 to 10 pages. I am not as easily distracted by noise when I am concentrating on something. This would be the most satisfying aspect for me. I think follow up sessions would be good. My reading benefit is starting to diminish."*

HEADWAY CLIENT,  
SIX MONTHS FOLLOWING TRAINING

### OUTCOMES

- » Attention training improved hearing comprehension and memory in people with traumatic brain injury.
- » Evidence for implementing attention training in rehabilitation after traumatic brain injury.

## HOW DOES THE BRAIN PROTECT ITSELF FROM HIV?

HIV/AIDS is one of the most devastating epidemics of modern times. Around 30 million people have died from AIDS-related complications since the early 1980s and more than 34 million people worldwide are currently thought to be infected. The virus establishes an infection by getting into cells in the human body and inserting its genetic material into the DNA of the cell, thereby hijacking the cell's machinery to make many new viruses.

But brain cells called neurons appear to be inherently quite resistant to HIV, and a HRB-funded study has pinpointed a factor in neurons that seems to block the virus.

"It is quite a mystery – it was known that neurons lack key receptors for HIV but beyond that there seem to be other blocks within neurons too," explains Dr Derek Walsh, who worked on the study at Dublin City University with Dr Mojgan Naghavi at University College Dublin.

Dr Naghavi screened for potential HIV-blocking factors and identified a molecule called FEZ1. Her experiments on neurons in the lab showed that FEZ1 is expressed at high levels in these cells

and seems to disrupt HIV's normal route into the nucleus of the cell, where the cell's DNA is found. And if HIV can't access the DNA in the cell's nucleus, the infection doesn't proceed in that cell.

The study could point to new routes for blocking the virus, explains Dr Walsh. "If you understand how the virus is interacting with the factor, you could potentially design a drug that mimics what FEZ1 is doing or that increases the amounts of FEZ1," he says, though he points out that any new therapy would be a long-term result.

The findings have also led to ongoing studies on whether and how FEZ1 could block other types of viruses in host cells.

### OUTCOMES

- » Identified a molecule that prevents HIV from entering the nucleus and establishing an infection.
- » Could inform potential new routes for therapies in the long term.





