MRC Medical Research Council

Shortlisted articles

Winner

Kirstin Leslie, Institute of Health and Wellbeing, University of Glasgow

Can big data mend a broken heart?

“When you do things right, people won't be sure you've done anything at all”

That’s actually a quote from the TV show Futurama but it’s also a clear way of explaining why people are not always good at taking their medications. Imagine: you‘re taking a drug to prevent yourself from having a heart attack.

But if you don’t feel any different after taking the drug, how can you know it’s even worked? Maybe you weren’t going to have a heart attack anyway? Maybe the drug you’re taking is giving you side-effects and besides, it isn’t worth it because you felt fine before. You don’t want to bother your doctor getting a new prescription and your blood pressure wasn’t *that* high anyway…So you stop taking your drugs and you hope for the best.

But heart disease is the leading cause of death worldwide. And it’s preventable.

This is particularly bad news if you happen to live in Scotland, where we lead the way in the number of heart attacks, strokes, and more-or-less everything that can go wrong with your heart. But why? We have access to lots of different types of drugs for your heart, and in each of these groups there are a range of specific drugs to choose from, so there should be something that works for everyone. Shouldn’t there? Unfortunately the problem isn’t that simple.

Once your doctor has identified high blood pressure, high cholesterol, or anything else that might increase your risk of a heart attack, a few steps have to happen to reduce that risk:

- Step 1 is prescribing a drug.
- Step 2 is taking the drug.
- Step 3 is the hard one.

Step 3 is taking the drug at the right time and continuing to take it for as long as you need to. And that’s hard. It’s hard because for the drugs we‘re talking about, ‘as long as you need to’ can mean ‘for the rest of your life’. And the rest of your life can be a long time.

So my research project will look at: how well people in Scotland manage to stick to Step 3, who is and who isn't sticking to Step 3, and whether sticking to Step 3 does actually improve your chance of avoiding a heart attack or stroke.

To do this, I'm going to be using patient data from across Scotland to look back over the years and see whether or not people are picking up their medications from the pharmacy on time. This might sound straightforward before you remember that there are over 5 million people in Scotland. And, as I said before, we are not the healthiest bunch. So that's a lot of people, with a lot of unhealthy hearts, and a lot of drugs prescribed by their doctors. To do this I'm going to have to enter a world that has always seemed distant, complicated, and honestly a little bit intimidating: the world of Big Data.

Firstly: what is Big Data? Is it Facebook working out your personality based on the number of cat pictures you like? Or apps predicting the next flu pandemic based on the number of people tweeting about a runny nose? Or targeted adverts based on your google history? The answer is, in a way, yes. Big Data is all those things and more. Big Data is what it says on the tin: data, but a lot of it.

For me, Big Data is looking at everyone in Scotland who has ever been prescribed a cardiovascular drug – or more simply, drugs for their heart – and looking to see if they picked up their next lot of drugs around about the time their first prescription should have run out. If they don't, it means they are more likely to be skipping days, having gaps, or they might have stopped taking them altogether. By linking this to medical records I can see if people who aren't taking their medications are statistically more likely to have a heart attack, stroke, or even die.

And by looking across the whole country I can also see if people are more likely to take their drugs if they fall into different groups: if they are older or younger, male or female, or if they are living in wealthier areas or not. By doing so, I will be able to see if certain groups of people are more likely to miss their medications, and with that information, I might be able to work out who needs help at sticking to Step 3. If we know who is at risk, we know who we can help.

And if we know who we can help, maybe we can mend a heart before it breaks.

Runner-up

Lara Morley, Leeds Institute of Cardiovascular and Metabolic Medicine

At the Placenta of Everything

With the emergency buzzer still ringing in my ears, I feel my adrenaline subside as I bring a much-anticipated new life out into the world and into the arms of its anxious parents. After all, the outcome of a pregnancy has profound implications for the lives of us all; ourselves, partners, sisters and friends. But in all the excitement of welcoming a baby into the world, the vital job of the placenta is often overlooked.

A successful pregnancy relies on a finely tuned balance of hormones, the environment in the womb, and the placenta; the rich network of blood vessels that supply the baby. The placenta is the lifeline through which the baby receives blood containing oxygen and nutrients essential for survival.

Poorly functioning blood vessels within the placenta can result in fetal growth restriction, where the baby does not put on weight as expected during the pregnancy, or even stops growing. If this goes undetected, a baby can be stillborn, with a devastating effect on the whole family. Sadly, around 1 in 200 pregnancies in the UK results in stillbirth – and growth restriction is one of the commonest causes. Being born smaller than expected also increases the risk of cerebral palsy and death as a young baby. And there can be lifelong consequences, like obesity, diabetes and heart disease.

Despite all modern medical advances, in 2017 we still have no means of treating a failing placenta. So when a baby is recognised to be small, or not growing, the only option is to deliver them. This decision can rest on a knife edge – forcing us to weigh up the risks associated with prematurity against the potential for stillbirth. Having experienced this scenario all too frequently, I felt driven to research the blood vessels within the placenta, looking for ways to increase the blood supply to the baby.

My project is taking place at a specialist institute for research in Leeds, where we study blood vessel function. Blood travels around the body through a network – a bit like a series of garden hoses. Lining the vessels are endothelial cells. Their job is to control the flow of blood by narrowing or widening the vessels – like someone squeezing or loosening their grip on a hosepipe to control the flow of water. But

how the endothelial cells behave is also controlled. ‘Gated’ channels regulate what goes in and out of these specialist cells. This triggers reactions that cause the blood vessels to adapt to your body’s needs. In the past, scientists have developed medications for treating high blood pressure by targeting these very channels.

The same applies to the network of blood vessels in the placenta. If the vessels are narrowed the oxygen and nutrient supply will be reduced and the baby put at risk. However, the identity of these channels in the placenta and how they work to control the endothelial cells remains a mystery.

What are these channels? How do they work? Could they be manipulated? The aim of my PhD is to explore these questions, thanks to generous support from the Medical Research Council and the Royal College of Obstetricians and Gynaecologists.

During this first year of my project I have been extracting endothelial cells from the placentas of women delivering their babies in Leeds. The cells have come either from women whose pregnancies have been affected by growth restriction, or from those with healthy placentas. I have grown cells from these two groups of women into colonies in an incubator in our laboratory.

My experiments have been looking for differences between the healthy and growth-restricted samples. I test each colony to see how they form new blood vessels and respond to blood flow forces. In the future I will be trying out new drugs to see if they improve the function of the cells and widen the blood vessels. Excitingly, I have found that a newly discovered channel is consistently present in the cells. Blocking this particular channel has a dramatic impact on how the cells perform in my experiments, suggesting that it has an important role to play.

Through understanding how channels operate within endothelial cells of the placenta, we will learn vital information about how blood flow to a baby is controlled. Being able to manipulate these channels would be a huge step towards developing treatments for a baby that is not growing.

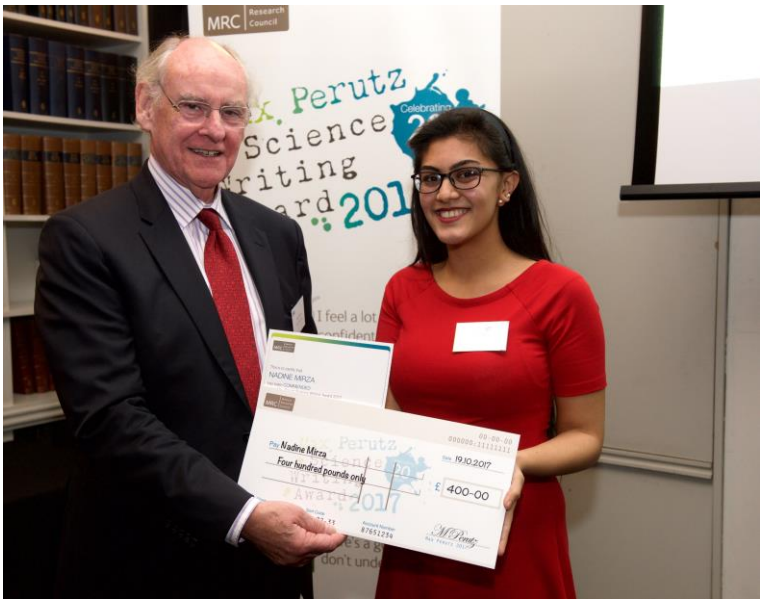
As I write this, I am eagerly awaiting the birth of my first baby, any day now! My excitement is tinged with inevitable anxiety, but also hope- that in the future we will have more to offer women whose babies are at risk.

After I’ve given birth, I’ll take more than just a passing glance at my placenta as it’s whisked away- the undervalued organ that has performed the most special of functions.

Runner-up

Nadine Mirza, The University of Manchester

Avoiding gibberish when assessing for dementia



Have you heard the saying "*No ifs ands or buts*"? Associated with grannies and teachers, you'd be hard pressed to find someone who hasn't. It's also a saying used in the ACE, a test implemented across the UK to detect dementia. An individual has to read the saying out loud with correct pronunciation. When directly translated into Urdu it loses meaning and becomes gibberish and reading out gibberish isn't a smooth task. Even a fluent Urdu speaker might fail. But would we attribute that to dementia? Apparently, yes.

On a national level we implement a one size fits all policy regarding tests for detecting dementia that examine cognition with tasks such as the above- child's play. But what if you're Caucasian and I asked you to read a Chinese idiom? Or memorise words in Arabic? Or recognise an illustration of a dohl- a South Asian oblong drum? You'd probably fail on more than one task but it wouldn't be attributed to dementia, but a mismatch in language and culture.

But when it comes to ethnic minorities we don't account for this bias. We administer English tests, assuming everyone is fluent, and ignore the fact that they were designed for specific European cultures. When ethnic minorities can't attempt these tests no diagnosis or treatment is given and when they manage to complete them, but fail due to this bias, they are presumed to have dementia, experiencing all the distress and depletion of time, effort and resources this diagnosis encompasses. Simultaneously, these incorrect diagnoses contribute to the already burdensome national £26 billion cost of attending to over 700,000 individuals currently diagnosed with dementia.

My supervisor and I saw this particularly in British South Asians, who are more likely to slip through the cracks or receive an incorrect diagnosis in a foreign and confusing system. Therefore, they became the centrefold in my attempt to level the playing field by developing a test for indicating dementia, unbiased by language or culture. *I decided to change the ACE*.

I asked others who had adapted the ACE for their own countries how they did it and learnt the underlying cognitions examined by each question of the test, be it attention, memory or fluency. I devised my own process for adapting the ACE for any culture and from the vast tongues and dialects of South Asia I decided to translate it into Urdu, the UK's fourth most spoken language. I avoided the Google translate shortcut and instead translated myself, word by word. Most importantly, I redesigned the cultural aspects of the test by including South Asians in the process.

During focus groups with South Asian elderly I showed an illustration of a kangaroo from the ACE and less than half the men and women correctly identified it. Why should they, I realised, with their roots in South Asia, where there are no kangaroos, not even in zoos. If they failed to recognise its likeness we couldn't attribute that to dementia so we picked another animal to replace it, one *they* chose to be suitable. This is how these men and women narrated their culture and came up with suggestions for each question of the ACE, not changing the underlying cognitive concepts but making them understandable and acceptable.

They were eager to contribute and relayed to me in between sips of their tea that dementia was known to all of them in some form or other; a friend, a brother, a wife, all lost, never diagnosed officially or receiving help far too late. These stories unfolded as a penguin became a peacock, Harry Barnes became Haroon Butt and "*No ifs ands or buts*" became the better known South Asian idiom "*You can't clap with one hand*".
With our blood, sweat, tears and my homemade Urdu keyboard on which I'd drawn the curvy script the Urdu ACE was born and administered to cognitively healthy elderly South Asians. Afterwards, I interviewed them, asking about their experience taking the test. The overwhelming consensus was positive.

The test was deemed "*straightforward*", with "*nothing vague about it*" and participants felt comfortable undergoing it, claiming "*everybody should be able to*". This was novel for them, a test that catered to their culture, which they could attempt with no barriers and they recognised just how important it was for their communities. One grandfatherly man handed me a celebratory candy and enthusiastically exclaimed "*It will help me and people around the world for diagnosis and better treatment!*"

Indeed I hope it will because no one should be denied treatment for not completing a test and no one should receive a life changing diagnosis on a technicality. Is the bias eliminated? Not yet but it's definitely a small win while we endeavour to level the playing field for good.

Runner-up

Sophie Quick, MRC Centre for Regenerative Medicine at the University of Edinburgh

Watering the strawberry fields of the mind

Strawberry picking might not seem like the place for scientific inspiration, but on a warm summers day just weeks into my PhD, I returned not just with a punnet of Scotland's finest fruits but a new take on my research. Sheltered by a gently flapping plastic roof I bent to pluck a handful of ripe berries, spotted fine tubes running along the soil and was struck by an idea. Our brain is just like the inside of a greenhouse, an isolated space protecting living things inside it. To keep the strawberry plants growing and maturing, the greenhouse had an irrigation system, just like the brains intricate network of tiny blood vessels that carry oxygen and nutrients to the brain cells.

Careful control of the brains irrigation system is essential as these oxygen-supplying blood vessels, or arterioles, can also carry other things that might interfere with the delicate chemical balance within the brain. Like strawberry-growers might use filtering pipes to spray water onto plants, the vessels are made of endothelial cells that only allow through water and certain molecules.

These tiny pipes threading their way around the brain can start to malfunction, and this is where my research comes in. I am interested in cerebral small vessel disease, a condition of these arterioles, the smallest of all the blood-carrying pipes. Though you might not have heard of it before, it's surprisingly common, with a third of people over 80 showing signs. With easy-to-miss symptoms of unstable walking and forgetfulness it can only be diagnosed with MRI scans, where doctors look for a loss of brain tissue. Looking even closer, there's narrowing and weakening of the vessels, leakage from the blood into the tissue and ultimately long-lasting damage to the brain cells. Back in the greenhouse, the irrigation pipes aren't filtering as they should, meaning that the plants are now unable to grow any strawberries.

These damaged brain cells can lead to dementia, with small vessel disease thought to be responsible for nearly half of all dementia cases. Weakened vessels also triple your risk of stroke, which can have other serious consequences. So, tackling this disease could really improve the lives of our ever-increasing aging population, the ultimate goal of my research. Specifically, I'd like to explore the sequence of events that happens as it progresses, and whether we're able to reverse them.

Understanding the condition has already come a long way, with a new view on small vessel disease being slowly uncovered. We now think the endothelial cells lining the walls of our blood vessels might be malfunctioning. Imagine that, rather than a faulty filter, the actual plastic tubes of our irrigation system were releasing chemicals stopping the plants from producing strawberries. Well, the endothelial cells in small vessel disease look like they're releasing molecules preventing brain cells from maturing.

To study these effects more in detail, we need to have these cells in the lab and not in the brains of patients. To do this we can use animals that mirror the condition - for small vessel disease, we use a type of rat showing the same risk of stroke, the same loss of brain tissue and even similar changes in behaviour.

One of the things we have learnt from this disease replica is that the cells have slightly different genetics to those from normal, healthy animals. Genes act as instructions and tell the cell what proteins to make, but small vessel diseased cells in these rats have a faulty instruction that means one of the proteins never gets made at all. When endothelial cells don't make this protein, they start to fail, causing a release of chemicals that stop neighbouring brain cells from maturing.

Growing these cells in a dish lets us study what makes them malfunction and exactly what chemicals are released. It's also possible to treat the rats with drugs we think might reverse the disease and monitor their improvement.

While it isn't a perfect representation, one day we should be able to apply the same principles and understanding to humans. It's like building your own mini greenhouse to practice with before making any changes to the strawberry farm.

Changing pipes in the greenhouse irrigation system would be a huge job, and replacing the brains blood vessels is simply impossible. So we need to find a way to repair the vessels inside to give brain cells the best chance of maturing. As I filled my basket with perfectly ripe berries on that uncharacteristically sunny day, I couldn't help but wonder about the carefully controlled balance of nutrients that had guided their growth. If we can repair the pipes in the brain, we can ensure a fine crop of mature brain cells to keep our brains fruitful for longer.

Alexander Kaltenboeck, Department of Psychiatry, University of Oxford

If you let the sunshine in your brain, what will it do?

Two years ago, I made a surprising discovery. Over the past summer holidays, I had been exposed to a potent antidepressant without being aware of it. The same was true for my family, my friends, and—most likely—for you as well.

What might sound like the beginning of a conspiracy theorist's blog entry, is in fact based on rigorous psychiatric research. However, the antidepressant I am referring to is not a drug. It is sunlight.

Since ancient times, healers have assumed that light can have beneficial effects on our health and well-being. But only in the last few decades have scientists started to put this idea to the test—and what they have found is indeed fascinating. Recent studies not only show that decreased exposure to sunlight can put people at risk for developing psychological problems, but psychiatrists have also discovered that treatment with artificial sunlight can work equally well for depression as antidepressant drugs—while having fewer side effects!

Given these important findings, one might assume that we are long underway to investigate the mechanisms through which light exerts these effects. After all, that's what researchers do with drugs all the time: we are not satisfied with merely knowing *that* they work for patients, we also want to understand *why* they work. This is vital information. Once we know the mechanisms through which a drug affects our body, we can develop ideas of how to improve it, and we can also deduce what hidden side effects it might have.

However, as it turns out, we actually know very little about the mechanisms through which light works as an antidepressant—in fact, we know a lot more about almost all antidepressant drugs.

In my current research, I am addressing this problem by studying how sunlight affects the way our brain handles emotional information. The underlying idea is simple: We already have a good understanding of how antidepressant drugs change emotion-related brain processes; if sunlight works for depression, then it could have similar effects.

Researchers believe that antidepressants work by inducing what they call "positive biases". Simply put, this means that the brain starts to favour positive over negative emotional information. After the induction of such biases, a person starts to pay more attention to positive events in their environment,

for example, or becomes better at remembering pleasant experiences. In the long run, the brain registers an increasing amount of positive information which eventually causes mood to go up.

In a current study, I am investigating the theory that—similar to antidepressant drugs—sunlight could also induce positive biases. However, since the sun is no reliable partner for experiments—especially so in the UK—I use bright light exposure, a medical treatment that mimics natural sunlight, as a surrogate. Basically, I shine very bright light on the faces of volunteers and, after I have done that, I measure how their brain deals with emotional information.

For the latter part, I use specific psychological tasks with which I can measure whether someone has developed emotional biases. In one of these tasks—to give an example—I show participants very subtle facial expressions of different emotions and ask them to tell me which emotion they see. If they have developed a positive bias, participants will become better and quicker at correctly identifying expressions of positive emotions (such as happy smiles), and will also more likely mistake negative emotions for positive ones. In another task, I show participants words that describe personality traits—both favourable and unfavourable ones—and ask them to imagine, for each of these words, overhearing someone describing them in these terms. After some distraction, I then ask the study participants to name as many of the words as they can. Again, if they have developed a positive bias, they should recall more of the favourable personality descriptors.

If I can show in my experiments that bright light exposure can indeed induce positive biases, then this is exciting news. For a start, it would mean that we have identified a potential mechanism through which light can help people suffering from depression and—as in drug research—this can provide the basis for further tweaking in order to improve and fully harvest the beneficial effects of this alternative treatment.

More importantly, however, it would also imply that the sun might be nothing less than a ubiquitous psychoactive influence that can interfere with how our brains work. This would suggest that the way we perceive, think, feel, and act might—at least to a certain extent—be subject to how much sunlight we are exposed to, and if this is indeed the case, then we better start learning more about it.

Fiona Calvert, Wellcome Trust Sanger Institute

Alzheimer's Disease: The puzzle we're so desperate to solve

"But Alzheimer's is me, unwinding, losing trust in myself, a butt of my own jokes and on bad days capable of playing hunt the slipper by myself and losing. You can't battle it, you can't be a plucky "survivor". It steals you from yourself." – Terry Pratchett 2008.

Author Terry Pratchett, who was diagnosed with a form of Alzheimer's disease in 2007, worked tirelessly until his death to beautifully articulate what living with dementia was like for him. Not just the memory loss, but also the loss of independence, personality, of your ability to maintain relationships and ultimately the loss of yourself. He gave people robbed of their memories, and themselves, a voice.

Dementia is estimated to affect 46.8 million people worldwide, with the number predicted to double every twenty years. In 2015 there were nearly 10 million new dementia cases, that's one new diagnosis every three seconds. Alzheimer's disease is the most prevalent form of dementia but it's about more than just facts and figures: it's about the people whose lives it steals.

Any diagnosis can be daunting for a patient, but a diagnosis coupled with no effective treatment, let alone a cure, is terrifying. Terry Pratchett used his voice in the best way, to fight for more exposure and to fight for a cure. As a scientific community it is our responsibility to take up that fight. In order for effective treatments to reach patients we have to understand the disease we're fighting. My PhD will hopefully help to do just that.

At the Sanger Institute, where my PhD is based, we are fascinated by all things genetic, which may seem a long way from a patient suffering from Alzheimer's disease. Yet we know that certain gene mutations (a small error in a gene) can increase your risk of getting Alzheimer's disease and now we are working to understand how and why that is.

Creating a list of Alzheimer's disease risk mutations is like having all the edge pieces of a puzzle put together – it doesn't show us the full picture but it creates a guideline that makes filling in the middle a little bit easier. The puzzle of Alzheimer's is huge and so, although the hope is that one day we will see the full picture, today, I'm looking at just one corner.

The edge I spend my days looking at, trying to understand how the puzzle pieces fit, is the part that involves your immune system. The same immune system that helps you fight off a cold plays a vital role in Alzheimer's disease. We didn't really know this until we found the edge pieces of our puzzle - that list of gene mutations that increase your risk of getting Alzheimer's disease includes some that affect your immune system.

So we have the edge of our puzzle, but what next? I'm taking those small errors in genes and looking at how they affect your brain's specialised immune system. This is where, for me, the science gets really cool and it's the part of my day-to-day that reminds me why I am so fascinated by science.

Until recently, studying the brain's immune system was nigh on impossible – these cells are not exactly accessible. However, we hope that a new form of stem cell, induced pluripotent stem cells, are going to change that. These cells are incredible: they have the potential to turn into any other cell in the body and all we need to create them is a tiny skin sample. Then with a bit of reprogramming (and a lot of patience), we can turn that sample into stem cells.

I'm taking these stem cells, that have the specific gene errors from our list, and turning them into microglia. Microglia are an integral part of your brain's immune system. They act like scavengers, hunting for things that definitely don't belong, ingesting and destroying them. Being able to make these cells in a lab means that we can finally understand their role in Alzheimer's disease (something that is currently very unclear) and how those genes from our list can change their behaviour.

Sometimes my days are spent so focused on my small corner of the Alzheimer's disease puzzle, it is easy to forget why we are doing this in the first place. Every day people across the world suffering from Alzheimer's disease lose that little piece of their memory, that little piece of themselves.

I am proud to work on a small corner of this much larger puzzle, in the hope that one day soon we'll be able to pull all our small corners together. I am proud to be part of the fight, the fight that gives patients hope that one day they may be "plucky survivors".

Ioannis Pavlidis, MRC Centre for Reproductive Health at the The University of Edinburgh

Born too soon: what would Hippocrates do?

When I was at school, everybody in the class knew that our classmate Alex was born too soon. Yet, as Alex was like any other kid, nobody could really understand what that meant. Years later, when I found out that Alex had spent his first Christmas, Easter and summer in hospital, I realized Alex was a hero who had made it despite being born too soon.

How soon is “too soon”? According to the World Health Organisation, any time before 37 weeks of pregnancy. And why is this a problem? Because, honestly, it’s very, very risky.

Babies born too soon are immediately exposed to a whole bunch of dangers. First and foremost, as it happens with many heroes, 1 out of 15 such babies is not going to survive the very first month of their life once they are born. Among the survivors, many will struggle with serious problems in their brain, lungs and heart. Some of these problems will never fully resolve, leaving behind lifelong conditions like a learning disability.

But how often does this happen? Take a moment to think if you know people like Alex. Chances are you already have several in mind as 1 baby out of 10 is born too soon. And quite frustratingly, despite extensive research in the field taking place over the past decades, these numbers are still up there. The reason for this is that we simply don’t really understand why and how this happens. And this makes the need for new research approaches all the more urgent.

One of the things the scientific community is very confident about is that bugs are the number one reason of why babies are born too soon. Once an infection occurs, the baby is in danger. During pregnancy the womb is bug-free, so those bugs need to come from somewhere. In most cases, this “somewhere” is the vagina, which is, at the same time, so close and yet so far away from the womb. So close, because they are literally a few inches apart and so far away, because of what comes between them: the cervix.

Think of the cervix as a small tube that connects the vagina to the womb. During pregnancy it has a very important role. Not only does the cervix seal the womb, allowing the baby to remain in place, but it also manages to fight off harmful bugs before they reach the baby.

However, what happens if the cervix is damaged? Unfortunately, this increases the chances of the baby being born early but still, we don't know how this happens. So my research seeks to find this out. I'm building knowledge by creating an artificial system where I deliberately damage cells of the cervix in a laboratory setting and then study how this changes its protective function.

The first step was to find a substance that could damage the cervix and test it in the laboratory. The substance of choice is called N-9. Think of it like a very strong soap. When I exposed individual cells from the cervix to this soap, the cells started to die. When I exposed a layer of these cells to the soap, the layer was broken, much like a stone wall being hit by a catapult.

Next, I had to try and do the same under the more complex conditions of a living organism. Due to obvious ethical restrictions, I couldn't do such experiments on women during pregnancy. So I had to perform the experiments on pregnant laboratory mice. Everything done on laboratory mice is highly regulated and we are always trying to use as few as possible and treat them in the most humane way.

After applying the soap on the cervix of mice, I noticed a similar picture as in the laboratory. The cells of the cervix started to die. I also noticed that a special group of cells, known to be present during injury, was present.
This leads me to the next stage of my research, which is to find out how bugs manage to break into the womb through a damaged cervix. This stage is currently ongoing and by the end of it I hope to have a clear idea of what exactly goes wrong in the cervix that allows the bugs to reach the baby.

This will increase our understanding and could lead to potential new treatments and diagnostic tools. Overall, the goal of my research is to help babies being born when they are strong enough, by keeping the bugs out of the womb at all times - preventing rather than treating. Just as Hippocrates wanted. And maybe then, people like Alex won't need to be heroes to be like any other kid.

Karolina Punovuori, MRC Centre for Regenerative Medicine at the University of Edinburgh

Stem cell biology: decoding the manual for a self-building machine

To understand how a machine works, you have to take it apart and put it back together piece by piece. Disassemble your laptop and you'll discover its vital organs: the motherboard, battery, hard drive and processor – and all the tiny wires hooking them up to each other. In many ways, your body is the same: a collection of highly specialised cells and organs, all elegantly connected to create a living, breathing, thinking human. But there's one big difference: the human body is not just an assembly of pre-made components fixed together in a factory. Instead, it's a hugely complex machine that builds *itself*, with each of the specialised parts originating from just a single cell at the very beginning – the fertilised egg.

After fertilisation, the egg divides: first in two, then four, then eight identical cells. From there, the cells start to behave differently, having to make decisions about what part of the developing human they are going to form. Five days after conception, a small group of cells – called embryonic stem cells – emerge in the early embryo. It is this little population of a few hundred cells that will go on to create all the diverse organs of the human body.

In my research, I use mouse stem cells in a dish as a model for human development, and I study how the earliest cells make decisions on what to become. Embryonic stem cells are pluripotent, meaning that they can differentiate into any given cell type in the body: a round blood cell to circulate oxygen, a strong bone cell for support, or a long nerve cell for communication. In my project, I want to know how pluripotent stem cells go on to generate the nervous system, and what signals drive the cells to adopt that identity.

I study a family of proteins called cadherins. They are found on the surface of many types of cells and tightly glue them together, like the mortar in a brick wall. During the early stages of nerve formation, stem cells turn off one cadherin, called E-cadherin, and switch on another, termed N-cadherin. By changing the way they stick to each other, this cadherin switch allows cells to move to the parts of the developing embryo where the brain and spinal cord are being built. But emerging research shows that these sticky proteins may also be able to transmit messages from the cell's surface to its inside, or from one neighbour to another. These signals can influence how cells respond to their environment, and may change the decisions they make about what to become – as if changing a screw could fundamentally alter the function of a machine.

In the lab, I've used genetic engineering to create stem cells in which I can turn on the N-cadherin protein whenever I wish, simply by adding a single chemical. This gives me control of the cadherin switch, and enables me to study how it affects the cells' behaviour. So far, I've found that prematurely turning on this protein seems to encourage the cells to become part of the nervous system more quickly, suggesting that it is acting not only as an adhesion molecule, but that it can also influence cell decisions. I now want to map the molecular communication network that makes this possible. I'm decoding the manual that our body naturally follows to build its nervous system.

By studying this instruction guide for the self-construction of the human body, we might be able to find ways to fix the machine when one of the parts stops working – or, even better, to find ways to make it fix itself. Stem cell science brings with it a hope of treatments that were previously difficult to imagine. By understanding how organs are formed in the first place, we may be able to engineer stem cells to replace body parts lost in patients through injury or disease. What's more, many diseases – including several cancers – are believed to be caused by faulty decisions during different stages of cell maturation. It is possible that by studying the cellular processes taking place in early development, we may shed light on the same processes when they occur again later in life, sometimes with disastrous consequences. Understanding how these diseases develop on a molecular level should help in designing new treatments for them.

The next time you're puzzling over a complex machine you don't understand, take pride in the fact that *you* are a much more impressive feat of engineering than anything built by humankind. We will probably never create a machine with trillions of individual moving parts that constructs itself from a single screw, but we are slowly decoding each chapter in the manual for the remarkable self-construction of the human body.

Maria Spyrou, University of Aberdeen

Orchestration of chitin synthesis: Could understanding this process be a deadly fungus kryptonite?

Imagine being able to look into the microcosm of a living cell. You're a silent observer in a dark, cold room – tracking proteins, seeing them interact with each other and trying to decipher their behaviour. How do I do that you ask? Using live-cell fluorescence microscopy, which I consider to be the next best thing since sliced bread. And just like making bread, my work includes working with yeast. Not the delicious beer and bread making kind, but the nasty opportunistic fungal pathogen *Candida albicans*.

Since the early 1980s, fungi have emerged as major yet underappreciated culprits of human disease, particularly in people with weakened immune system. *C. albicans* can live quite happily inside our gut or genital tract without causing any issues. That is until it senses a weakness in the defence system of its host, compelling it to pursue a literal interpretation of a strategy commonly used in politics: divide and conquer.

Cell division is a fundamental process where a cell stretches until it splits in two cells. It's part of a cell's life cycle as it's essential for growth and enables spreading inside a host. As a fungal cell divides, it forms a barrier between the 'mother' and 'daughter' cell which we call 'septum'. This structure keeps the cells from bursting during the final stages of cell division right before they split from each other. Synthesis of the septum requires chitin, the second strongest material in the natural world which is found in a number of species excluding humans. Chitin is also an integral part of the wall surrounding the cell. The way I see it, chitin is to a fungal cell what a tree is to a tree house. This is what makes the study of chitin synthesis so appealing to me: Without chitin, the cell would completely fall apart as it would lack its skeleton – meaning that the chitin making factory could be a potential target.

Very little is known about the production of chitin in *C. albicans*. We know that it is made by four proteins called 'chitin sythases': Chs1, which is essential for septum formation, Chs2 and Chs8 which offer stuctural support when the cell is under attack by drugs and Chs3 which produces most of the chitin on the cell wall. All four proteins work together to make the septum and compensate for each other when needed. What we don't know is how or when they get to the cell division site. These are the two questions I aim to answer in my research.

To answer when these events happen, I tagged two Chs proteins in the same cell with different coloured fluorophores – those are smaller proteins that emit light under the right conditions. This way I am able to track them in living cells and see how they behave in relation to each other. I still remember the first time I took a movie of the dividing cell. I Saw the daughter cell growing, becoming equal to its mother and slowly pulling apart. Then suddenly, flashes of light appeared at the septation site. My tagged proteins were there! Beautiful bright rings right where the septum was about to form. While the septum was being made those rings slowly formed a spot in the middle of the septum and finally disappeared. I immediately went to my supervisors office for a crisp high-five. Now we knew that all four proteins were at the same exact location.

Making more cells with different combinations of tagged Chs proteins I also noticed that one of them goes there a few minutes before the rest. *Is it preparing something before the others arrive? Why are they all there at the same time? How do they get there?* Those are just some of the questions raising though my head when I go back to my time-lapse movies trying to interprete the steps of the Chs proteins intricate dance.

But I also need to keep my eyes on the bigger picture. The ultimate goal of my project is this: Once we know when and how the Chs proteins go to the septation site, we can then use the information that we obtain against them. Interrupting cell division and ultimately replication of the fungus is surely an attractive antifungal strategy.

My research is still at its infancy. But that’s the exciting part - I will literally see it grow.

Monica Kuteesa, MRC/UVRI Uganda Research Unit on AIDS

Alcohol, weed, sex: the high trinity

In a Kigugu bar buzzing with activity, closed blackout curtains hide dawn's light. The still air is filled with a choking smell of weed, and a fresh aroma of distilled *Waragi,* a local gin. The semi darkness is enveloped with the heavy bass of a popular tune with the lyrics '*In heaven there is no beer, that's why we take it here'.* I slump into an old scruffy sofa to join the early shift of patrons. Across the room, about fifteen teenage boys and girls of the night stare on with blank expressions, and visibly red eyes. Tellingly, they are caught up in some heaven, high on weed, or have had one *Waragi* too many. Others continue mumbling as they smoke away.

I attempt to engage the seemingly happy youngsters in a conversation about life and leisure. I learn that most are parents with multiple sexual partners, demanding jobs, and suffer high levels of financial stress. 'For most young people, trying new things and taking risks is part of growing up,' one explains. Another, Haguna, retorts wearing a wide grin 'I started taking *Waragi* and weed at 11 years… we called it *super-combo*...when armed with *super-combo*, there is never a dull moment, you know'. Kaka 15, asks, 'How else can a boy prove that he is a man unless he conquers the three W's—*Waragi*, Weed and Women'? I shy away for lack of a clever response. In Kigugu, it is the norm for young people to engage in heavy drinking and drug use. It is what separates real men from boys.

Others I speak to agree, in voices slowed to a slur, that *super-combo* provides not just sensual pleasure, but also a feeling of comfort, security, strength and companionship, all of which are important and make life worth living. 'Oh yes', chuckles Wole, 'one needs a daily dose of *super-combo* to brave the lake, and to catch many fish in the night…. and when we survive the waves, whoa, we return to the village to celebrate with the girls, fish for sex!' Unfortunately, this experience is not unique to Kigugu. Hundreds of similar fishing communities across the African great lakes region are major, lively trade hubs for alcohol, weed and sex.

The World Health Organisation considers substance use and its related risk taking behaviors a key risk factor for poor health, globally. The consequences of which can be disastrous, ruining lives of substance using individuals, devastating families, and damaging the fabric of communities. In fact, these consequences may hinder sustainable development of a nation through lost productivity, disability and decreased quality of life. However, there is an additional danger lurking in the background of fishing

communities such as Kigugu, and that is HIV. For Kigugu youth, substance use may pose a greater hazard, in multiple ways – first, it can lead to higher risk of HIV acquisition. Second, it can lead to faster HIV/AIDS disease progression, and consequently premature death.

Going by our prolonged conversation, and the murmurings in the bar. It is hidden in plain sight that young people in Kigugu are as clueless on the harmful effects of substance use, and its wider consequences, as are many of us. It is deeply worrying what real dangers await Kigugu youth while they continually mix high-risk sex with substance use!

My PhD will describe the nature, extent and context of substance use, and sexual behaviours in Kigugu and how they increase young people's vulnerability to HIV. We will interview 1300 young people aged 15-24 years, in Kigugu using computers that speak their local language. We will also test their blood for alcohol levels, drugs, and HIV and another sexually transmitted disease called HSV2. Beyond scratching the surface on the burden of the problem, in quantitative terms, we will hold open, honest conversations with young people, local leaders, parents and guardians. To better understand the reasons for, and meanings of alcohol and drug use.
While our work will not necessarily offer a quick solution to substance use in Kigugu, it will evaluate the depth and breadth of substance use among young people in fishing communities in Uganda; the reasons behind it, and its impact on their community in a more in-depth manner. This will help us better understand and face the threatening reality of substance use and HIV in this community. This is the first step towards solving any problem. Who knows, our findings might hold solutions for future generations on how to help deal with problems associated with youthful fantasies of living on *Waragi*, weed and sex in a hell of a heaven on earth.

As Kaka staggers away, with eyes cast over his weed collection, he reminds me that he does not worry about tomorrow. 'I have many problems that is why I need my *super-combo*…with it I can do anything', he echoes.

Sonja Klingberg, MRC Epidemiology Unit at the University of Cambridge

Childhood obesity in South Africa – is it a problem?

It's mid-morning at a primary school in a South African township. The sun is almost at its highest point, and the schoolyard is crowded with children in school uniforms who are having their first break of the day. What are they doing? In my version of this scenario, the children are gathering around snack vendors, spending their lunch money on crisps, or perhaps ice lollies.

After doing some field work in South Africa earlier this year, this is my most vivid memory from visiting schools. Snacks, everywhere. But if snacks were not the first thing you thought of, I am not surprised. The simplified image of hunger and famine in Africa seems difficult to shake, and in reality undernutrition is still a big problem in South Africa. However, it has been joined by the challenges many wealthier nations have been battling for years: overweight and obesity.

My research thus looks at possible ways to prevent childhood obesity in a township called Soweto in South Africa. I am interested in understanding what works, and what doesn't, when it comes to promoting healthy eating and exercise among children in this urban setting that has seen many rapid changes over the years. I am currently going through existing research on childhood obesity to identify what makes prevention programmes succeed or fail. Over the coming years, I will be examining the causes of weight gain in childhood years, and what can be done to make environments that South African children spend a lot of time in, like day-care, more conducive to forming healthy habits.

When I tell people here in the UK what I do, they often ask me whether childhood obesity really is a problem in South Africa. Unfortunately, it is. One in four girls age 2 to 14, and one in six boys in the same age group, are overweight or obese. However, current figures are not the only reason why it is worthwhile to dedicate research to addressing childhood obesity in South Africa. In public health, it is important to think about how health conditions affect us at different stages of our lives. We know that children who are overweight or obese are likely to be overweight or obese as adults. They may also be affected by diseases related to obesity, such as diabetes, later in life or already at a young age. A striking statistic from South Africa is that two thirds of adult women are overweight or obese, and so it is clear that the problem only gets worse as children get older. Preventing childhood obesity is therefore not only about improving children's health, which is an essential goal on its own. It is also related to preventing obesity, ill-health, and premature deaths among adults.

Research has shown that it is very difficult to get people to lose weight once they are already overweight or obese. Therefore, it makes sense to explore opportunities to prevent overweight and obesity from arising in the first place. In addition, if prevention is successful, savings can be made in terms of treating obesity-related illnesses in the future. This is worth remembering because a majority of the world's overweight or obese children under the age of five live in low- and middle-income countries like South Africa. These are also the countries with the most limited budgets for public health and health care, particularly when it comes to what are called non-communicable, as opposed to infectious, diseases. With this in mind, one of the motivations for researching exactly what works to prevent childhood obesity is to help ensure that money is not wasted on programmes that have no impact.

Another reason to research childhood obesity prevention in South Africa is that relatively little is known about it. While much is being done to tackle the problem of undernutrition in African countries, childhood

obesity has not received as much attention yet. Therefore, most of what is known about addressing obesity among children is based on research in completely different settings, like the United States and European countries. Since obesity is linked to what we eat and how physically active we are, and these behaviours are context-specific, it is important not to assume that research from one country can be directly applied in another.

Ultimately, I am working towards designing a prevention programme that uses what we already know about addressing childhood obesity in other settings but is tailored to the specific context of Soweto. For example, schools in many countries restrict children's snacking in different ways – would these approaches work in Soweto? Childhood obesity is certainly a problem in South Africa, and it is becoming a global one. Nevertheless, we will continue to need locally appropriate solutions, while drawing on lessons from around the world.

Upasana Tayal, Imperial College London

Big hearts and giant genes: What lies at the end of the yellow brick road?

“Hearts will never be practical until they can be made unbreakable”, said the Wizard of Oz. “But I still want one”, replied the Tin Woodsman.

Your heart makes you human, makes you love, and keeps you alive. In just one year, it will beat 40 million times, without rest or time off for good behaviour. A pretty impressive piece of machinery you might agree, no wonder the Tin Man wanted one so much.

And like many things in life, he may have wished for a big heart at the end of the yellow brick road.

He would be forgiven for imagining a big heart to be a good thing, extra caring and compassionate, and if the Tin Man was scientifically inclined, more effective at doing its job of pumping blood around the body.

Unfortunately for the 1 in 250 people in the world living life with a big heart, the reality is very different.

A heart muscle disease called **dilated cardiomyopathy** causes hearts to get bigger and actually less effective at pumping blood around the body.

You might have heard of this condition recently as George Michael was found to have died from it.

For people with this condition, a big heart means taking medicines every day to stop their lungs filling up with the fluid that their big and stretched hearts cannot pump around their body.

Dilated cardiomyopathy is the leading reason for heart transplants worldwide and unfortunately 1 in 5 people will die within five years of their diagnosis. We urgently need better ways to identify who will develop complications from their disease.

In up to half of patients, we do not know why the condition develops in the first place.

However, recent research has found abnormalities in a giant gene, called **titin**, in 25% of people with dilated cardiomyopathy

Curiously however, the journey on the yellow brick road is not straightforward and not all people with an abnormal gene will go on to develop the disease and in those people who do develop the disease, the severity can vary.

Even more curiously, up to 1 in 100 healthy people carry the same genetic variations in the titin gene that are found in people with dilated cardiomyopathy.

Our genes are inherited from our parents but one theory is that factors in our environment cause genetic abnormalities to have different effects in different people.

My research uses in depth pictures of the heart taken from MRI scans, together with detailed clinical information and genetic data in over 700 patients with dilated cardiomyopathy, to understand more about the effects of genetic variations in the titin gene on the heart.

We have found that the hearts of people with genetic variations in titin are lighter than the hearts of people without these variations, which gives us clues as to how the disease might have developed.

We also find that people with the abnormal gene have an almost 3 fold increased risk of dangerous heart beats (abnormal heart rhythms) early in their disease course.

Finally, we find that in patients with the abnormal gene, the consumption of moderate amounts of alcohol leads to a much more severely damaged heart than would be expected from either having the gene abnormality alone or from the consumption of alcohol alone.

This research therefore provides evidence for how genetic data can be used to tailor care for patients with dilated cardiomyopathy. This may improve how doctors manage people with the condition and lead to improved survival for patients with this heart breaking disease.

Darren Thomas, University College London

A predilection for prediction

Amidst the hullaballoo of a shanty, post-war Kampala, an intrepid surgeon-cum-researcher was baffled by something rather odd. Why, despite living 'largely off the land' and having little access to a most basic Ugandan healthcare, a puzzled Dennis Burkitt pondered, were the humble locals seldom stricken with the same bowel cancers he had seen afflict the clinics at the forefront of mid-twentieth-century medicine?
"Western diets are so low on bulk [fibre] and so dense in calories," an eagle-eyed Burkitt would later conclude, "that our intestines just don't pass enough volume to remain healthy."

Overindulging on growth signals, absconding arrest from the immune system, and perhaps even crossing borders to far-flung organs, bowel cancers tend to remain well-hidden for two-to-three decades. They may be there, squatting in the dank alimentary alleyway—silent, multiplying, biding their time—but before long their loitering will cause discomfort, sending an unseased patient for medical attention. Most often it is too late.

We know that the earlier we can detect these clumps of cancerous cells, the easier it is to carve them out. But leave just one cancerous cell behind, and one can split into two into four into *ad finitum*.

What's more, should some cells splinter from the mass and lodge themselves into distant organs, the challenge to remove every cancerous cell is too often insurmountable. Their early detection is key.

The National Health Service has since 2010 offered hope for better outcomes for the forty-odd thousand Britons afflicted with bowel cancer each year. By looking for smidgens of blood not visible to the naked eye in faeces—a major symptom of bowel cancer—it aims to sniff and then snuff out these cancers-in-hiding far earlier than normal. But while this screening programme is no doubt lifesaving, my research aims to make it even better—and get more bang for British taxpayer's bucks.

Burkitt's work in East Africa was groundbreaking. Yet, the many studies conducted by countless scientists since have unravelled the causes of bowel cancer to be more complex than his 1970s bestseller *Don't Forget Your Fibre* could envisage. But he *was* on to something.

Bowel cancers are still to this day a rarity in rural Africa and a major burden for developed countries. Coincidentally, those emigrating from countries of low risk soon acquire the risk of their new compatriots. The exuberances of modern living are unquestionably to blame.

Fags, booze, meaty menus, and our tendency to whittle away hours in front of the box all increase your risk to varying degrees. What's more, the maladies of modern living, like diabetes and inflammatory bowel diseases, can increase one's risk too.

My research will scrutinise how the demographics of women who develop bowel cancer in the UK vary from their cancer-free peers. How, for example, do they differ in their age, ethnicity, medical history, and lifestyles? And how much more likely is, say, a smoker or a drinker to develop bowel cancer to abstainers? A diabetic from a non-diabetic? And a sixty-year-old from a fifty-something?

I am toiling toward an algorithm which, when you plug in data about you and your lifestyle choices, crunches the numbers and spits out a personalised risk score. We could then tailor bowel screening based on your personalised risk score: the higher your risk, the more you should be kept an eye on.

But why does this matter? Invitees to screening are an exclusive club reserved for the 60–74-year olds—an age when bowel cancers are more likely to develop. But the issue lies in the math. Some of this group will be of high risk (and will benefit from frequent screening), while others will have a low personal risk (and will not benefit from frequent screening).

A tailored screening programme, bespoke for each person, would be more efficient. It would also be indiscriminate to age, throwing a lifeline to more of the 16% of all patients who receive their diagnosis before their screening invite.

As a bookish youngster, I thumbed my way through stacks of dog-eared paperbacks during the solitary Suffolk summers. I spent hours with Philip K. Dick's *Minority Report*. In some forty-odd pages, Dick depicts a fictional 'utopia' wherein the city's Precrime system would apprehend those 'accused not of crimes they have committed, but of crimes they will commit'. Wrongdoings were all but eradicated.

It was only later, undertaking this research—a stone's throw from Burkitt's 'retirement' laboratory in London—that this literary fanaticism took on a higher level of poignancy: I was vying to become Commissioner Anderton. What if, just as Anderton's invention would remedy events before they occurred, we could—to paraphrase Phillip K. Dick—treat bowel cancers accused not of symptoms they have shown but of symptoms they will show?

Jessica Potter, Queen Mary University of London

Accessing healthcare – what's the story?

There is a bacteria that has infected a quarter of the world's population. More people have died from it than any other infectious disease in history. In 2016, it killed a population the size of Northern Ireland – 1.8 million people. That disease is tuberculosis (TB) and it is completely treatable.

TB spreads through coughing so there are three key principles to controlling it: preventative treatment; early diagnosis; and effective drugs. For those who become unwell with TB, the longer they remain without adequate treatment, the more unwell they become, the more people they may infect, and the more likely they are to die.

Ali had been unwell for three months before he thought about asking for help. He put his cough and fevers down to a stubborn winter cold, and his excessive tiredness down to working 80 hours per week. Eventually he broke. He needed help. Late one night Ali went to Accident and Emergency (A&E) who diagnosed a chest infection and sent him away with antibiotics.

Several weeks later, Ali had drenching night sweats and was losing weight. No longer able to work, his landlord was threatening to throw him out. He had tried to register with a GP but was told he did not have the right paperwork, so he went back to A&E. He had a chest x-ray and was referred to see a lung specialist the following week. Meanwhile he continued to cough.

To reduce the time between a person becoming unwell and getting the treatment they need, I am exploring pathways to diagnosis. Ali's story of health-seeking did not end when he walked through the front door of A&E. Healthcare access is a complex and dynamic process that takes place in continuously changing environments.

In richer countries with not much TB, like the United Kingdom, the vast majority of cases occur in migrants. Globalisation, the recent refugee crisis, a worldwide financial crash and the rise of terrorism have all conspired to create an environment which is hostile to foreigners. In these times of austerity there is no room to consider healthcare as a human right and people question others' 'deservingness'.

Policies reflect these sentiments with ID checks, surveillance to detect access abuses and the imminent threat of upfront charges for those without the correct paperwork.

People come to the UK in a multitude of different circumstances, from increasingly diverse countries and cultures, and with different experiences of health systems. These experiences not only affect their risk of developing TB but also their ability to get help when they do. I am therefore particularly interested in how migrants with TB access healthcare in the UK. To do this, I am using a research method that asks migrants to tell me *their stories.* I give them a space in which to speak without fear of interruption and in which my agenda is only imposed after they have taken as much time as they wish to talk about theirs. This open, qualitative approach to eliciting stories provides a richer picture and potentially deeper understanding than methods which use prescriptive answers to pre-defined questions.

Language is my biggest challenge. Ali speaks three languages but not one that I share. The inability to speak English fluently prevents migrants from participating in many forms of research. In any case, including only English-speakers would introduce bias as the sample would not be representative of the wider population. My data is language so collaboration with a cohort of well-trained interpreters is integral to ensuring that what a person wants to tell me is what I eventually hear.

It is also important to reflect on ways in which my identity influences the research process. I have not hidden my belief in human rights, my love of the NHS or my intolerance of racism and xenophobia. I use my research to drive for social change and advocate for my patients. Some have suggested that this may affect its validity. I would argue that scientists are human and therefore, to ensure our findings are robust, it is vital for researchers in all fields to critically reflect on how this 'humanness' impacts the work we do.

Returning to Ali, he eventually got the treatment he needed but four months after he first felt unwell. By this time TB had eaten a hole in his lungs which may never heal. Just one of his housemates tested positive for TB and required treatment. Ali is currently sleeping on a friend's sofa but is back in work now so hoping to arrange a more permanent solution soon.

Stories are powerful. By listening to people like Ali I hope to improve healthcare access, thereby reducing the devastating impact this disease has not just on him but everyone in society.