PACIFIC LIFE RE

Vital Insights

Pacific Life Re's latest medical research roundup

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Slimming Down

How emerging drugs battle obesity

In this issue

Welcome

Welcome to our latest edition of Vital Insights. Here we've put together a collection of articles covering some of the major issues of the day with a specific focus on how they could impact mortality and morbidity. From emerging drugs which battle obesity to a review of the effectiveness of new blood tests both to detect cancer and to help slow down Alzheimer's, we hope these insights help keep you up to date with the latest in medical research.

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About Pacific Life Re

Our global team, comprised of the best minds in the industry, are not afraid to disrupt and challenge industry thinking to provide the best mortality, morbidity, longevity, and capital reinsurance products and services possible.

We pursue personalised, bespoke solutions for every one of our clients and our commitment to cutting-edge technology reflects our ambition to offer the most sophisticated answers to the most challenging reinsurance questions.

We are proud of our beginnings, and we celebrate our youth because it is what keeps us tenacious, agile and energised. We are equally proud of the security and freedom we possess from having the backing of our parent company Pacific Life. With a heritage of more than 150 years, Pacific Life provides strength and resilience to our business which enables us to bring our fresh and dynamic approach to the marketplace.

Slimming down

How emerging drugs battle obesity

Heavily touted by celebrities and influencers, many of whom have no medical need to lose weight, a new generation of weight loss drugs has now well and truly arrived. Obesity contributes significantly to some of the most common causes of death including heart disease and cancer, as well as affecting quality of life for millions.

In this article we look at these increasingly available drugs offering hope to more people with obesity. We consider their potential to broadly improve health, their limitations and what the next generation of drugs might offer.

Being overweight kills at least 2.8 million people globally each year. In most countries it is a growing problem; the number of people with obesity has approximately trebled since 1975.[1] This epidemic has provided significant headwinds for mortality improvements. Advances in medical science have driven increases in human life expectancy for decades. However, the pace of improvement noticeably slowed across a broad range of high-income countries in recent years, even before the pandemic, with the USA and UK among the worst affected.

One key factor driving this trend is a slowdown in improvements relating to cardiovascular conditions. In part this occurred due to lower beneficial contributions from things like improved surgical techniques and reduced smoking. However, experts believe poor diet, increasing rates of obesity and related increases in diagnoses of type 2 diabetes contribute materially to the impact seen.

A medical problem in need of a medical solution

Obesity is a complex issue and often unfairly stigmatised. For many reasons simple behavioural changes are insufficient remedies for a large number of affected people. Instead, factors like genetics, gut hormones and addictive behaviour either mean that diets don't work or that people are unable to adhere to them. Other factors, including poverty and availability of healthy food, contribute to an environment which does little to help people live optimal lifestyles.[2]

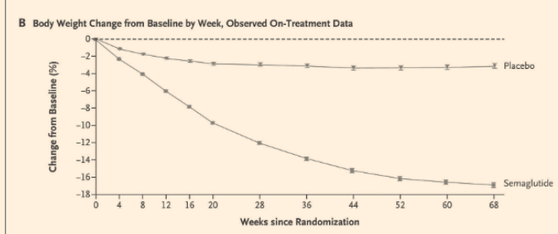
Successfully thinking about obesity as a medical problem, rather than an individual failing, is only half the battle. Until recently, medical options were extremely limited. For the most obese, surgery such as a gastric bypass could help, but it's an extreme option typically thought of as a last resort. Available drugs, such as orlistat, were quite commonly used but often unsuccessful. Otherwise, the message was just: diet, exercise and willpower.

Introducing GLP-1 agonists

New drugs can help to change this. A class of drugs exists which has been used in recent years to improve blood sugar control in type 2 diabetics. Related products have now achieved widespread approval to encourage weight loss in people who do not have diabetes. There are several drugs which have this action including semaglutide, liraglutide and tirzepatide.
Of these semaglutide is the most well-known, especially under the brand names Ozempic and Wegovy, of which Wegovy is the product approved specifically for weight loss. Semaglutide is generally the most widely used, partly because trials show it is effective, and partly because it requires 'only' a weekly injection, whereas liraglutide requires daily self-administered injections. Tirzepatide is not yet so widely available but does appear more effective than semaglutide in trials[3] and may overtake it in popularity in the medium-term.

This family of drugs is known as GLP-1 agonists. Glucagon-like peptide 1 (GLP-1) is a hormone the body produces naturally after we eat. In diabetics, these drugs help control the amounts of insulin and glucose in the body by mimicking GLP-1. When used to treat weight loss their key action is to slow the movement of food from the stomach to the intestines. People feel fuller more quickly and for longer, and eat less. GLP-1 agonists may additionally help lower the risk of heart and kidney disease, and improve blood pressure and cholesterol, but scientists are not sure yet whether that is just a secondary effect caused by weight loss, or whether some mechanism of the drugs helps directly treat these conditions.[4]

Body Weight Change from Baseline by Week, Observed On-Treatment Data



Focusing on semaglutide, its potential impacts are undeniable. The STEP 1 trial published in 2021 showed that over half of people taking the drug lost over 15% of their body weight inside one year, and one in three lost over 20%.[5] Those taking a placebo lost only 2-3%. A typical obese person measuring 173cm (5ft 8in) and 120kg (265lbs, or 18st 13lbs) could expect their weight to fall to 102kg, which would mean a significant drop in BMI[6] from 40 to 34.

This sort of drop – if sustained – could have significant impacts on mortality and morbidity. For example, a recent paper studying the US population found all-cause mortality, after a median follow-up of nine years, was approximately 20% higher for people with BMI 35-40 than for those with BMI 30-35, and the incremental impact on mortality is even larger at higher weights.[7]

This paper found that for otherwise healthy people who had never smoked, relative to people with an ideal BMI of 22.5-24.9:

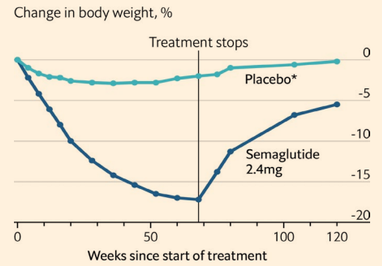
- People with BMI 30.0-34.9 had mortality 21% higher
- People with BMI 35.0-39.9 had mortality 44% higher
- People with BMI 40 and above had mortality 108% higher

All risks were higher for younger adults. Older adults, above age 65, were not at significant risk until BMI exceeded 35.

Beware the rebound

Approximately 30% of adults in the UK, Canada and Australia are currently obese (BMI > 30) and this is nearer 40% in the United States.[8] It is not difficult to see how weight loss on the level seen in the semaglutide trial could have a significant impact on mortality and health if it were sustained. However, that is the problem. A key limitation of these drugs is that doctors currently recommend them for use for a maximum of two years partly due to lack of evidence relating to more sustained usage. Studies show that once people stop using GLP-1 agonists, it is typical for much of the weight lost to be regained. In the trial shown to the right, the average semaglutide user regained around 70% of the weight lost. If this wasn't bad enough, 'yo-yoing' weight can have detrimental physical impacts on the body, eventually affecting metabolism and increasing risk of diabetes and heart disease.[9] It can also be psychologically devastating for some.

Semaglutide weight-loss drug trial. [10]



It would also be unrealistic to expect that a person losing weight when using these drugs would immediately revert to the mortality associated with their new, lower, BMI, even if they do keep the weight off long-term. Prior years with higher weight exert stresses on the body which will take many years to wear off, and may never completely do so.

Moreover, GLP-1 agonists also come with side-effects. While rarely serious, feelings of nausea and vomiting are reasonably common, preventing some people from engaging with the drugs for long enough to allow them to work.

All of this reduces the likely potential impact of the drugs significantly. Instead of expecting users to indefinitely sustain reductions of 15-20% of their body weight, we can perhaps expect the weight to be lost for a period of two or three years in many people. The impact of spending this period of time at a lower weight may still be beneficial, but far less than if this were maintained long-term, and potentially offset by some of the physical and psychological effects of 'yo-yo' dieting described above. Underwriters should also be aware of the increasing possibility that an applicant disclosing usage of the drug at time of application may have a significantly higher 'natural' weight to which they may soon return.

Looking at the pipeline

Medical science doesn't stand still, especially when there are fortunes to be made. The markets involved here are enormous, with manufacturers of current approved drugs – Novo Nordisk (semaglutide, sold as Wegovy) and Eli Lilly (tirzepatide, sold as Zepbound) – expecting revenues measured in the billions. Several drugs in the pipeline could build on the early promise shown by the first generation of GLP-1 agonists.

Some drugs are seeking to improve on the durability of weight loss. Early phase trials of a drug called MariTide suggest it could achieve similar weight loss to its competitors, but could be tapered down and administered less frequently over time without patients regaining substantial weight. In small trials, weight loss was maintained for 70 days after the last dose and further investigations will determine whether this holds over the longer term.[11] Other drugs, such as retatrutide, are looking at whether the levels of weight loss associated with semaglutide can be bettered. Phase 2 trial results showed it achieved 17.5% mean weight reduction at 24 weeks and 24.2% reduction at 48 weeks, significantly in excess of the first generation of drugs.[12]

Currently authorised GLP-1 agonists require regular injections into the stomach, presumably nobody's favoured means of taking a drug. In response, Pfizer have designed a once daily tablet which would be preferable for many users. Known as danuglipron, it initially struggled in early trials due to poor side effect profiles when given twice daily.[13] The company hopes reducing to once daily may achieve the right balance of effective weight loss and tolerable side effects.

Finally, several companies seek to fill more niche roles, targeting obesity alongside other conditions such as liver fibrosis or chronic kidney disease. Recent results for survodutide, for example, suggest it effectively treats both obesity and metabolic dysfunction-associated steatohepatitis (MASH), a liver disease.[14] GLP-1 agonists may have broad application across cardiovascular, renal, and metabolic spectrums.

Next generation drugs could:

- Achieve more durable weight loss
- Achieve better weight loss
- Replace injections with tablets
- Treat more than just obesity

Weighing up industry impacts

Ultimately, we expect these drugs will have a positive impact on medical outcomes including heart attacks, strokes and deaths from a variety of causes, most notably relating to cardiovascular health.

A study published late in 2023 provides the best early evidence that semaglutide will have a significant impact on mortality and morbidity at least for people with quite severe preexisting cardiovascular disease.[15] Scientists enrolled over 17,000 patients, all aged over 45 and with a BMI of 27 or higher. All had a prior heart attack, stroke or symptomatic peripheral arterial disease. After a mean follow-up of a little over three years, incidence of cardiovascular death, and non-fatal heart attacks and strokes were 20% lower in those taking semaglutide, though for death the finding did not quite achieve statistical significance. It is true that many lives comparable to those in this study would currently struggle to purchase insurance due to their complex medical histories. However, this hints at the scale of possible benefits, over a longer period, among those who appear more commonly in protection books and raises hopes insurers could one day offer cover to a broader pool of applicants.

'incidence of cardiovascular death, and non-fatal heart attacks and strokes were 20% lower in those taking semaglutide'

We expect the impacts of GLP-1 agonists on mortality and morbidity will be more significant for those at highest risk, i.e. those who weigh most. This is because a higher proportion of mortality risk for this group is associated with weight. The benefit of using GLP-1 agonists will therefore reduce with a person's weight.

At the other end of the scale, people who are not overweight at all can, and do, use these drugs. The desire to lose weight is not restricted to those with significant medical need. However, this group may well experience negligible benefit, on balance, with minor harms offsetting possible minor benefits associated with secondary impacts on future cardiovascular health.

Protection insurers can expect wider rollouts of these drugs to be broadly beneficial for in-force business, especially the small proportion of lives initially rated for obesity.

Conclusion

This class of drugs appears here to stay. In the short term, the way these drugs are used can, and likely will, change, as early supply issues ease and scientists learn more about long-term effects.

In the longer-term other drugs taking advantage of this mechanism might surpass the current generation, perhaps with stronger effects and more benign side-effect profiles.

Social media influencers and celebrities are encouraging use of these drugs, presenting them as a life-changing technology, typically to groups with little medical need for them. This increases demand, reducing availability for those most in need, and leads to the appearance of more dangerous 'off-brand' versions.[16]

However, used properly, and with improved supply, it is likely that we can expect material health impacts for many individuals who will lose significant weight. At a population level, there are reasons to temper our expectations somewhat, but the number of people affected by obesity is so large that even modest per-person benefits could have reasonably significant impacts on the health of the population at large.

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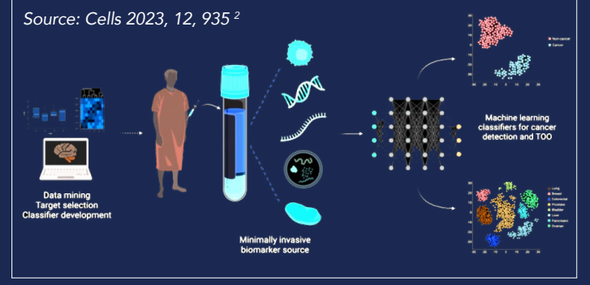
New screening technologies widen the MCED testing landscape

When counted together, cancers are the second leading cause of death worldwide, accounting for an estimated 1 in 6 deaths[1]. In theory we could avoid much of this mortality if it were easier to identify cancers when they were still at early stages. However, most cancer deaths occur due to cancer types for which no approved screening test exists, and even then these tests can be inaccurate, invasive and costly.

Recently, a range of multi-cancer early detection (MCED) tests have emerged, aiming to identify early-stage cancers before symptoms appear using a single blood sample. These tests typically look for differences in cancerous genes compared to normal ones, a complex process known as gene expression. This can be monitored and measured using a variety of biological molecules, also called biomarkers, as indicators.

The MCED test landscape is progressing at speed, with many companies jostling for primacy. Although the products under development may appear similar, they utilise many different technologies. In this article we compare three emerging products to demonstrate some of the differences, and how these impact performance.

Source: Cells 2023, 12, 935 [2]



GRAIL's Galleri test - using cell-free DNA

The most well-known MCED test is the Galleri test developed by the company GRAIL[3]. The test is currently being assessed for population-level efficacy in a collaborative clinical trial between GRAIL and the UK National Health Service. Initial results are expected soon, but had not been reported at the time of writing.

The Galleri test looks for DNA that is circulating in the blood, known as cell-free DNA (cfDNA), which has been shed from our body cells, both healthy and cancerous. The DNA is checked for specific chemical changes called methylation. The location and pattern of this modification affects whether genes are expressed or 'switched on'. All genes have a region known as a promoter which controls their expression. If a promoter is methylated, the gene is inactive, or 'switched off'. Conversely, if the promoter is unmethylated the gene is switched on and can be expressed.

In cancer cells, genes that slow down or restrict growth, known as tumour suppressor genes, will typically be switched off, whilst the cancer will switch on genes that stimulate cell growth and division, known as proto-oncogenes. By analysing the combination of genes with altered methylation patterns, scientists can identify if the patient has cancer in addition to which part of the body it originates in. GRAIL claim the Galleri test can identify over 50 different cancer types, making its breadth a potential area of competitive advantage relative to many other tests.

'GRAIL claim the Galleri test can identify over 50 different cancer types'

Overall, trials to date suggest the Galleri test can correctly identify cancer in approximately 52% of patients, and has a high specificity of over 99%, meaning false positive results occur rarely.

Its sensitivity varies significantly by the site of cancer. The test was also more sensitive to late-stage cancers which, while unsurprising given the greater imprint these will have in the blood, does partially diminish its ability to identify cancers at treatable stages.

Novelna's test – using proteins

Whilst DNA is the starting material in which genes are written or encoded, proteins are the end-product of the gene. It is the protein which performs the function of that gene within our cells and tissues. Recently, the biotech firm Novelna[4] announced development of a new MCED test which looks at the levels of certain proteins circulating in a patient's blood sample. Of itself, testing for levels of specific proteins in blood is nothing new. For example, blood tests measuring prostate-specific antigen (PSA) and cancer antigen 125 (CA-125) are routinely conducted to screen for prostate and ovarian cancer respectively. However, the current detection methods lack sensitivity, particularly for early-stage disease where protein levels in the blood may be very low. This means they can fail to pick up true cancers. They also struggle to accurately identify those patients without cancer who would benefit from further screening.

'Novelna's ... apparent strength is its potential to identify a greater proportion of early-stage cancers.'

A key feature of the Novelna test is that they have identified 'panels' or sets of proteins that are present at different levels in those with and without cancer, and which are different between men and women. Novelna utilises methods which allow scientists to detect, identify and quantify low abundance proteins. This is followed by sequencing, and incorporation into their machine-learning derived algorithms.

Novelna's technology targets a pool of 18 cancers, far smaller than Galleri's 50 or more. Instead its apparent strength is its potential to identify a greater proportion of early-stage cancers, thus leading to a potentially greater improvement in long-term survival outcomes than Galleri.

Moreover, the true difference in breadth is more modest as the 18 cancers covered include many of those with the highest incidence rates. Key cancers not covered include melanoma (skin) as well as lymphomas and leukaemias.

Early results[5] across 440 blood samples suggest the test can detect stage I cancers in 93% of men and 84% of women, and that it only falsely identified cancer in healthy patients around 1% of the time.

The test was also able to correctly identify which type of cancer a patient had in over 80% of cases, using a larger set of proteins. This type of sex-specific early cancer detection could be revolutionary, as many cancers possess a gender incidence bias, such as bladder cancer in men and thyroid cancer in women, whilst female cancers are typically more aggressive at younger ages.[6, 7]

Further, Novelna predict that it could cost less than $100 USD/£80 GBP per patient, nearly 10 times less than the current cost of the Galleri test. This could make it an attractive option for the public and healthcare providers alike.

Although the Novelna protein test appears to have a greater sensitivity than GRAIL's Galleri DNA test, particularly for early-stage cancers, the low numbers of participants involved in early proof-of-concept studies mean further research will be required to confirm initial promising results across much larger populations.

miRXES' GASTROClear test - using micro RNA

Another biomarker of interest in the MCED test sphere is non-coding RNA (ncRNA). Unlike messenger RNA (mRNA), ncRNAs do not get translated into protein. Instead, these plentiful and diverse molecules perform their functions directly, many of which are related to regulating gene expression.

A type of ncRNA called micro RNA (miRNA) is being used as a blood sample biomarker in the GASTROClear MCED test developed by the company miRXES[8]. These short, single RNA strands are often implicated in cancer and other diseases due to their ability to regulate gene expression by interfering with mRNA to destabilise it and reduce the level of protein made. This test measures a panel of 12 miRNAs, 11 of which are associated with gastric cancer, to generate a risk score.

'studies also suggest an ability to identify high-grade dysplasia, which is a precancerous condition.'

This product focuses specifically on gastric cancers, although miRNA technology could also be developed for other forms of cancer and miRXES plan to turn their attention to eight other sites including colon, breast, lung and liver cancers. Compared to its competitors it appears relatively cheap.

The miRXES test has been evaluated for early gastric cancer detection in large clinical studies involving more than 5000 patients across Singapore and Korea[9]. Stage I and II cancers were detected in 87.5% and 89.5% of patients respectively, with an overall test sensitivity of 87% and a specificity of 68%. These studies also suggest an ability to identify high-grade dysplasia, which is a precancerous condition.

The relatively low specificity implies the test would lead to high numbers of false positive results, where patients without cancer are given a positive result. This is obviously undesirable, but is less concerning when we note the test is designed to precede endoscopy tests. As such it is calibrated to err on the side of caution. Its purpose, if widely adopted, would be to identify a pool of people considered 'at risk' on whom to perform more accurate, but more invasive and time consuming, endoscopies. Future studies are required to evaluate the test on a wider population demographic and to validate the individual miRNA's role in cancer progression in laboratory studies.

Other tests are available

The above analysis is by no means exhaustive. We have not chosen these three because we judge them to be superior, but because out of the leading candidates they offer interesting comparisons in terms of underlying technology, breadth of coverage and accuracy – both overall, and in terms of specific cancers at specific stages.

Other tests, some using different technologies, are also progressing through clinical trials, and of these some look potentially highly competitive. These include Chopon, whose test analyses circulating tumour cells, and targets a broad range of cancers, with potentially promising results at earlier cancer stages.

Implications for insurers

Whilst MCED tests are still largely under development and clinical testing they have the potential to eventually revolutionise early detection of many cancers. Through early and accurate detection, many cancers could be treated more effectively, ultimately leading to longer life expectancies through improved survival rates.

While this would have obvious benefits for mortality business, impacts on critical illness books of business would be more subtle. These tests would tend to bring diagnoses forward, both in time and to earlier stages of disease. Sudden changes in the prevalence of MCED use in the insured population could affect incidence patterns. Bringing forward claims could lead to larger payments on policies with decreasing sums insured, and fewer premiums collected prior to the claim event. Some diagnoses could occur within a policy's term which would otherwise have occurred after expiry.

Diagnoses at earlier stages of disease could lower claim impacts, but only if the disease was found at stages associated with lower payments, such as pre-cancerous disease. This is something most of the current generation of technologies appears to struggle to achieve, though exceptions exist. We saw above that miRXES' test could pick up on some precancerous gastric cancers, thus preventing some valid claim events from occurring in the first place.

Insurers may choose to use these tests. For example, adoption of MCEDs as part of the underwriting process for larger policies could increase the strength of the underwriting process. Alternatively, tests could be offered to existing policyholders as an additional policy benefit to promote future good health. Insurers should also be aware that the widespread presence of these tests could create scope for anti-selective behaviours.

Currently, the leading tests are expensive and to an extent unproven. However, competition from alternative MCED technologies will eventually make testing more accessible. If MCEDs prove successful, then whether insurers make direct use of them or not, they have the potential to help customers lead longer, healthier lives.

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Could we eliminate cervical cancer within a generation?

For over a decade now, adolescent girls in many locations have been vaccinated against the human papilloma virus (HPV), which can cause several types of cancer, most notably cancer of the cervix. 15 types of HPV are collectively responsible for causing up to 99% of cervical cancers. Data is beginning to emerge on the real-life impacts of these vaccines on patients, and results are extremely positive.

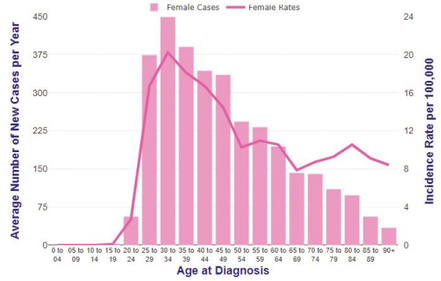
A new study from Scotland[1] looks at cancer rates in women who received the 'bivalent' vaccine, protecting them against the two most common cancer-causing forms of the virus, HPV types 16 and 18, detected in approximately 70% of cervical cancers.

'the study found no cases of cancer at all in Scotland in women vaccinated as adolescents.'

The vaccine has been widely available since 2008. As it was primarily given to girls aged 12 and 13, the vaccinated cohort is now approaching age 30. Unlike many cancers, cervical cancer tends to occur at young ages. The age distribution in the graph to the right[2] shows incidence risks are highest when a women is in her 30s, and already appreciable during her 20s. For example, in the UK as a whole there are over 400 cases per year in people aged under 30, which is 12% of all cases. This means we should start to see a reduction in cases by now if the vaccine works.

And we do! Remarkably, the study found no cases of cancer at all in Scotland in women vaccinated as adolescents. In women given the vaccine post adolescence cases did occur, but rates were more than halved. The vaccine is now also given to young men, both because it can reduce risk of other cancers, such as of the head and neck, which men can get, and because reducing HPV prevalence indirectly helps women by reducing their chance of catching the virus from sexual partners.

Cervical cancer (C53), Average Number of New Cases per ear and Age-Specific Incidence Rates per 1000,000 Female Population, UK, 2016-2018



Cervical cancer causes 850 deaths per year in the UK, almost all of which could be prevented by vaccines. Given these exciting results we can expect to see this cancer reduce materially as a cause of death over the next decade and beyond. Globally cervical cancer is the fourth most common in women. In the UK it is responsible for around 3% of all female deaths between ages 30 and 39, with lower percentages at other ages. This means we can expect medium-term impacts on overall protection-age mortality and morbidity which are certainly not negligible.

Prevention of these deaths is only the most prominent impact of this vaccination campaign. HPV is also responsible for thousands of cancers each year in other sites, including the back of the throat, anus, vulva, penis and vagina. In addition, for every case of cervical cancer there are nearly 20 cases of precancers requiring unpleasant and invasive treatments, with diverse impacts including anxiety and problems during pregnancy.

Furthermore, in recent years the development of next generation vaccines could make this technology even more effective. The newer '9-valent' vaccine which protects against a further five cancer-causing HPV types is now used in some locations. These types are typically associated with cervical cancers diagnosed at later ages than HPV types 16 and 18[3]. Excitingly, these developments have scientists talking about the near eradication of cervical cancers within 20 years, which would be a fantastic feat of science.

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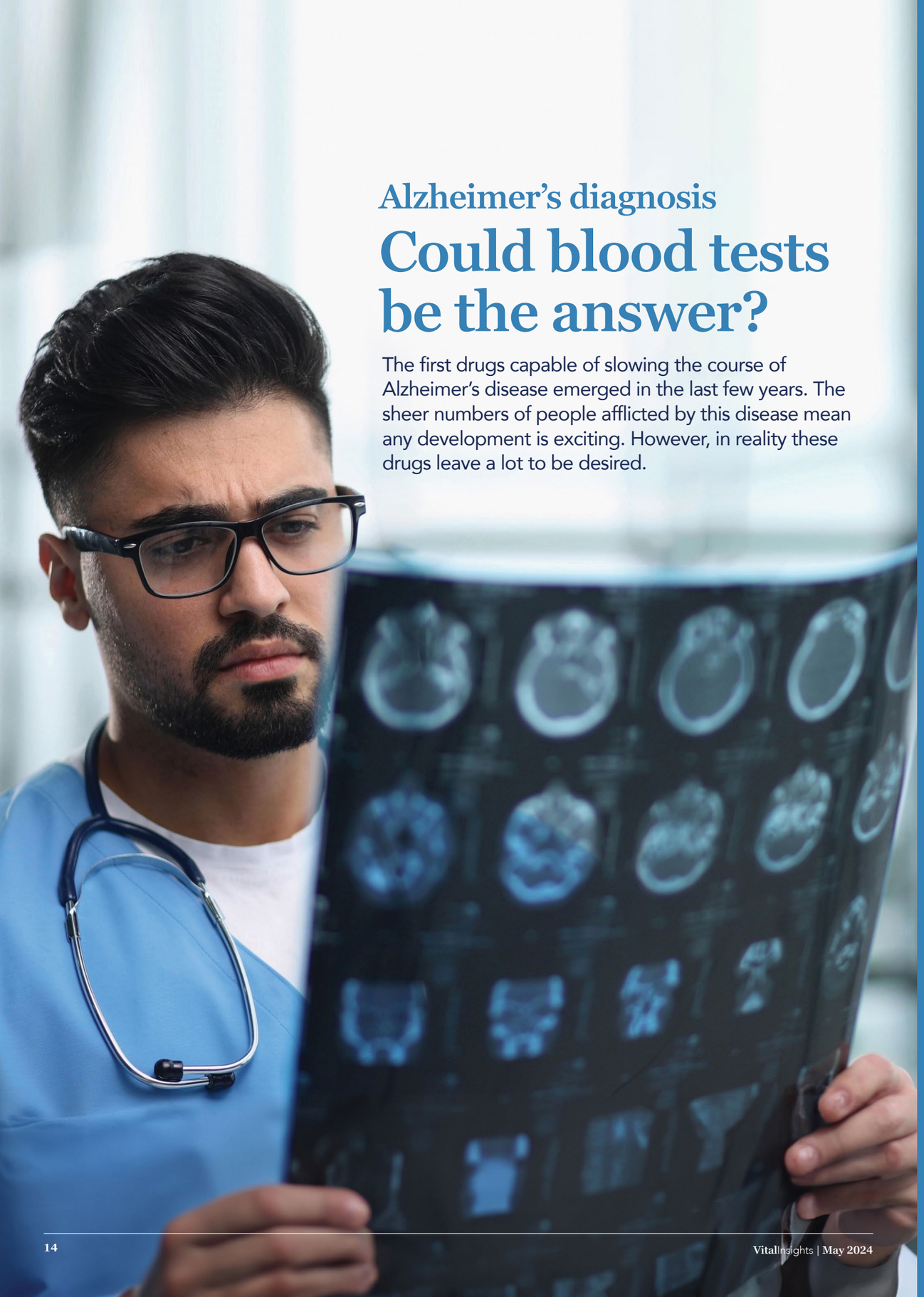

Alzheimer's diagnosis

Could blood tests be the answer?

The first drugs capable of slowing the course of Alzheimer's disease emerged in the last few years. The sheer numbers of people afflicted by this disease mean any development is exciting. However, in reality these drugs leave a lot to be desired.

The most successful drug only modestly slowed the progression of the disease in its trials, and even then, in ways described as 'statistically significant but clinically irrelevant'.[1] They are also associated with high cost and potentially serious side effects including loss of brain mass, brain swelling and bleeding. As a result, only some of the drugs have been approved, typically only in the US, and not without controversy.

It may be that the drugs just don't work very well and that we will need to develop a whole new class of drug to use instead of, or in addition to, these ones. However, some scientists propose that even though their trials were highly selective for patients with early-stage disease, the drugs were simply given too late. Leading candidate drugs, like lecanemab, successfully break down build-ups (plaques) of a protein called amyloid, which is thought to contribute to Alzheimer's' clinical symptoms. But maybe by the time these plaques have built up to the point where they cause symptoms it's already too late?

'In future, blood tests may be used to screen apparently healthy patients for Alzheimer's.'

Alzheimer's is difficult to diagnose. Symptoms progress slowly and begin imperceptibly. They overlap with the symptoms of other conditions, and initially can be confused with the more benign effects of ageing. Confirmatory tests include brain imaging or unpleasant 'spinal taps' often only requested when alternative diagnoses have been ruled out. This can take months or years. In any event, researchers suspect the condition begins to damage the brain at least a decade before symptoms appear.

However, the deployment of blood tests could accelerate Alzheimer's diagnoses. These tests – looking for circulating proteins, including amyloid – already exist and have reasonable, though far from perfect, accuracy. Various studies are underway to try to develop a more accurate predictive test, by identifying combinations of protein levels which represent a unique signature of early Alzheimer's [2, 3]. Ongoing trials are assessing whether lecanemab might prevent or delay dementia in people with amyloid plaques but no symptoms. [4]

In future, blood tests may be used to screen apparently healthy patients for Alzheimer's. These drugs, or some future version of them, might then be offered to prevent the disease. In fact, an influential panel at a major Alzheimer's conference in 2023 proposed redefining the disease such that people with positive blood tests and no symptoms might be classified as having 'Stage 1' Alzheimer's. [5] While drug companies would no doubt

'a proliferation of early diagnoses could lead to 'severity creep' as positive tests prime customers to notice subtle changes in their ability to remember, reason and express ideas'.

love widespread preventative adoption of their products, at present there is no evidence there is anything useful we can do for patients with positive tests, and such a result might achieve little more than cause anxiety.

These developments are clearly of interest to insurers, especially those providing Critical Illness and medical expense coverage. Most Critical Illness policy definitions require customers to meet a severity-based definition and would not be especially sensitive to a new medical definition of Alzheimer's. However, a proliferation of early diagnoses could lead to 'severity creep' as positive tests prime customers to notice subtle changes in their ability to remember, reason and express ideas, key facets of typical policy definitions. Certainly the introduction of more accessible accurate tests could accelerate a material proportion of Alzheimer's diagnoses.

For patients, the joint potential of new drugs and blood tests is more exciting than either one in isolation. But significant doubts remain, especially relating to the efficacy of our current arsenal of drugs. And there are dangers, too, in diagnosing and treating some who may never need it. However, through testing and learning how to use these tools in tandem, we may eventually get closer to making a genuine difference for the millions susceptible to this terrible disease.

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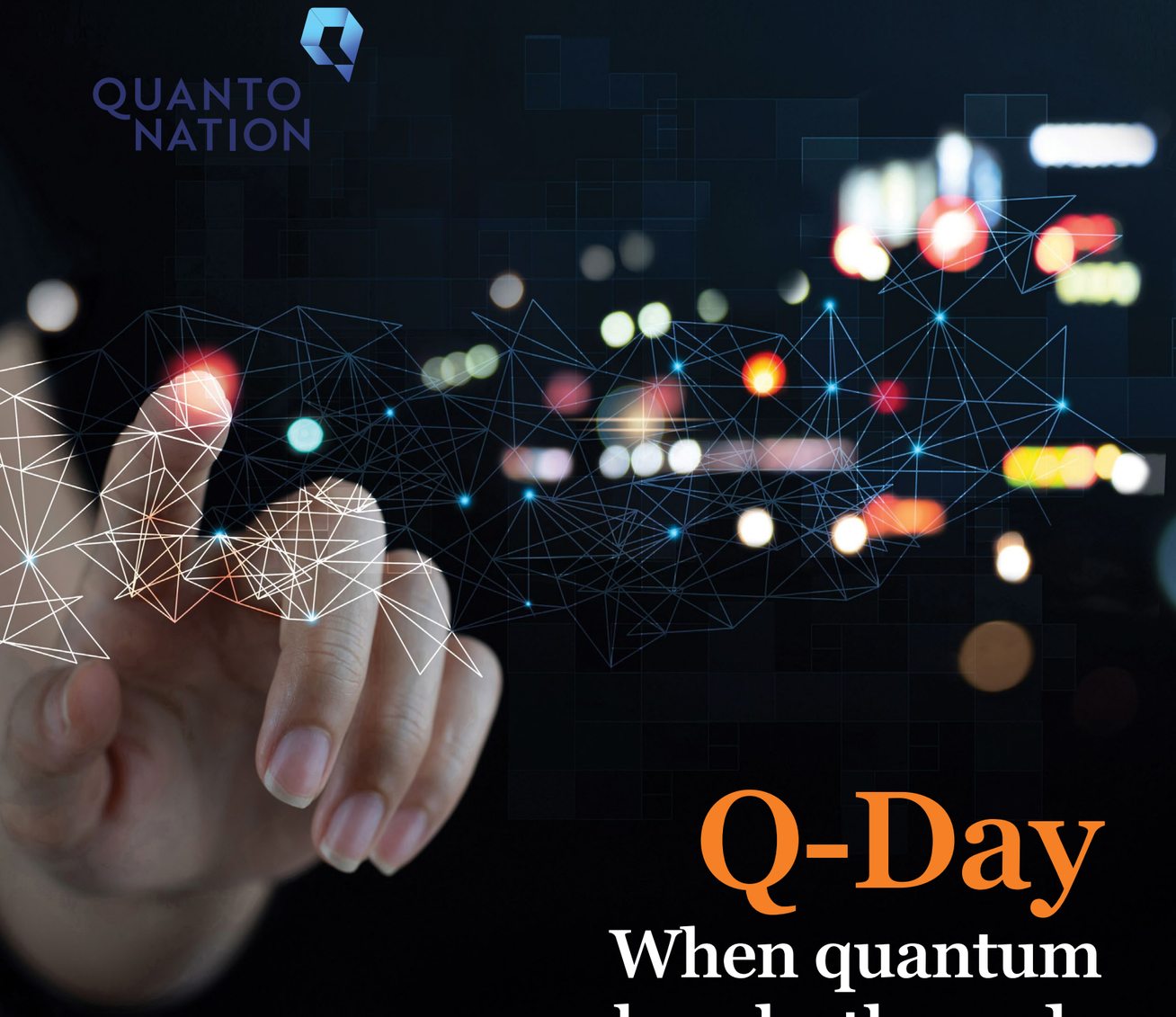

Q-Day

When quantum breaks the code

Pacific Life Re is proud to have invested in Quantonation[1], a venture capital fund for start-ups in the quantum technology sphere. Medical use-cases of this technology include drug discovery and improved scanning technology. However, in this article we analyse one of the non-medical implications of advances in quantum computing: vastly improved encryption and decryption capabilities. Our societies have come to rely heavily on secure encryption, and its future vulnerabilities could have severe consequences for us all.

Introducing Q-Day

Q-Day is the term coined for the day when quantum computers crack the encryption codes that safeguard our digital data on the internet. This would jeopardise the security of our financial transactions as well as other vital infrastructure. Some experts believe that Q-day may be just around the corner.[2] Quantum computing sceptics, on the other hand, point to some material barriers to building sufficiently powerful quantum machines. So, who is right and how worried should we be?

Encryption commonly relies on the concept of factorising an extremely large number into its still very large prime components. Although computers can quite easily multiply large numbers together, they typically lack the computing power to perform this process in reverse. The strength of encryption relates to the difficulty in finding the factors of semi-prime numbers (i.e. two prime numbers multiplied together), and the length of these numbers.

If you use a large enough number, it is effectively impossible for even the largest conventional super-computers to derive its prime factors. This is not because the problem is logically difficult – after all you could in theory try each integer in order and check the remainder to see if it is a factor. However, even using more efficient methods the computation has so many steps that the problem can't be solved in a useful timeframe. In 2009 researchers were able to crack a 768-bit RSA key using a conventional computer with about 1000 cores[3]. But the process took 2 years![4]

In the binary system, a single bit can store the values 0 or 1. The complexity grows exponentially. Eight bits have 256 combinations, allowing the storage of all values from 0 to 255. Keys in the most common encryption method, RSA, were a minimum 1024 bits long until 2015, after which the industry standard increased to 2048.

To give a sense of the difficulty in factorising numbers of this size, the following is a number released in 1991 as a challenge to encourage research in this field. Despite a $100,000 prize on offer until 2007 and many more attempts since, it has never been factorised, so if you fancy a challenge on your next lunch break, feel free to have a go. 2048-bit numbers are twice as long, with at least 617 digits.

1024 bit Semi-Prime number

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135066410865995223349603216278805969938881475605667027524485143851526510604859533833940287150571909441798207282164471551373680419703964191743046496589274256239341020864383202110372958725762358509643110564073501508187510676594629205563685529475213500852879416377328533906109750544334999811150056977236890927563
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The move to 2048-bit encryption increases the complexity but, fundamentally, most current encryption methodologies still rely on computational difficulty.

Quantum scaling

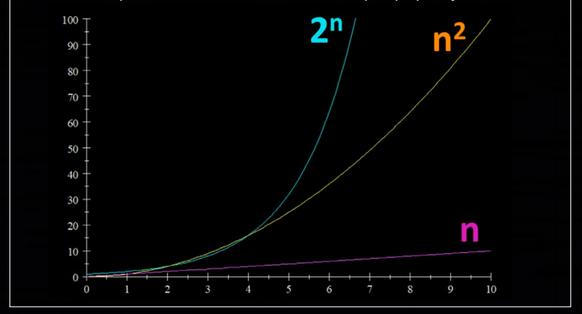
If we think of conventional computers as being built out of bits then quantum computers are built out of qubits. The big difference is that the qubits have a property called superposition (a binary qubit exists as a superposition of both 0 and 1) and can be entangled, which is where they share a single quantum state. This increases by orders of magnitude the complexity of information that can be stored, as illustrated by the table and chart below:

No of Qubits	Memory Equivalent*	Approximate Bits
10	210 = 1024 bits ~ 1 kilobit	10^3
20	1 megabit	10^6
30	1 gigabit	10^9
40	1 terabit	10^{12}
50	1 petabit	10^{15}
60	1 exabit	10^{18}

** n entangled qubits can be represented by a 2^n-dimensional vector space*

This allows quantum computers to attack problems in completely different ways to conventional computers and theoretically they can crack them much faster and without the sort of scaling barriers met by conventional computers. However, this doesn't in itself solve the problem of encryption.

The scale of quantum machines' memories ramps up quickly



It turns out quantum computers are error-prone. Their qubits are unstable and vulnerable to interference. Although an algorithm to achieve decryption using quantum technology does exist, it would need thousands of perfect fault-tolerant, error-free qubits, and perhaps millions of today's noisy error-prone ones.

'If you use a large enough number, it is effectively impossible for even the largest conventional super-computers to derive its prime factors.'

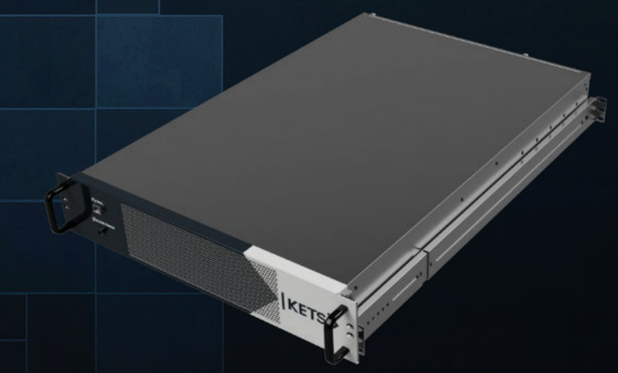
In 2001 a group at IBM 'cracked' 15 = 3 x 5 using a 7 Qubit machine and a quantum algorithm[5,6]. Underwhelming, but important baby steps. Later (2017)[7] Zapata Quantum Computing managed to deduce that: 1,099,551,473,989 = 1,048,589 x 1,048,601. This is a touch more impressive, since the start number has 41 bits, but well short of decrypting an RSA key and well within the powers of a conventional computer to solve in a millisecond.

So, quantum computers currently are less good at hacking encryption than conventional super-computers. However, if technical issues like error correction and stability could be overcome then theoretically the quantum approach should leap ahead due to superior scalability.

If these technical challenges might temporarily encourage a sense of security, then it is worth reflecting that criminal entities (and some governments) are likely already warehousing encrypted information in anticipation of Q-day. In a sense the first hackable 2048-bit encrypted communication has already been sent.

Quantum encryption

If you find the pace of advancements in decryption alarming, then there is some good news. Quantum physics can also be harnessed to improve encryption techniques. Rather than relying on computational complexity for encryption there are alternatives. One example has been developed by Kets[8], a UK based company.

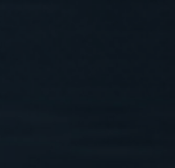


Kets have developed Quantum Key Distribution (QKD) which sends and receives cryptographic keys. If the encrypted message is intercepted, then the act of interception corrupts the quantum state of the key and so the recipient knows the transaction is unsafe and can abort it. This approach uses an immutable law of quantum physics, which is that to measure the quantum state of a quantum system you need to interact with it and in doing so the superposition collapses.

Along with other innovations QKD gives a very real hope of developing widespread quantum encryption for use within a safer quantum internet of the future.

Quantonation

Kets are supported in part by Quantonation who provide financing and development advice to a range of companies, some start-ups, others more mature, in the field of quantum physics. Through investment in Quantonation, PL Re gains broad insights into the newly emerging quantum 'ecosystem'. As well as quantum computing and cryptography, applications extend to areas like machine learning / AI and financial modelling. Further, as previously mentioned, there are numerous medical applications ranging from enhanced drug design to sub-cellular level resolution quantum sensing techniques to improve diagnostics. All these fields are highly relevant to the future of life and health insurance.



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It's a dog's (long) life

Large dogs live shorter lives than smaller ones. While small breeds typically live at least twelve years, and often longer, a Great Dane or a Newfoundland breed will very often die from natural causes before its eighth birthday. Now, a US biotechnology firm, Loyal[1], has convinced the FDA – the US' drug regulator for humans and animals – that a drug to correct this gap has a reasonable chance of success.

Typically larger animals live longer. However, the difference between sizes of dog breeds is the result of many decades of selective breeding and is not natural. Scientists have found that large dogs have high levels of a hormone called IGF-1. This hormone is implicated in short lifespans, so researchers at Loyal devised a drug to lower IGF-1. Achieving even pre-approval from the FDA required a paradigm shift for the regulator because they typically measure drugs' activity against a known disease. Here, the aim is simply to stop a dog ageing so fast. There is no 'disease' to treat.

So far, the drug has been tested to ensure safety, but not for its true effect on longevity. Researchers have scheduled trials for 2024-25 to test if their theory works, and the recent FDA authorisation allows these to proceed. Implications for humans would be indirect but still potentially significant as links that have been found between IGF-1 and human ageing. A recent study[2] compared IGF-1 levels with the morbidity and mortality data of almost 450,000 adults in the UK Biobank. They found that higher levels of the hormone in older adults were associated with increased incidence of death and diseases such as Alzheimer's, whilst in younger adults high IGF-1 levels appeared to correlate with lower health risks overall.

'higher levels of the hormone in older adults were associated with increased incidence of death and diseases such as Alzheimer's'

In all likelihood we don't have any one hormone that makes us age and so treating human longevity would be more complex. However, regulatory approval of even the theory that ageing can be treated medically, marks an exciting milestone in attempts to extend human lifespan.

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