

# Notable advances 2022

This year saw breakthroughs in several fields, spurred by research in basic science and technology. Here is our selection of critical developments that moved medicine forward in 2022.

### Cancer therapy

#### RET inhibitors go tumor-agnostic

Pralsetinib and selpercatinib are selective inhibitors of the receptor tyrosine kinase RET – which is abnormally activated by *RET* gene fusions in certain cancers. These inhibitors were originally approved for patients with *RET* fusion-positive lung and thyroid cancers, but *RET* fusion also occurs in a range of other solid tumors (albeit less frequently).

In August, results of the ARROW study were published, followed closely by LIBRETTO-001 – two phase 1/2 studies that evaluated pralsetinib and selpercatinib, respectively, for tumor-agnostic use in patients with advanced *RET*-altered solid tumors. Although neither trial had a comparator arm, both reported clinically meaningful response rates and survival outcomes, with toxicity profiles as expected – which led to tumor-agnostic approvals for both agents.

**Original references:** <https://doi.org/10.1038/s41591-022-01931-y>; [https://doi.org/10.1016/S1470-2045\(22\)00541-1](https://doi.org/10.1016/S1470-2045(22)00541-1)

### Cardiovascular disease

#### A Mediterranean diet is good for the heart

In recent decades, both a low-fat diet and a Mediterranean diet have been shown to help prevent cardiovascular events. The PREDIMED study supported the recommendation of a Mediterranean diet for primary prevention, but clinical evidence of its role in secondary prevention has been lacking.

This year saw the long-awaited readout of the randomized CORDIOPREV study, which compared the efficacy of a low-fat diet versus that of a Mediterranean diet for the prevention of recurrent cardiovascular events. About 1,000 people with established coronary heart disease were enrolled and followed up for 7 years, longer than any other study in this setting. The results suggested that both diets may be beneficial, but the Mediterranean diet was significantly better at preventing recurrent cardiovascular events, especially in men – in support of the recommendation of a Mediterranean diet for secondary prevention.

**Original reference:** [https://doi.org/10.1016/S0140-6736\(22\)00122-2](https://doi.org/10.1016/S0140-6736(22)00122-2)

### Infectious disease

#### Tackling the burden of RSV

Respiratory syncytial virus (RSV) is a major cause of hospitalization and death in older adults, young children and infants worldwide.

One approach to protecting infants is the direct administration of monoclonal antibodies. Nirsevimab is a long-acting antibody that prevents the entry of RSV into cells; in March, a phase 3 study showed that it is 75% effective at protecting healthy infants born at or near full term from RSV infection.

Another approach involves vaccinating pregnant women to help protect infants after birth; in a phase 2 study, a protein-based vaccine elicited in vaccinated women neutralizing antibody responses that transferred effectively across the placenta, and a post-hoc analysis provided early evidence of protection in infants. Another study evaluated the same vaccine in healthy adults (18–50 years of age) using a human challenge approach; it protected them against symptomatic RSV infection and viral shedding and is now being evaluated in older adults.

**Original references:** <https://doi.org/10.1056/NEJMoa2110275>; <https://doi.org/10.1056/NEJMoa2106062>; <https://doi.org/10.1056/NEJMoa2116154>

### Technology

#### From ‘wearables’ to ‘invisibles’

A team of researchers has developed a non-invasive, artificial intelligence-enabled approach to the detection and monitoring

of Parkinson’s disease (PD) – using a stationary, touch-free radio device to analyze signals bounced off a person’s body. In one study, this approach was used to monitor nocturnal breathing, which enabled detection and assessment of PD. This addresses a major unmet need, as current diagnostic methods are suboptimal – which often results in late-stage diagnoses.

In a separate study, radio devices were used to monitor gait and movement in people with PD during normal activities at home. The approach was tested in 50 people for 1 year and performed better than the ‘gold standard’ clinical assessments. Crucially, it was able to monitor fluctuations in response to treatments, which could prove useful in future drug trials.

**Original references:** <https://doi.org/10.1038/s41591-022-01932-x>; <https://doi.org/10.1126/scitranslmed.adc9669>

### Technology

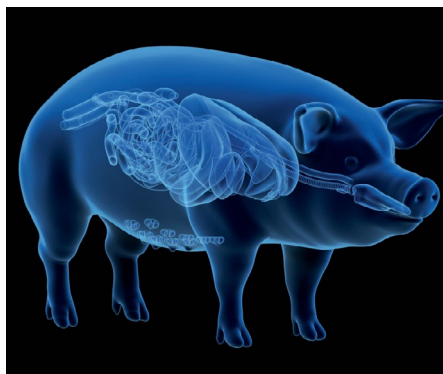
#### Transforming transplant medicine

Xenotransplantation research has been ongoing for decades, but progress has been slow. This year, a brief but pivotal study saw pig kidneys (from genetically modified animals) transplanted for just over 2 days into two brain-dead humans, where they functioned well and avoided rejection.

Soon after, a 57-year-old man with severe heart failure (and no remaining treatment options) was given a transplanted heart from a genetically modified pig. The heart seemed to function normally for 49 days – at which point complications occurred. The patient passed away on day 60 after transplantation, but the procedure marks a watershed moment that will guide future research.

In yet another key development, researchers developed a whole-body reperfusion system that partially revived pig organs up to an hour after death. This has implications for human transplant medicine, as enhanced preservation could lead to better quality and availability of transplant organs.

**Original references:** <https://doi.org/10.1056/NEJMoa2120238>; <https://doi.org/10.1056/NEJMoa2201422>; <https://doi.org/10.1038/s41586-022-05016-1>



## Neurological disease

### Mounting evidence for EBV links to multiple sclerosis

Most people infected with Epstein–Barr virus (EBV) do not develop multiple sclerosis (MS). Nonetheless, EBV infection has long been implicated as a potential contributor to MS development – although a direct causal link has remained elusive.

In January, two new studies provided the strongest evidence so far of an epidemiological link and a mechanistic link, respectively, between EBV and MS. A longitudinal study of over 10 million US military personnel over about 20 years showed that EBV infection increased the risk of MS by 32-fold. A second study offered a mechanistic link, by way of a phenomenon known as ‘molecular mimicry’ – whereby antibodies against EBV protein EBNA1 show strong cross-reactivity with GlialCAM, a host central nervous system protein. These findings will have implications for future research and therapeutic strategies for MS.

**Original references:** <https://doi.org/10.1126/science.abj8222>; <https://doi.org/10.1038/s41586-022-04432-7>

## Mental health

### Putting mental health center stage

The COVID-19 pandemic has taken a huge toll on population-wide mental health, and has



revealed the shortcomings in mental health care systems globally.

In June, the World Health Organization released its World Mental Health Report, which represents the largest review of world mental health since the turn of the century. The report argues for the generation of resilient mental health care systems rooted in communities and the transformation of environments that influence mental health – providing a guide for governments and policymakers worldwide.

**Original reference:** <https://go.nature.com/3UGG30t>

## Cell therapy

### CAR T cells beyond cancer

Chimeric antigen receptor (CAR) T cells have been used with great success in the treatment of certain cancers – which laid the foundation for the development of CAR T cells for the treatment of other diseases.

Early this year, researchers used mouse models to show that CAR T cells can be used to treat cardiac fibrosis by eliminating activated fibroblasts, key mediators of the condition. By encapsulating the T cell-reprogramming materials in injectable nanoparticles, they were able to generate transient CAR T cells in vivo (rather than in the lab).

Then, in September, another group showed that a single infusion of ex vivo-generated CAR T cells directed against the B cell surface antigen CD19 reduced disease activity in five patients with systemic lupus erythematosus. The treatment led to extensive depletion of B cells, the main source of pathogenic anti-nuclear antibodies. Although very preliminary, the data suggest a promising new strategy for the treatment of autoimmune disease.

**Original references:** <https://doi.org/10.1126/science.abm0594>; <https://doi.org/10.1038/s41591-022-02017-5>

## Metabolism

### Obesity treatments gather momentum

Last year, clinical trials of semaglutide provided the first meaningful progress in the pharmacological treatment of obesity in many years, marking a new era in this field. Then in July of this year, a phase 3 trial of tirzepatide showed substantial and sustained reductions in body weight in people with obesity.

Over 2,500 adults (most of whom had a body-mass index of 30 or more) were enrolled in the international trial, and most of those who received tirzepatide had a reduction of at least 5% in body weight. In the higher-dose groups, over half the participants had a reduction in body weight of 20% or more; there were also improvements in cardiovascular and metabolic risk factors.

**Original reference:** <https://doi.org/10.1056/NEJMoa2206038>

## Infectious disease

### The next generation of COVID-19 vaccines

One advantage of mRNA vaccines is the ability to modify them rapidly and efficiently to target new variants. This year, Moderna developed and tested two updated, bivalent vaccines that target the Beta variant and Omicron variant, respectively, of the coronavirus SARS-CoV-2 (as well as the ancestral strains).

Data from two phase 2/3 studies indicated that booster doses of the updated vaccines generated better neutralizing antibody responses than did boosters with the original mRNA-1273 vaccine. Further research is needed to definitively evaluate efficacy and real-world effectiveness – but these studies suggest that updating the vaccines is beneficial as the virus evolves.

**Original references:** <https://doi.org/10.1038/s41591-022-02031-7>; <https://doi.org/10.1056/NEJMoa2208343>