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Eleven clinical trials that will shape medicine in 2025

Nature Medicine asks leading researchers to name their top clinical trial for 2025, from gene therapies for prion disease and sickle-cell disease to digital tools for cancer and mental health.

2024's big winners were the pharmaceutical companies behind the blockbuster weight-loss drugs semaglutide (Novo Nordisk's Wegovy) and tirzepatide (Eli Lilly's Zepbound). With other biotechnology and pharmaceutical companies now rushing to enter the weight-loss market, obesity will surely be a priority for 2025. Against this fizz of excitement, it is difficult to predict what other discoveries will attract the biomedical industry's attention.

We asked 11 experts which trials in the coming year are likely to have an outsized impact on medicine (Table 1).

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Gene therapy for prion disease

Sonia Vallabh: I retrained from being a lawyer to do biomedical research after I discovered I was at risk for dying of genetic prion disease. Prion disease is not ultra-rare, since it kills 1 in 6,000 people, but it is rare. I helped establish the preclinical proof of concept that has led to a phase1/2 trial to evaluate the safety, tolerability and pharmacokinetics of intrathecally administered ION-717 in patients with prion disease.

ION-717 is an investigational antisense oligonucleotide developed by Ionis Pharmaceuticals and was designed to inhibit the production of prion protein. As of right now, there are 16 clinical trial sites for ION-717 around the world. This trial has enrolled really quickly because this is a very active community that will show up. I see my work as campaigning for earlier treatment across the spectrum of neurodegeneration, as the earlier you get there, the more you can do to preserve brain function. We may see the first data by late 2025.

Sonia Vallabh is a senior group leader at The Broad Institute of MIT and Harvard, Cambridge, MA, USA.

Precision nutrition in a diverse cohort

Leanne Redman: People experience a large variation in health benefits in response to foods and diets. Traditional approaches to dietary intervention studies (comparing diet A to diet B or C) inform US dietary guidelines, despite the fact that such trials typically study the effects of diet in narrow groups of the population (without the full range of adult age, gender groups and socioeconomic classes). Basing guidelines on the efficacy of a diet in an entire group ignores people who, for whatever reason, had a smaller or greater benefit of that diet on health outcomes. The US National Institutes of Health-funded Nutrition for Precision Health project (which is partnered with the All of Us research program) seeks to explore the factors that explain why people respond differently to the same foods.

The project will study more than 8,000 adults, with few exclusion criteria, in the context of their usual medications and health conditions, which is intended to expand the reach of current nutritional guidelines. After mapping how a person's usual diet, genetics, microbiome, lifestyle habits and medical and health history influence their response to a meal test, scientists will use this information to predict how they will respond to three types of eating patterns after 2 weeks. As the three eating patterns differ in their amounts and types of carbohydrates, fats, proteins, fruits and vegetables, fiber, nuts, fish, dairy and processed and unprocessed foods, for example, the scientists will rely on advanced statistical models and machine learning to first identify the factors or individual-level features with the greatest relevance to a dietary response, and then to predict those foods and eating patterns likely to foster benefit for people. All data collection will be completed by the summer of 2026. We expect papers providing a first look at the data in early 2025.

Leanne Redman is a physiologist at the Pennington Biomedical Research Center of the Louisiana State University System, Baton Rouge, LA, USA.

CBD to prevent psychosis

Philip McGuire: I lead a study called Stratification and Treatment in Early Psychosis (STEP) that uses a cannabidiol (CBD) product (a constituent of the cannabis plant) that has already been approved for the treatment of severe epilepsy. STEP includes three clinical trials

Table 1 | Clinical trials to watch in 2025

Treatment	Organization	Description	Phase	Indication
ION-717	Ionis Pharmaceuticals	Antisense oligonucleotide, to inhibit the production of prion protein	Phase 1/2	Prion disease
Dietary intervention	US National Institutes of Health	Participants receive one of three different diets for 2 weeks	Randomized trial	Nutrition
Cannabidiol	University of Oxford and Jazz Pharmaceuticals	CBD treatment in people at risk of psychosis	Randomized trial	Psychosis
BEAM-101	Beam Therapeutics	Safety and efficacy of autologous base-edited CD34$^+$ HSCs and progenitor cells	Phase 1/2	Sickle-cell disease
Cool roofs	Heidelberg Institute of Global Health, Harvard T.H. Chan School of Public Health, Africa Health Research Institute and CRSN Burkina Faso	Health, environmental and economic outcomes in households in rural Burkina Faso with and without cool roofs	Randomized trial	Heat stress
Lutetium-177 vipivotide tetraxetan (Pluvicto)	Novartis	Radioligand targeted to PSMA-positive cancer cells	Phase 3	Minimally treated hormone-sensitive prostate cancer
Artificial intelligence chatbot	International Agency for Research on Cancer	Multi-language artificial intelligence chatbot decision aid for HPV testing	Randomized trial	Cervical cancer
mSELY	NYU Langone Health and University of Nairobi	Mobile health toolkit for adolescents and parents	Randomized trial	Mental health
Precision cancer screening	European Union	Polygenic risk score combined with other risk factors such as family history and breast density	Randomized trial	Breast cancer
Home gardening with nutrition and health counseling	KEMRI, CRSN Burkina Faso and Heidelberg Institute of Global Health	Height-for-age score of children in Kenya and Burkina Faso who received the intervention or not	Randomized trial	Malnutrition
GuessWhat	Stanford University	Educational game to recognize and understand emotion	Randomized trial	Autism

and involves 30 sites in 11 countries. The trials will assess around 1,000 participants with psychosis, before and after treatment with CBD, using a range of neuroimaging techniques such as magnetic resonance imaging and spectroscopy to clarify how CBD acts. The study also uses clinical, digital, cognitive, neuroimaging and blood measures to try to identify biomarkers that can be used to predict treatment success.

Each trial includes participants at a different stage of psychosis. The first involves people who are at a high risk of psychotic disorders and aims to test if CBD can stop them from progressing to full-blown illness. The second involves people who have recently developed psychosis, and the third involves people who are treatment resistant. In 2025, we will get the first results on the efficacy, safety and tolerability of CBD in psychosis. We also hope that this research will clarify whether we can prevent psychiatric disorders using CBD.

Philip McGuire is a professor of psychiatry in the Department of Psychiatry at the University of Oxford and an associate director of research and development at Oxford Health NHS Foundation Trust, Oxford, UK.

Base editing for sickle-cell disease

David Liu: Base editing has been successful in both ex vivo and in vivo clinical trials, so the community is anticipating the results of the first base-editing clinical trial that targets hematopoietic stem cells (HSCs). These cells are critical for treating blood disease, since all of our blood cells, including immune cells, are ultimately derived from HSCs.

Several years ago, Beam Therapeutics launched the BEACON trial, an open-label, single-arm, multicenter, phase 1/2 study evaluating the safety and efficacy of autologous base-edited CD34$^+$ HSCs and progenitor cells (BEAM-101) in patients with severe sickle-cell disease. The HSCs are edited ex vivo with base edits that mimic single-nucleotide polymorphisms seen in people with hereditary persistence of fetal hemoglobin. These edits should increase levels of fetal hemoglobin and improve symptoms.

The death of a patient in this, or any, clinical trial is very sad news. Busulfan is a drug used to create space in the bone marrow prior to transplantation and is part of the current standard of care for sickle-cell disease. It seems the patient who died in this trial died of lung injury, a known side effect of bulsulfan, rather than from a consequence of base editing.

It is never wise to get ahead of the results of a clinical trial, but I am hopeful that clinical base editing will work in HSCs, given that there are three other base-editing clinical trials that have already yielded positive clinical outcomes.

David Liu is director of the Merkin Institute of Transformative Technologies in Healthcare, vice chair of the faculty at the Broad Institute and a professor of natural sciences at Harvard University, Cambridge, MA, USA.

Cool roofs to prevent heat-related disease

Aditi Bunker: Our group conducts pragmatic, real-life trials around the world to test various climate-change-adaptation interventions, with a focus on improving population health and environmental and economic outcomes. One of the interventions we are currently studying is the use of 'cool roofs', which are highly reflective roof coatings that help reduce indoor temperatures by reflecting solar radiation and preventing heat transfer

into buildings. These roofs are easy to implement and affordable and have immediate benefits, which makes them ideal for vulnerable communities affected by extreme heat, such as those in regions like West Africa, where heat exposure is causing death and illness. We are working with the local community and employing and training local people to implement cool roofs for community members.

Our trial in Burkina Faso, in West Africa, included 1,200 participants from 600 households in 25 villages; it recently ended, and we are analyzing the results. We randomly assigned the households to receive the cool roof or not, and tracked outcomes over 2 years, focusing on heart rate as the primary marker, owing to its sensitivity to heat exposure. Secondary outcomes we measured included blood pressure, body temperature, blood glucose, dehydration and stress. We also explored mental health, sleep quality and even gender-based violence, as heat has wide-ranging effects on people's wellbeing.

The goal is to determine if there is a causal link between the cool-roof intervention and improvements in human health. By using both objective measures (such as biomarker data) and subjective measures of participants' reported experiences, we aim to capture the full picture of how heat impacts health and how well interventions such as this can mitigate those effects. This trial will help us determine whether these interventions should be scaled up locally. We believe this work has the potential to improve the lives of people in some of the world's most heat-affected regions.

Aditi Bunker is an epidemiologist and coordinates the Climate Change and Health Intervention Working Group at Heidelberg University, Heidelberg, Germany.

Radiopharmaceuticals for prostate cancer

Oliver Sartor: The idea of using lutetium-177 as a therapy for cells that express prostate-specific membrane antigen (PSMA) dates back over 15 years, but true progress in this field has been more recent. Things really started moving after Novartis acquired the biopharmaceutical company Endocyte, which focused on radioligand therapies. With the US Food and Drug Administration (FDA) approval of Lu177-PSMA-617 therapy (marketed as Pluvicto) for the treatment of adult patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with inhibitors of the androgen receptor pathway and taxane-based chemotherapy, there is considerable support for moving lutetium-177 therapy earlier in the treatment paradigm for prostate cancer. Several trials are exploring this, such as PSMAfore, which recruited chemotherapy-naive patients with mCRPC; I presented this trial at the 2023 European Society for Medical Oncology Congress. It is currently before the FDA, with a decision expected in 2025. If it is approved, this would move Pluvicto into an earlier treatment space, instead of just being used after chemotherapy, as it was in the VISION trial for which Pluvicto got FDA approval.

The PSMAddition trial, designed by myself and oncologist Scott Tagawa of Cornell University, compares treatment with Lu177-PSMA-617 plus standard of care versus standard of care alone in 1,126 patients with treatment-naive or minimally treated PSMA-positive metastatic hormone-sensitive prostate cancer (in which the cancer has spread beyond the prostate gland but can still be treated with hormone therapy). Hormone therapy may alter the expression and radiosensitivity of PSMA, which could affect the efficacy of Lu177-PSMA-617. The primary endpoint is radiographic progression-free survival. The main impact will be if Lu177-PSMA-617 gets FDA approval for the treatment of hormone-sensitive patients. This could be a potential game-changer for hundreds of thousands of patients with prostate cancer globally. However, the price of Pluvicto is high, which could limit global availability.

Cannabidiol, a constituent of the cannabis plant, is being tested to prevent psychosis.

Oliver Sartor is a medical oncologist in the Division of Medical Oncology of the Department of Oncology at the Mayo Clinic, Rochester, MN, USA.

Chatbot to aid cervical cancer screening

Farida Selmouni: France has included in their nationwide cervical screening program self-sampling of human papilloma virus (HPV) for women 30–65 years of age who have not been screened at a clinic, but studies showed that less than 20% of these women participated. To address this, my team has developed web-based tools aimed at encouraging women, particularly those with lower education levels and from disadvantaged areas, to test themselves at home. It is very important for a screening program to have a high participation rate, in order to reduce cervical cancer incidence and mortality.

Our multi-language decision aid is designed for women with lower education and is accessible via an artificial intelligence-based chatbot delivered through multiple smartphone channels. We conducted qualitative studies with women to assess their knowledge and identify their needs in cervical cancer and smartphone usage, and with healthcare professionals to gather recommendations for developing an educational tool. On the basis of this research, a first prototype of the chatbot was refined and presented to study participants and healthcare professionals to get their feedback for improvements.

The results indicated that women were happy with this chatbot and found that it

offers quick and accurate answers to their questions. A randomized controlled trial, now underway and expected to conclude in 2025, aims to assess the chatbot's efficacy in improving women's participation in the HPV-detection-based cervical-cancer-screening care pathway.

Farida Selmouni is a scientist at the International Agency for Research on Cancer, Lyon, France.

Mobile toolkit for mental health

Keng-Yen Huang: Adolescents in low- and-middle-income countries such as Kenya face developmental, sexual and reproductive health challenges, including exposure to multidimensional violence. The mobile health toolkit for screening and empowering the lives of youth (mSELY) study will address the burden of adolescent mental health disorders in Kenya by studying the effectiveness of digital toolkits for adolescents and their parents.

The version for adolescents aims to help them self-evaluate and manage their mental health needs while connecting with adolescent peers. The version for parents is designed to help them learn mental health strategies and provide resources for better parenting. The study will help elucidate the effectiveness of these digital interventions in a randomized control trial with numerous community-based organizations in Kenya.

We are probing the root causes that lead to behavioral violence, much of which is due to a lack of self-confidence and lack of problem-solving skills. In order to help the participants understand their own personal development, we return the data to them so they are more aware of the various areas that they need to pay attention to. We also hope that the digital tool for parents will reinforce the fact that parents need to have open communication with their children.

Keng-Yen Huang is an associate professor of population health and child and adolescent psychiatry at NYU School of Medicine, New York, NY, USA.

Personalized breast cancer screening

Suzette Delaloge: The My Personal Breast Cancer Screening (MyPeBS) trial addresses a major gap in breast-cancer screening by shifting from a one-size-fits-all approach to a more personalized, risk-based strategy. Currently, screening is based mainly on age, typically starting at 50 years of age in most countries, but this approach has limitations. Breast-cancer screening has reduced mortality by only about 20%, with high rates of overdiagnosis and unnecessary treatment.

Each woman has her own individual risk of developing breast cancer, depending on many factors, such as genetics, lifestyle or hormonal exposure. A more personalized approach could adjust the age of entry into the screening program and determine whether a woman needs more- or less-frequent screenings. For women at high risk, more-intensive risk-reduction measures could be introduced, whereas women at low risk might benefit from fewer mammograms, reducing the harm from unnecessary tests.

Our trial is the largest global study of its kind, to our knowledge, conducted in six countries, with over 53,000 women. The randomized controlled study will compare two groups of women: a group that will follow the current standard breast screening; and a group that will follow a personalized risk-based screening strategy. Half of the participants will undergo DNA testing via saliva samples. We will use a polygenic risk score derived from the Breast Cancer Screening Consortium, combined with other risk factors, such as family history and breast density. This approach allows us to assess risk with high precision, although we are mindful of the challenges, particularly in ethnic diversity and how well these tools perform across different populations. The primary endpoint of the trial is the incidence of breast cancer at stage 2 or higher at 4 years.

If the trial shows that risk-based screening is either as good as or superior to standard screening, it could revolutionize breast cancer prevention. We expect that this approach could improve outcomes for women at high risk while also minimizing unnecessary harm for those at lower risk.

Suzette Delaloge is a breast cancer specialist and an associate professor of medical oncology in the Department of Cancer Medicine at Institut Gustave Roussy, Villejuif, France.

Home gardening for climate-related malnutrition

Ina Danquah: ALIMUS is a multi-center, cluster-randomized controlled trial conducted in southeastern Kenya and rural Burkina Faso to address the impact of climate change on nutrition (I. Mank et al. *Trials* **23**, 449; 2022), particularly in populations reliant on staple crops such as maize, wheat and sorghum. These crops are increasingly affected by reduced levels of nutrients, such as zinc, iron, selenium and protein, due to climate change. This nutrient reduction poses a particular threat to children under 5 years of age and women of childbearing age.

The ALIMUS project focuses on home gardening combined with nutrition and health counseling. The goal is to increase dietary diversity to offset the nutrient loss from staple crops. Households in both countries were encouraged to grow vegetables and fruits close to their homes. These gardens were designed with the input of local people, who expressed preferences for specific crops, such as sweet potatoes and fast-growing fruits. Notably, the gardeners use only organic methods, avoiding chemical fertilizers and pesticides.

The trial began in 2020 but was delayed by the COVID-19 pandemic, with baseline data collected in 2021. Now in its final stages, the project involves 300 intervention households and 300 control households in each country. The primary outcome being measured is the height-for-age score of children, as it is a long-term indicator of nutritional status. We considered other measures, such as weight-for-height, but concluded that height-for-age would provide the most reliable data on the impact of the intervention on overall nutrition.

Results are expected in mid-2025, and we hope that the findings will inform future strategies for addressing malnutrition, particularly under climate-change scenarios. If successful, the model could be applied more broadly in regions facing similar climate-related challenges. The project also aims to integrate its methods into the routine practices of local health and agricultural ministries, ensuring sustainability beyond the trial.

Ina Danquah is a nutrition scientist specialized in epidemiology at the University of Bonn, Bonn, Germany.

Learning games for children with autism

Dennis P. Wall: Approximately 17% of minors in the USA at 3–17 years of age have a diagnosis of developmental or psychiatric conditions. The true prevalence is probably higher because of underdiagnosis in rural areas and for minority populations.

Children with autism struggle with social communication and restricted interests, but this struggle can be overcome by early intervention. We have designed a mobile game that is widely accessible to a diverse audience

and is effective at providing treatments that increase social eye contact, motivation and attention while decreasing restricted interests and anxieties.

The game forms a powerful social synchrony between the caregiver and child and has promise for reducing parental stress while ablating autism symptoms that negatively impact the child's social integration. Importantly, it gathers data during game play that can track progress, train artificial intelligence tools designed to understand autism signals, and personalize the experience for greater engagement and impact. To test the game, we have enrolled children with autism who are 2–8 years of age in a clinical trial.

Dennis P. Wall is a professor of pediatrics and biomedical data science at Stanford University School of Medicine, Stanford, CA, USA.

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