This December, Webster and Healey published a review in Nature Medicine regarding the clinical trials that will shape medicine in 2025. Please read through the excerpts from their article provided below, choose any **two (2)** topics to your favor, and elaborate the followings for each of them:

a. A graphic summary of the clinical trail. Use freely scheme plots, time lines, drawings etc. at your choice. (40%)
b. Your comment on the science behind this trial. (20%)
c. Your critique on the significance of this trial. (20%)
d. If the trial is to be conducted in Taiwan, Japan and France, what are some challenges you may expect to happen? (20%)

1. 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.

2. 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.

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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.

3. 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.

4. 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.

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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.

5. 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.

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