The Human Body & Human Health

Figures current as of October 2026

How the body works, how it fails, and what the evidence says about keeping it working: the cell and the genome, metabolism, the heart and lungs, the brain, the mind, hormones, immunity, movement, reproduction and aging, the causes of death, cancer, medicine's toolkit, the evidence on diet, exercise, and sleep, the systems that pay for care, and the new weight-loss drugs that are changing all of it.

MODULE 1 — Foundations

Goal: Set the body's numbers, the measures of health, and the vocabulary.

Some 30 to 37 trillion cells, 11 systems, 206 bones; life expectancy at 73 for the world, 79 for the United States, and 84 for Japan; healthspan against lifespan; homeostasis, metabolism, inflammation, and the difference between a risk and a cause.

MODULE 2 — The Cell and the Genome

Goal: Understand the unit everything else is built from.

DNA (deoxyribonucleic acid) to protein, the cell's economy, division and repair, epigenetics, what the genome does and does not determine, the first stem-cell therapies, and aging at the cellular level: senescence, telomeres, and the hallmarks.

MODULE 3 — Energy, Metabolism, and the Gut

Goal: Follow food from plate to cell.

Digestion, the macronutrients, insulin and blood sugar, the liver and kidneys as the chemical plant, the microbiome; obesity and type 2 diabetes as the metabolic disease of the era, and the glucagon-like peptide-1 (GLP-1) drugs; a day's energy budget, worked.

MODULE 4 — Heart, Blood, and Lungs

Goal: Read the world's first killer and its arithmetic.

Circulation, blood pressure, cholesterol and the lipid argument, respiration; cardiovascular disease, statins, smoking, and air pollution; the 2025 blood-pressure guideline, the risk-factor arithmetic, and the lipoprotein(a) trial that failed in 2026.

MODULE 5 — The Brain and Nervous System

Goal: Understand the organ that understands.

Neurons and networks, pain and the senses, sleep and its evidence, stroke as a race, dementia, the Alzheimer's antibodies and the dispute over them, and the new blood tests.

MODULE 6 — Mental Health

Goal: Read the disorders, the treatments, and the gap.

The measurement problem, the disorders in one table, what the trials show helps, the adolescent decline and the argument over screens, the returning drugs, addiction and the overdose turn, and suicide.

MODULE 7 — Hormones

Goal: Map the body's messaging system.

Thyroid, cortisol, insulin, the sex hormones; puberty, menopause, and testosterone; the 2025 reversal on menopause warnings; GLP-1 as physiology before it was a drug.

MODULE 8 — The Immune System

Goal: Understand the defense and its misfires.

Innate and adaptive immunity, how vaccines work, allergy and autoimmunity, infection and antibiotic resistance, what the COVID-19 (coronavirus disease 2019) pandemic taught and left, and the fight over the American vaccine schedule.

MODULE 9 — Muscles, Bones, and Movement

Goal: Follow what exercise does to every system.

Exercise physiology, strength against endurance, bone density, falls as the killer of the old, and back pain; the dose-response of exercise, worked.

MODULE 10 — Reproduction, Development, and Aging

Goal: Trace the body across a life.

Fertility and its decline, pregnancy, childhood and adolescence, the aging trajectory of each system, and the longevity science, from rapamycin to the first human reprogramming trial, separated from the longevity industry.

MODULE 11 — How the Body Fails

Goal: Read the causes of death and disability.

The causes of death, world and US, in one table; how death arrives; the chronic burden; why the leading causes changed in a century.

MODULE 12 — Cancer

Goal: Understand the second cause of death and its treatment revolution.

Two hundred diseases and one mechanism; the 2026 numbers and the two trends; screening's arithmetic by cancer and the first multi-cancer blood-test trial; surgery to immunotherapy, engineered immune cells, and personalized vaccines.

MODULE 13 — Medicine's Toolkit

Goal: Understand how medicine knows what it knows.

Diagnosis, imaging, drugs, surgery, and the evidence hierarchy from anecdote to randomized trial; artificial intelligence (AI) in diagnosis; the arithmetic of a positive test, worked.

MODULE 14 — What the Evidence Says

Goal: Grade the claims by their evidence.

Diet, exercise, sleep, alcohol, smoking, weight, stress, and supplements, each graded settled, probable, contested, or marketing; the trials behind the grades by name; the 2026 dietary guidelines and the argument over them; how to read a health claim.

MODULE 15 — Health Systems and the Cost of Care

Goal: Read what the money buys.

What the US buys for 18% of gross domestic product (GDP) and others for 10-12%; insurance, hospitals, and drug prices; the GLP-1 bill; the argument over prices and innovation; the countries gaining life expectancy and the ones that lost it.

MODULE 16 — Where Things Stand, and What to Watch

Goal: Assemble the picture and name what moves next.

The course's argument on a page, the five contradictions its evidence leaves open, the dated watch list from the GLP-1 era to the next pandemic, and the last word.

A note on evidence and on what this course is. Health is the subject where the weakest evidence attracts the loudest claims. So the course grades what it reports: settled science, contested science, and marketing are labeled as such, and Module 14 does this claim by claim. Where the evidence itself is in dispute, the course makes each side's case as its advocates make it before giving its own reading. The course explains how the body works and what the population evidence shows. It is education, not medical advice. It describes what studies find on average, and it cannot know any reader's history, medications, or risks. Decisions about a particular body belong with the people who can examine it.

Module 1 — Foundations

The Body in Numbers, the Measures of Health, and the Vocabulary

Recommended Reading / Reference

Book: Bill Bryson, *The Body: A Guide for Occupants*

Reference: The World Health Organization (WHO) *World Health Statistics* (annual) and the National Center for Health Statistics of the US Centers for Disease Control and Prevention (CDC), the sources for the life-expectancy and mortality figures throughout the course

1a. What a Body Is

A human body is some 30 trillion to 37 trillion human cells, depending on its size and on whose count is used, with bacteria living alongside them, most of them in the gut (Module 3). The cells come in about 200 types and form the organs and the eleven systems of 1e, and the whole is held near 37 degrees Celsius, with a fever starting at 38. It is built from instructions in its genes (Module 2), a full copy of which sits in nearly every cell that has a nucleus.

On the physiologist's account, the body is a machine for keeping its interior constant against a changing exterior. Temperature, blood sugar, acidity, salt, oxygen, and pressure are each held within a narrow range by feedback loops that run without instruction, and much of disease is the failure of one of those loops, or an attack on one.

The body is also a history. Its design was fixed in a world of scarcity, infection, and early death, and its instincts were adaptations to that world: store fat, crave salt and sugar, rest when possible, and inflame at any threat. In a world of abundance, the same instincts cause the diseases of abundance. The course reads the body system by system and then asks how it fails, how medicine knows what it knows, and what the evidence actually supports.

1b. The Numbers

Measure	Figure
Cells by type	Red blood cells are about four-fifths of the human cells by count
The genome	Fewer protein-coding genes than a grape; 98.8% identical to a chimpanzee's genome, and 99.9% identical between any two people
Organs	About 78; the skin is the largest, at about 2 square meters, and the liver the largest internal one
Skeleton and muscle	206 bones, from about 270 at birth; muscle is 30-40% of body weight
Heart	About 2.5 billion beats in a lifetime
Brain	About 1.4 kilograms, 2% of body weight
Turnover	The gut lining is replaced in days, skin in weeks, and red cells in four months; neurons and heart muscle mostly not

Standard physiology references; the cell counts of 1a are from Sender, Fuchs, and Milo (2016) and Hatton and colleagues (2023).

1c. The Measures of Health

The summary measure of a population's health is life expectancy at birth, the years a newborn would live if the year's death rates held for a lifetime, and its story is the largest achievement in human history. Worldwide it rose from about 32 years in 1900 to about 73 today, and most of the gain came from clean water, sanitation, vaccines, food, and antibiotics, well before surgery and the drugs for chronic disease made much difference.

The differences within the present are the material of Module 15. Japan, Switzerland, and Spain stand at about 84 years and Britain and Germany at about 81, while the United States reached a record 79.0 in 2024 after falling to 76.4 in 2021 during the pandemic. China stands near 79 on its own figures and 78 on the United Nations' estimate, India at about 72, and the Central African Republic at about 58.

The measure the field increasingly prefers is healthy life expectancy, the years lived without serious disability. On the WHO's estimates for 2023, released in October 2026, it is about 72 years in Japan and 65 in the United States, a gap of seven to eight years that is wider than the one between their lifespans. That gap is the reason 'healthspan' has become the goal of the medicine this course describes.

Two other measures recur through the course, and Module 11 reads both: the cause-of-death table, and the disability-adjusted life year, which counts years lost to illness as well as years lost to death.

1d. Risks, Causes, and the Vocabulary of Evidence

- **A risk factor is not a cause** — smoking causes lung cancer, because the mechanism is known, the dose-response is steep, and removing the exposure removes most of the risk. Coffee is associated with lower mortality in observational studies, which may mean that coffee protects or that coffee drinkers differ in ways the studies cannot see. The distinction runs through Modules 13 and 14.
- **Relative and absolute risk** — 'doubles the risk' means nothing without the base rate, since doubling a one-in-a-million risk is trivial and doubling a one-in-ten risk is not. The course reports absolute numbers wherever the sources allow.
- **Homeostasis** — the feedback control of 1a, which holds each variable the way a thermostat holds a room's temperature.
- **Metabolism** — the sum of the chemical reactions that turn food into energy and tissue, and back again; how much it differs between people is taken up in Module 3.
- **Inflammation** — the immune system's response to injury or infection, which heals when it is acute and harms when it is chronic (Module 8).
- **Acute and chronic** — an acute disease arrives and resolves, as an infection or an injury does, while a chronic disease persists and is managed, as diabetes, heart disease, and depression are. The shift from the first kind to the second is the frame for Module 11.

1e. The Systems

System	What it does	Module
Integumentary (skin)	Barrier, temperature, sensation, vitamin D	1
Skeletal and muscular	Structure, movement, blood-cell production, mineral storage	9
Nervous	Sensation, control, thought; the brain, spinal cord, and nerves	5, 6
Endocrine	Hormonal signaling: thyroid, adrenal, pancreas, gonads, pituitary	7
Cardiovascular	Circulation of oxygen, nutrients, hormones, and waste	4
Respiratory	Gas exchange: oxygen in, carbon dioxide out	4
Digestive	Breaking down food, absorbing nutrients, and the microbiome	3
Urinary	Filtration and fluid and salt balance: the kidneys	3
Lymphatic and immune	Defense, fluid return, the lymph nodes and white cells	8
Reproductive	Eggs and sperm, sex hormones, pregnancy	10

Module 1 Key Points

Foundations

• The body is some 30-37 trillion cells in eleven systems, held steady by feedback loops whose failure underlies much of disease.

• Instincts built for scarcity — store fat, crave sugar, inflame at any threat — cause the diseases of abundance.

• Life expectancy rose from 32 years to 73 in a century, mostly from water, sanitation, vaccines, antibiotics, and food.

• Healthy life expectancy is about 72 in Japan and 65 in the United States, a wider gap than their lifespans show.

• A risk factor is not a cause, and 'doubles the risk' means nothing without the base rate.

Module 1 Quiz

Check Your Understanding

1. About how many human cells make up an adult body?

A) About 30-37 trillion
B) About 3 trillion
C) About 370 trillion cells
D) Roughly 37 billion in all

2. What does healthy life expectancy count?

A) Years lived before any diagnosis
B) Years lived without serious disability
C) Years lived with no hospital stay
D) The years a newborn would live if the year's death rates held for a lifetime

3. By count, what share of the body's human cells are red blood cells?

A) Roughly a quarter of them
B) About half, the rest mostly neurons
C) About four-fifths
D) Under a tenth, since most cells are in muscle, skin, and the lining of the gut

4. Why does 'doubles the risk' mean little on its own?

A) Because relative risks come only from observational studies
B) Because no risk can be measured in an individual
C) Because a doubling is within the margin of error of most studies
D) Because without the base rate, a doubling may be trivial or serious

5. What brought most of the gain in life expectancy since 1900?

A) Clean water, sanitation, vaccines, antibiotics, and food
B) Surgery and modern hospital care
C) Drugs for heart disease and cancer
D) Genetic screening and newer medicines

Module 2 — The Cell and the Genome

The Unit Everything Else Is Built From

Recommended Reading / Reference

Book: Siddhartha Mukherjee, *The Song of the Cell: An Exploration of Medicine and the New Human*

Reference: The public genomics resources of the National Human Genome Research Institute (genome.gov), part of the US National Institutes of Health (NIH), and the 2023 'Hallmarks of Aging' update in *Cell*, the reference for the aging biology in 2e

2a. The Cell's Economy

A cell is a chemical factory a few hundredths of a millimeter across, bounded by a membrane, with the DNA held in its nucleus. Its mitochondria burn glucose and fat with oxygen to make adenosine triphosphate (ATP), the energy currency every process spends, while ribosomes assemble proteins from the genetic instructions and a skeleton of filaments gives the cell its shape and lets it move. The membrane is studded with receptors that read the body's signals and with pumps that keep the inside different from the outside.

Proteins do nearly everything: they are the enzymes that run the reactions, the structures that hold the cell together, the receptors that receive hormones, the antibodies of the immune system, and the hemoglobin that carries oxygen. The genes of 2b encode them, and alternative readings of those genes make many more kinds than there are genes, each folded into a shape that determines its function, and at the molecular level most disease is a protein that is missing, misfolded, overproduced, or hijacked.

The cell's energy budget is the body's. A resting adult's mitochondria turn over roughly their own body weight in ATP each day, and their decline with age, as they become fewer, leakier, and less efficient, is one of the mechanisms of aging in 2e.

2b. DNA, Genes, and What They Determine

The genome is 3 billion base pairs of DNA in 23 pairs of chromosomes, but only about 1.5% of it, the 20,000 genes, codes for proteins; much of the rest regulates when and where those genes are read. A gene is copied into ribonucleic acid (RNA), and the RNA is translated into protein. The surprise of the Human Genome Project, completed in 2003, was how few genes there are, because much of the body's complexity lives in regulation: which genes are switched on, in which cells, when, and how strongly.

That regulation is epigenetics, the chemical marks on DNA and its packaging that let a cell be a liver cell rather than a neuron. The marks respond to environment and behavior, and they drift with age in ways so regular that 'epigenetic clocks' now estimate a person's biological age from a blood sample.

What the genome determines is a matter of degree. A handful of diseases, such as cystic fibrosis, sickle cell disease, and Huntington's disease, are written in a single gene, but the common diseases are different. Heart disease, diabetes, most cancers, and depression each involve hundreds of genetic variants that contribute a little, combined with environment, so a 'polygenic risk score' that adds the variants up shifts the odds without deciding them.

Height is about 80% heritable, and longevity is the harder case. Twin studies put its heritability at 20-25% and a 2018 analysis of family trees below 10%, while a 2026 study in *Science* found about 50% once deaths

from accidents, infections, and other outside causes were set aside. For nearly every condition, the honest answer to 'is it genetic?' is 'partly, and the rest is the subject of this course.'

2c. Division, Repair, and Error

The body replaces about 300 billion cells a day by division, and each division copies about 6 billion base pairs, one genome from each parent, with repair machinery holding the error rate to about one new mutation per division. That machinery is the reason cancer is not universal, and its failures are the reason cancer is common. Every cell accumulates mutations across a lifetime, and cancer, the subject of Module 12, is a cell that has acquired the particular set that lets it divide without limit, ignore the signals to stop, evade the immune system, and recruit a blood supply.

The same arithmetic explains three patterns. Cancer risk rises with age because more divisions mean more errors, and the tissues that divide most, such as skin, gut, blood, and breast, produce most cancers. A mutagen like tobacco smoke or ultraviolet light is effective because it raises the error rate in exactly the cells that divide most.

Cells also die on purpose. Apoptosis, programmed cell death, removes damaged and surplus cells by the billions every day, sculpting the fingers in the embryo and shrinking the thymus (10c), and when a cancer cell disables it, the cancer lives.

2d. The Cell's Neighbors

- **Stem cells** — the reserve: unspecialized cells in bone marrow, gut, skin, and muscle that divide to replace what wears out, and whose exhaustion with age is a hallmark of aging (2e). Medicine has used them since the first bone-marrow transplants of the late 1950s, and since 2006 scientists have been able to reprogram adult cells into stem cells. In March 2026 Japan gave the first conditional approvals to therapies built from reprogrammed cells, nerve cells for Parkinson's disease and sheets of heart muscle for heart failure, while a trial of lab-grown insulin-making cells for type 1 diabetes paused dosing in late 2025 and resumed in 2026.
- **Signaling** — cells talk by chemistry: hormones through the blood (Module 7), neurotransmitters across synapses (Module 5), cytokines between immune cells (Module 8), and growth factors between neighbors. Most drugs act on one of these signals (13d).
- **The extracellular matrix** — the collagen and scaffolding between cells that gives tissues their structure, whose stiffening with age is why arteries harden, skin wrinkles, and joints lose their give.
- **The microbiome** — the bacteria the body hosts, mostly in the colon, whose work and whose evidence Module 3 sets out.

2e. Aging at the Cellular Level

Aging is not a single process but a dozen linked ones, and the field's 2023 consensus lists twelve hallmarks, set out in the table below. Two terms need a gloss: telomeres are the protective caps on the ends of chromosomes, and senescent cells, nicknamed 'zombie' cells, have stopped dividing but do not die.

Each hallmark is a target. Senolytic drugs aim to clear the zombie cells, rapamycin and metformin to reset nutrient sensing, precursors of nicotinamide adenine dinucleotide (NAD), a molecule the mitochondria depend on, to restore them, and epigenetic reprogramming to reset the marks. Module 10 sorts the interventions with human trial evidence from those with mouse data and a marketing budget.

What the cellular account settles is whether aging is a disease or a program, and the answer is neither: it is a set of processes, several of which can now be measured in a blood test. The best-studied lever is calorie restriction, which acts through the nutrient-sensing pathways and extends life in many laboratory species, from yeast to mice, though it shortens life in some strains of mice. The two long studies in monkeys split, and a joint analysis in 2017 found benefits to health and survival when restriction began in adulthood.

Hallmark (2023)	What it is	Where it appears
Genomic instability	Accumulating DNA damage and mutation	Cancer (Module 12)
Telomere attrition	Chromosome caps shorten until division stops	Cell senescence; some cancers re-lengthen them
Epigenetic alteration	The regulatory marks drift	Epigenetic clocks; reprogramming research (Module 10)
Loss of proteostasis	Proteins misfold and accumulate	Alzheimer's and Parkinson's (Module 5)
Deregulated nutrient sensing	The insulin and growth pathways that sense nutrients miscalibrate	Metabolic disease (Module 3); rapamycin and metformin (Module 10)
Mitochondrial dysfunction	Energy production falls, damage rises	Muscle loss and fatigue (Module 9)
Cellular senescence	Zombie cells accumulate and inflame	Senolytic drugs (Module 10)
Stem-cell exhaustion	The reserves run down	Slow healing, anemia, muscle loss
Altered communication; chronic inflammation; dysbiosis; disabled autophagy	Signals degrade, inflammation rises, the microbiome shifts, the cell's disposal slows	The common thread of Modules 3-8

López-Otín and colleagues, 'Hallmarks of Aging: An Expanding Universe,' Cell (2023).

Module 2 Key Points

The Cell and the Genome

• A cell runs on ATP from its mitochondria and on proteins of many kinds; most molecular disease is a protein gone wrong.

• The genome holds 20,000 genes; the complexity lives in regulation, whose drift lets epigenetic clocks read biological age from blood.

• Common diseases come from hundreds of small variants plus environment, so 'is it genetic?' is nearly always 'partly.'

• Every division risks a mutation, which is why cancer rises with age and concentrates where cells divide most.

• Aging is twelve linked processes, each measurable and each now a drug target with evidence Module 10 grades.

• Japan's March 2026 approvals made reprogrammed stem cells a medicine, two decades after scientists learned to make them.

Module 2 Quiz

Check Your Understanding

1. What was the surprise of the Human Genome Project, completed in 2003?

A) Humans have far more genes than any other animal.
B) Most human genes code for structural proteins rather than for enzymes.
C) Humans have only about 20,000 genes; complexity lives in regulation.
D) The genome turned out to be almost identical in every person sequenced so far.

2. What does an epigenetic clock estimate?

A) How many divisions a cell has left before its telomeres run out.
B) Biological age, from chemical marks on DNA.
C) How quickly a person's mitochondria make ATP at rest and in exertion.
D) The share of the genome that has mutated since birth in the blood cells.

3. Why does cancer risk rise with age and concentrate in tissues that divide most?

A) Old tissues stop making tumor-suppressing proteins
B) Dividing tissues have the shortest telomeres
C) The immune system weakens with age and attacks dividing cells much less often than it attacks resting ones
D) Every division risks a mutation, and cancer needs a particular set

4. What did Japan approve in March 2026?

A) The first senolytic drug for frailty
B) Therapies made from reprogrammed stem cells
C) A gene therapy for sickle cell disease
D) Lab-grown insulin cells for type 1 diabetes, the first approval of its kind

5. What does the module say about calorie restriction?

A) It extends healthy life in every species tested, monkeys included
B) It works in yeast and worms but has never extended a mammal's life
C) It shortens life in most mammals, which is why the monkey studies stopped
D) It extends life in many species, not all

Module 3 — Energy, Metabolism, and the Gut

From Plate to Cell, and the Metabolic Disease of the Era

Recommended Reading / Reference

Book: Herman Pontzer, *Burn: New Research Blows the Lid Off How We Really Burn Calories, Lose Weight, and Stay Healthy*

Reference: The CDC's National Diabetes Statistics Report and its National Health and Nutrition Examination Survey (NHANES), with Gallup's National Health and Well-Being Index for self-reported obesity and drug use, the sources for the US figures in this module

3a. Digestion

Food's route through the body is about nine meters long and takes a day or two. Chewing and saliva begin the breakdown, and the stomach's acid and enzymes reduce a meal to a slurry over two to four hours. The small intestine, about seven meters long, absorbs nearly everything of value through folds that give it about 30 square meters of surface, roughly half a badminton court rather than the tennis court of older textbooks. Bile from the liver emulsifies fat there and enzymes from the pancreas finish digesting carbohydrate and protein, while the colon reclaims water and salt and hosts the microbiome (3e).

The three macronutrients arrive as glucose from carbohydrate, amino acids from protein, and fatty acids from fat, and the body's bookkeeping treats them differently. Glucose is the ready fuel and the brain's preferred one, stored as glycogen in the liver and muscles in about a day's supply. Fat is the long-term store and effectively unlimited, at 9 kilocalories a gram against 4 for the other two, while protein is structure first and fuel last.

Hormones govern appetite: ghrelin rises from the empty stomach, leptin reports the size of the fat stores, and gut hormones such as glucagon-like peptide-1 (GLP-1) are released as food arrives. These signals, worked out in recent decades (Module 7), became the most consequential drugs of the decade.

3b. Insulin, Blood Sugar, and the Chemical Plant

The pancreas holds blood glucose near 5 millimoles per liter with two hormones: after a meal insulin moves glucose into muscle, liver, and fat, and between meals glucagon releases it. Type 1 diabetes is the immune system's destruction of the insulin-making cells, about 5-10% of cases, usually beginning young and fatal until insulin was first used in 1922. Type 2 diabetes is the body's resistance to its own insulin, produced most often by excess fat in the liver and muscle and followed by the exhaustion of the pancreas.

About 38 million Americans have diabetes, most of it type 2, and nearly 98 million adults have prediabetes. When the national survey measured it in 2021-23, 15.8% of adults had diabetes and more than a quarter of them did not know it. Worldwide, a 2024 analysis in *The Lancet* counted 828 million adults with diabetes in 2022, about four times the number in 1990.

The liver is the chemical plant: it stores and releases glucose, makes cholesterol and the clotting proteins, and processes every drug and toxin. Overloaded with fat, it develops what was long called fatty liver disease, renamed in 2023 for its metabolic cause, a condition that affects about a third of adults and is the fastest-growing reason for liver transplants.

The kidneys are the filters, with two million nephrons that filter about 180 liters of fluid from the blood each day and return nearly all of it, holding salt and water balance to the gram. Diabetes and high blood pressure damage them first, kidney disease is among the leading causes of death (Module 11), and dialysis is its most expensive chronic treatment.

3c. The Energy Budget

Worked example — a day's energy budget

Take a 40-year-old man of 80 kilograms and 178 centimeters, or a woman of 65 kilograms and 165 centimeters, and do the arithmetic the body does. The basal metabolic rate is what the body burns lying still, awake, and fasting, and by the standard Mifflin-St Jeor equation it is about 1,720 kilocalories a day for him and 1,320 for her. It is the largest item in the budget, roughly 60-70% of everything burned, with the brain alone taking about 400, and digesting food costs about a tenth of what is eaten.

Activity is the rest, and the surprise of the last decade's research is how small and constrained it is. Herman Pontzer measured energy use with doubly labeled water, a tracer method, in hunter-gatherers and office workers alike, and found that a sedentary day adds about 300-500 kilocalories of activity and an active one perhaps 600-800. Because the body compensates for sustained exercise by trimming other spending, total daily expenditure lands in a narrow band, about 2,300-2,800 kilocalories for the man and 1,800-2,200 for the woman, almost regardless of lifestyle.

The budget's meaning for weight is subtler than the old rule of thumb, which says a pound of fat holds about 3,500 kilocalories, so that a lasting surplus of 100 a day, about one soft drink, adds ten pounds a year. The body does not keep that simple account: a heavier body costs more to run, so the same surplus adds about ten pounds in all, half of it in the first year, and then levels off. In the other direction, the body defends its weight by lowering expenditure and raising appetite, which is why most dieters regain most of what they lose within a few years, and why the GLP-1 drugs, which act on appetite rather than arithmetic, succeed where the arithmetic did not.

The budget's meaning for 'metabolism' is modest. Basal rates differ by about 200-300 kilocalories a day between people of the same size, mostly because of lean mass, a difference that is real but is not the reason most people weigh what they weigh.

3d. Obesity, Diabetes, and the GLP-1 Era

Obesity is defined as a body-mass index (BMI) of 30 or more, an imperfect measure that the field is supplementing with waist size and body-fat measures. Measured obesity among American adults rose from 13% in 1960-62 to 40.3% in the national survey of 2021-23. Worldwide about one adult in eight is obese, a share that has more than doubled since 1990, and 2.5 billion adults were overweight in 2022. Obesity carries much of the risk of type 2 diabetes, high blood pressure, heart disease, sleep apnea, arthritis, and thirteen cancers.

Its causes are argued between two accounts. One is energy balance, more calories in and fewer burned; the other asks why appetite changed and points to ultra-processed food, sugar, and the food environment. The evidence favors the environment as the cause and the arithmetic as the mechanism.

The change of the era is a drug class. The GLP-1 drugs semaglutide and tirzepatide are weekly injections that mimic gut hormones and reduce appetite, and they produced weight loss of 15-22% in trials; about one American adult in eight was taking one by late 2025. Two weight-loss pills followed, an oral semaglutide

approved for weight in December 2025 and Eli Lilly's orforglipron, sold as Foundayo and approved on April 1, 2026. In Gallup's national survey, self-reported obesity fell from 39.9% in 2022 to 37.0% in 2025, the series' first sustained decline, though the measured national survey, whose latest data run to 2023, has not yet shown it.

The trials made the drugs more than weight drugs. The trial known as SELECT (Semaglutide Effects on Cardiovascular Outcomes in People with Overweight or Obesity) found 20% fewer heart attacks, strokes, and cardiovascular deaths among people with overweight or obesity and heart disease, and 19% fewer deaths from any cause, and benefits for the kidneys, the liver, sleep apnea, and heart failure followed. Not every hope held: two large trials of oral semaglutide in early Alzheimer's disease failed in November 2025, while a small 2025 trial found less heavy drinking on low doses, a signal for addiction that larger trials are now testing.

The questions the era has not answered are the ones Modules 14 and 15 hold. Most of the weight returns when people stop, the muscle lost alongside the fat matters for the old, and a drug taken for life by a tenth of the population costs a great deal. Nor is it clear yet whether a pharmacological answer to an environmental cause is a solution or a subscription.

3e. The Microbiome

The colon's bacteria number about 38 trillion, from several hundred species in each person, and they weigh about 0.2 kilograms, not the kilogram or two once claimed, while carrying about a hundred times as many genes as the human genome. They ferment fiber into short-chain fatty acids that feed the colon's lining and signal to the immune system, make vitamin K and some B vitamins, crowd out pathogens, and train the immune system in infancy (Module 8).

The evidence grade is the issue. Two findings are settled: antibiotics disrupt the microbiome, and a fecal transplant cures recurrent *C. difficile* infection in most patients, about 80-90%. A second finding is established but silent on direction, since the microbiome's composition differs in obesity, depression, autism, and a dozen other conditions without showing which causes which. A third claim, that a probiotic yogurt or supplement changes any of these in a healthy person, is unsupported apart from a few narrow exceptions.

What the settled evidence supports is unglamorous: fiber and a diversity of plant foods feed the bacteria that studies consistently associate with health, and most Americans eat about 15 grams of fiber a day, half the recommended 25-30.

Module 3 Key Points

Energy, Metabolism, and the Gut

• Glucose is the ready fuel and fat the unlimited store, governed by appetite hormones that became the decade's most consequential drugs.

• Type 2 diabetes is insulin resistance from fat in the liver and muscle; 828 million adults worldwide had diabetes in 2022.

• The basal rate is 60-70% of energy spent; activity is smaller than assumed, and the body defends its weight.

• About one American adult in eight takes a GLP-1 drug, which cut heart attacks, strokes, and cardiovascular deaths 20% in trials.

• Of the microbiome claims, antibiotics' disruption and C. difficile transplants are settled, most probiotics are not, and fiber holds up.

Module 3 Quiz

Check Your Understanding

1. Why do the GLP-1 drugs succeed where calorie arithmetic failed, in the module's account?

A) They act on appetite, which the body uses to defend its weight against a deficit
B) They raise the basal metabolic rate by several hundred kilocalories a day
C) They block the absorption of fat in the small intestine
D) They turn stored fat directly into muscle

2. About how much do the colon's bacteria weigh?

A) About 2 kilograms
B) Between one and two kilograms
C) About 0.2 kilograms
D) About five kilograms in all

3. What share of daily energy spending does the basal metabolic rate account for?

A) About a fifth, with activity the largest share
B) About 60-70%
C) About a third, split evenly with digestion and activity
D) About half, rising to two-thirds in trained athletes

4. What did two large trials of oral semaglutide in early Alzheimer's disease find in November 2025?

A) A 30% slowing of decline
B) Slowing in gene carriers only
C) No slowing of the disease against placebo
D) A halt in memory loss

5. What happens to weight under a lasting surplus of 100 kilocalories a day, in the module's account?

A) It rises ten pounds a year for as long as the surplus lasts.
B) It does not change, because the body burns off any small surplus of energy.
C) It rises steadily for a decade before the body's metabolism finally adjusts to it.
D) It rises about ten pounds in all, half in the first year, then levels off.

Module 4 — Heart, Blood, and Lungs

The World's First Killer and Its Arithmetic

Recommended Reading / Reference

Book: Sandeep Jauhar, *Heart: A History*

Reference: The American Heart Association (AHA) annual *Heart Disease and Stroke Statistics* and the 2025 guideline for high blood pressure from the AHA and the American College of Cardiology (ACC)

4a. The Circulation

The heart is a fist-sized pump of specialized muscle that beats about 100,000 times a day without instruction, driven by its own electrical pacemaker. At rest it moves five liters of blood a minute, and up to 25 in exertion, through two circuits, one to the lungs for oxygen and back and the other to the body and back, in a closed system of about 100,000 kilometers of vessels.

Arteries carry blood out under a pressure with two numbers, the systolic peak when the heart contracts and the diastolic trough between beats, and a normal reading is below 120/80 in millimeters of mercury. Capillaries, a single cell wide, are where the exchange happens, and veins return the blood with help from the squeeze of the muscles and from one-way valves.

The blood itself is about 5 liters: red cells that carry oxygen on hemoglobin, white cells that defend, and platelets that start clots, all suspended in plasma that carries nutrients, hormones, waste, and the proteins of clotting and immunity. The bone marrow makes about 2 million red cells a second. Clotting is the system's double edge, because it stops bleeding in minutes but in the wrong place causes the heart attack, a clot in a coronary artery, and the stroke, a clot or bleed in the brain, which together kill more people than anything else. Cardiovascular disease as a whole kills about 20 million people a year worldwide, about a third of all deaths.

4b. How Arteries Fail

Atherosclerosis is the disease behind most heart attacks, most strokes, and much of dementia and kidney disease, and it begins in childhood and takes decades. Cholesterol carried in low-density lipoprotein (LDL) particles lodges in the artery wall and the immune system responds, producing plaque that narrows the vessel and, when it ruptures, triggers a clot.

Four accelerants have been known for more than half a century. High blood pressure damages the artery wall, high LDL cholesterol supplies the material, smoking inflames the wall and promotes clotting, and diabetes does both.

Genetics and trials settled the lipid argument, the long dispute over whether cholesterol causes heart disease: people born with variants that lower LDL have a low lifetime risk of heart disease, and people born with high LDL develop it early. Lowering LDL by any means, whether statins, ezetimibe, the newer injectable drugs and pills, or diet, lowers events in proportion to how much and for how long. Statins cut heart attacks and strokes by about a fifth for every millimole per liter of LDL they remove, cost pennies, and are among the most studied drugs in history.

The persistent controversy over statins concerns the absolute benefit in people at low risk, which is modest, and muscle aches. In blinded trials aches were nearly as common on placebo as on the statin, and the drug

itself caused about one extra case per hundred patients in the first year. In ordinary use far more patients blame the statin, and expectation does much of the work.

The frontier was lipoprotein(a), an inherited particle that is elevated in about a fifth of people and that statins do not lower, and in September 2026 the first outcome trial of a drug aimed at it failed. Novartis's pelacarsen lowered lipoprotein(a) substantially in 8,323 patients with heart disease, but it did not reduce the combined rate of heart attacks, strokes, cardiovascular deaths, and urgent heart procedures. Rival drugs remain in outcome trials, and the result is the course's recurring lesson in miniature: lowering a marker is not the same as preventing the disease.

4c. Blood Pressure and the Risk Arithmetic

High blood pressure is the most common and most modifiable risk factor for death in the world, developing in about half of adults without symptoms. It multiplies the risk of stroke, heart attack, heart failure, kidney failure, and dementia in proportion to the number, so that in middle age the risk of dying of heart disease or stroke doubles with every 20 points of systolic pressure above 115.

The American guideline published in August 2025, the first major revision since 2017, kept the diagnosis threshold at 130/80 and recommends drugs for everyone at 140/90 or above. Between 130/80 and 139/89, it recommends drugs at once for people with heart disease, diabetes, or kidney disease, or with a ten-year risk of 7.5% or more, while others get three to six months of lifestyle change first. The target is below 130/80, with a systolic reading below 120 encouraged, and risk is now estimated with the equations known as PREVENT (Predicting Risk of Cardiovascular Disease Events), which add kidney function and drop race as a predictor.

The arithmetic of risk factors is the module's lesson: they multiply rather than add. An illustrative 55-year-old man with normal pressure and cholesterol, no diabetes, and no cigarettes has a ten-year risk of a heart attack or stroke of perhaps 4%. Add high blood pressure and it is about 8%, add high cholesterol and it is about 15%, and add smoking and it is about 30%, an eightfold difference from three modifiable numbers in the same man at the same age, before diabetes is even counted.

That arithmetic explains the largest gain of the past half-century. Cardiovascular death rates in rich countries have fallen by about two-thirds since 1970, with roughly half of the fall attributed to treatment and half to lower risk factors, smoking's decline above all. It also explains the stall since about 2010, as obesity and diabetes took smoking's place.

4d. The Lungs

The lungs are a gas exchanger of 300 million to 500 million alveoli, tiny air sacs with a combined surface of about 70 square meters, roughly a quarter of a tennis court, moving about 6 liters of air a minute at rest and 100 in exertion. The brainstem controls breathing by reading carbon dioxide rather than oxygen, which is why holding one's breath becomes unbearable long before oxygen runs low, and why opioids, which blunt that reading, kill by stopping breathing.

The lungs' diseases are mostly inhaled. Smoking causes about 85% of lung cancer and most chronic obstructive pulmonary disease (COPD), the core of the chronic lung diseases (Module 11), and it causes about one cardiovascular death in four. Its decline among American adults, from 42% in 1965 to about 9% in 2025, is the largest public-health success of the century.

Air pollution is the other great inhaled killer, fine particles from combustion that reach the alveoli and then the blood. The WHO attributes about 7 million deaths a year to it worldwide, most of them in Asia and Africa and most through heart disease rather than lung disease.

Asthma, the airway inflammation that affects about one person in twelve, completes the chronic list. Lung capacity peaks in the twenties and declines about 1% a year after, faster in smokers, on a path that exercise slows.

Module 4 Key Points

Heart, Blood, and Lungs

• Clotting stops bleeding in minutes and, in the wrong place, causes the heart attacks and strokes that kill more people than anything.

• Atherosclerosis has four accelerants known for more than half a century: blood pressure, LDL cholesterol, smoking, and diabetes.

• Statins cut events about a fifth per millimole of LDL lowered; in blinded trials, the drug causes few of the aches blamed on it.

• Risk factors multiply: three modifiable numbers move an illustrative 55-year-old's ten-year risk from 4% to 30%.

• The first lipoprotein(a) drug lowered its marker but not heart attacks in 2026; a marker is not the disease.

• Smoking's fall from 42% to about 9% of American adults is the century's largest public-health success.

Module 4 Quiz

Check Your Understanding

1. Which four accelerants of atherosclerosis does the module name?

A) Blood pressure, LDL, smoking, diabetes
B) Stress, salt, sugar, and age
C) Obesity, alcohol, smoking, gout
D) Saturated fat, stress, salt, and genetics

2. What did the first outcome trial of a lipoprotein(a)-lowering drug find in September 2026?

A) It cut cardiovascular events by about a fifth
B) It failed to lower lipoprotein(a) at all
C) It lowered lipoprotein(a) but did not reduce heart attacks or strokes
D) It cut heart attacks by about half, but only in patients with the very highest levels

3. Why does holding one's breath become unbearable long before oxygen runs low?

A) The alveoli collapse within seconds once airflow stops.
B) The brainstem controls breathing by reading carbon dioxide.
C) The lungs can store only a few seconds' worth of oxygen at a time.
D) The heart speeds up sharply as oxygen falls, which the brain reads as distress.

4. How much do three modifiable risk factors change the module's illustrative 55-year-old's ten-year risk?

A) From 4% to about 30%
B) From 4% to about 8%, since each factor adds a point
C) From 10% to 15%, as the risk factors partly cancel
D) Hardly at all, since risk factors only add, and three of them together raise the risk by a few points

5. What is the main dispute over statins, according to the module?

A) Whether lowering LDL reduces heart attacks at all.
B) Whether statins raise the risk of cancer over decades.
C) Whether they work as well in women as in men of the same age and risk.
D) Their absolute benefit in people at low risk, and how many muscle aches the drug really causes.

Module 5 — The Brain and Nervous System

The Organ That Understands

Recommended Reading / Reference

Book: Matthew Walker, *Why We Sleep: Unlocking the Power of Sleep and Dreams*, read with the caveat that several of its strongest claims outrun the evidence, which Module 14 grades

Reference: The Alzheimer's Association's *Facts and Figures* (annual) and the American Heart Association's stroke statistics

5a. Neurons and Networks

The brain is about 86 billion neurons and about as many support cells, wired by some 100 trillion synapses into networks that run on electricity within cells and chemistry between them. An impulse travels the length of a neuron as a wave of charge and crosses to the next as a squirt of neurotransmitter, which the receiving cell reads at its receptors; dopamine, serotonin, glutamate, and gamma-aminobutyric acid (GABA) are four of a hundred such chemicals.

Nearly every drug that acts on the mind acts at that gap. Antidepressants raise serotonin's availability, opioids mimic the brain's own painkillers, and stimulants raise dopamine, while alcohol enhances GABA and blunts glutamate and anesthetics silence the traffic.

The organ is organized by region and by network at once. The brainstem runs breathing and heartbeat, the cerebellum coordinates movement, and the limbic structures handle emotion and memory, while the cortex handles sensation, movement, language, and planning, and the frontal lobes that do the planning finish maturing only in the mid-twenties. The brain is also plastic, rewiring with learning, after injury, and in response to use, which is the basis of rehabilitation and the reason a lifetime's skills change its structure. It uses a fifth of the body's energy, has no pain receptors of its own, and is the only organ whose failure ends the person rather than the body.

5b. Pain and the Senses

The senses are transducers: the eye's more than 100 million photoreceptors, the 15,000 or so hair cells in each inner ear, and the skin's, tongue's, and nose's detectors of pressure, temperature, and chemistry. The brain's reconstruction of their signals is the world a person lives in, and their decline is part of the aging in Module 10. Hearing loss raises the risk of dementia (5e), perhaps because a brain deprived of sound withdraws from the world.

Pain is two things, which is why the course treats it separately. Acute pain is a signal from damaged tissue, carried by dedicated fibers and modulated at every relay by the brain's own opioids, which is why fear amplifies it and distraction blunts it. Chronic pain, which affected about a quarter of American adults in 2023 and limited daily life for about one in twelve, is often the nervous system continuing to fire after the tissue has healed, sensitized at the spinal cord and amplified in the cortex. That is why drugs aimed at the tissue often fail, and why therapies that retrain the brain's reading of the signal have done better in trials.

The opioid epidemic was the confusion of the two kinds: drugs that work on acute pain were prescribed for chronic pain at a scale that produced addiction in millions, and the overdose deaths of Module 6.

5c. Sleep

A third of life is spent asleep, cycling about every ninety minutes through light sleep, deep slow-wave sleep, and the rapid-eye-movement sleep of dreams. Deep sleep is when the body repairs and the brain consolidates the day's memories. Two processes time sleep: a clock in the hypothalamus, set by light, and the pressure of adenosine, a chemical that builds through the waking hours and that caffeine blocks.

A widely reported 2013 finding held that the brain clears its waste mainly during sleep, through a drainage system described the year before, and that account is now disputed. A 2024 study in mice found clearance slower during sleep, a 2025 study found that slow pulsing of the blood vessels in deep sleep drives it, and the first human studies are small, so the idea that sleep cleans the brain is plausible but not proven.

The evidence on duration is one of the field's more consistent findings and one of its most overstated. In pooled studies of more than a million people, mortality is lowest at about seven hours and rises on both sides, modestly for short sleep and more steeply for long sleep, though long sleep is largely a marker of illness rather than a cause of it.

The trials show what restriction does. Cutting sleep to four or five hours raises blood pressure, blood sugar, and appetite within days, slows reaction time, and impairs the consolidation of what was learned that day, and a night without sleep impairs a driver about as much as a blood-alcohol level near the legal limit. Shift work, which fights the body clock, raises cardiovascular and metabolic risk, in studies that cannot fully separate the work from the lives of the people who do it.

Sleep apnea, the collapse of the airway during sleep, affects nearly a billion adults aged 30 to 69 worldwide, most of them undiagnosed, and it raises blood pressure and stroke risk. Machines that hold the airway open treat it, and since December 2024 so does one GLP-1 drug, tirzepatide. Insomnia, the most common sleep disorder, responds better to cognitive-behavioral therapy than to the sedatives most people are prescribed, and those sedatives, the benzodiazepines and the 'Z-drugs', carry dependence, falls, and, in the old, a cognitive cost.

Several popular claims lack support. The evidence does not show that any night under seven hours damages the brain or that sleep debt can never be repaid, and melatonin helps jet lag and some older adults but little else. The sleep trackers on a hundred million wrists do not measure sleep stages accurately, and the anxiety they produce has a name in the clinics that see it: orthosomnia.

5d. Stroke

A stroke is a clot blocking an artery to the brain, in about 85% of cases, or a vessel bleeding into it. Strokes strike about 795,000 Americans a year and killed about 167,000 in 2024.

Treatment is a race, because the brain loses about two million neurons for every minute an artery stays blocked. Clot-dissolving drugs work within four and a half hours of onset, and a second such drug, tenecteplase, was approved for stroke in March 2025. Removing the clot through a catheter, the largest advance in stroke care in a generation, has been standard since 2015 and works up to twenty-four hours in selected patients. Hence the public message of symptom recognition, in the 'face, arm, speech, time' formula, and stroke centers that run around the clock.

Prevention is Module 4's list, with blood pressure first. Then comes atrial fibrillation, the irregular rhythm that throws clots, found in about a tenth of people over 80 and treated with anticoagulants, followed by cholesterol, smoking, and diabetes. A transient ischemic attack, a stroke whose symptoms resolve within a day, warns that the next one may be coming, and it is the moment when prevention matters most.

5e. Dementia and the Alzheimer's Drugs

Dementia, the loss of memory and function severe enough to end independence, affects about 57 million people worldwide, and Alzheimer's disease causes most of it: about 7.4 million Americans aged 65 and older have Alzheimer's. Prevalence doubles every five years after 65, and vascular damage, Lewy bodies, and frontotemporal degeneration account for most of the rest, with mixed causes the rule in the very old.

Alzheimer's disease is defined by two proteins, amyloid plaques between neurons and tau tangles inside them, which begin accumulating up to twenty years before symptoms. The era's change is that both can now be measured. Amyloid has been visible on positron emission tomography (PET) scans since 2012, and since May 2025 blood tests have done much of the same work at a fraction of the cost. By August 2026 the US Food and Drug Administration (FDA) had cleared four of them, the latest being the first single-protein test cleared both to rule the disease in and to rule it out.

Two antibodies that clear amyloid reached the market, lecanemab in 2023 and donanemab in 2024, and in early-stage patients they slowed decline by 27% and 35% over eighteen months. That slowing, about five months' delay, is the first to change the disease's course, at the price of regular infusions and $26,500-32,000 a year. Brain swelling or small bleeds appear on scans in a fifth to a third of patients, depending on the drug, most of them silent and a few fatal. A slower starting dose of donanemab, approved in 2025, cut the swelling from about 24% of patients to 14%, and in 2026 lecanemab became available from the start of treatment as a weekly injection given at home.

The argument over the antibodies

The case against, as the April 2026 Cochrane review made it. The review pooled 17 randomized trials of seven antibodies in 20,342 people and found that the average difference after eighteen months, on cognition and on the main dementia rating scale, was small, well below what patients and doctors would notice. The harms were not small, about 107 more cases of brain swelling per 1,000 people treated, and the authors concluded that removing amyloid does not appear to produce a clinically meaningful benefit.

The case for, as the drugs' defenders made it. Leading researchers and the Alzheimer's Society answered within days, and 37 clinicians published a fuller critique in July 2026, arguing that the review averaged the two drugs that work with five that failed, some of which barely removed amyloid. Judged on their own trials, lecanemab and donanemab met their goals, and their makers report that the gap between treated and untreated patients widens over three years of follow-up, with early patients gaining the most.

The evidence between them. Both sides accept the two drugs' trial results and differ over what that slowing is worth against the risks, the infusions, and the cost. The follow-up data suggesting a widening benefit come without placebo groups, so the prevention trials, which treat people who have amyloid but no symptoms, are the test that can move the argument (Module 16 gives their dates).

The course's reading. The two approved drugs do slow the disease, by an amount most patients will not feel within eighteen months, at real risk and cost. Whether they matter more depends on timing.

What is not in dispute is the prevention evidence. The 2024 Lancet Commission attributed about 45% of dementia to fourteen modifiable risks, the largest being hearing loss and high LDL cholesterol at about 7% each, with blood pressure, diabetes, smoking, inactivity, isolation, and depression among the rest. In 2025 an American trial of 2,111 at-risk adults aged 60 to 79 found that a structured lifestyle program improved cognition modestly more than a self-guided one, and both groups improved. The hope that GLP-1 drugs would protect the brain did not survive its first large trials (Module 3).

Module 5 Key Points

The Brain and Nervous System

• Nearly every drug that acts on the mind acts at the synapse, mimicking or altering a neurotransmitter at its receptors.

• Pain is two things — an acute signal and a chronic misfire — and the opioid epidemic was the confusion of them.

• Mortality is lowest near seven hours of sleep; restriction raises pressure, sugar, and appetite; trackers misread the stages.

• Stroke is a race: the brain loses about two million neurons each minute an artery stays blocked.

• The Alzheimer's antibodies slow decline about five months over eighteen; a 2026 review of the class disputes that it matters, and prevention trials will decide.

• About 45% of dementia traces to fourteen modifiable risks, led by hearing loss and high LDL cholesterol.

Module 5 Quiz

Check Your Understanding

1. How much of the body's energy does the brain use?

A) About a twentieth
B) Roughly half of it
C) About 2%, matching its weight
D) About a fifth

2. What did the April 2026 Cochrane review conclude about the anti-amyloid antibodies?

A) Their average benefit was too small to notice, and their harms were real.
B) They halt decline in most early-stage patients for two years.
C) They were unsafe and should be withdrawn from the market at once.
D) They slow decline by about half when they are started before any symptoms appear.

3. Why is stroke treatment called a race?

A) Clot-dissolving drugs work only in the first hour
B) The brain loses about two million neurons a minute while the artery is blocked
C) A blocked artery bursts if it is not reopened within about thirty minutes of the first symptoms
D) Every hour of delay doubles the risk that a second stroke follows within the week

4. What does the module say about the claim that sleep clears waste from the brain?

A) It has been settled science since its discovery in 2013
B) It has been confirmed in large human trials
C) It is plausible but disputed: a 2024 mouse study found clearance slower during sleep
D) It was disproved in 2025, when scans showed that no such drainage system exists

5. What are the two largest modifiable risks for dementia, on the 2024 Lancet Commission's estimate?

A) Smoking and heavy drinking, at about 10% each.
B) Hearing loss and high LDL cholesterol, at about 7% each.
C) Air pollution and head injury, at 7% each.
D) Poor sleep and a diet high in sugar, together about a fifth of all cases.

Module 6 — Mental Health

The Disorders, the Treatments, and the Gap

Recommended Reading / Reference

Book: Andrew Solomon, *The Noonday Demon: An Atlas of Depression*

Reference: The prevalence statistics of the NIH's National Institute of Mental Health (NIMH), the National Survey on Drug Use and Health, and the CDC's provisional overdose and suicide data, the sources for the figures in this module

6a. The Measurement Problem

Mental illness is among the largest causes of years lived with disability in every rich country, and it is measured by symptom, not by test: no blood marker, scan, or gene diagnoses depression. The diagnostic manuals are lists of symptoms that a clinician counts, with thresholds set by committee, and the two in use are the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM), now in a revised fifth edition, and the WHO's International Classification of Diseases (ICD).

That is the source of the field's progress, because a shared vocabulary made research and trials possible, and the source of its disputes, because the boundary between illness and ordinary suffering is drawn by convention and moves. The manuals have grown from 106 disorders in 1952 to nearly 300, and in 2013 the manual stopped excluding the recently bereaved, so that grief can now be diagnosed as depression after two weeks of symptoms. Whether rising diagnoses measure rising illness or falling thresholds is a question that runs through every statistic below.

The biology is real and incomplete. Depression is about 40% heritable and schizophrenia about 80%, and both involve identifiable circuits and neurotransmitters and respond to drugs that act on them, but no mechanism yet explains any psychiatric disorder the way plaque explains a heart attack. The 'chemical imbalance' account that sold the antidepressant era was a simplification that the field has largely retired, and what the course can say with confidence is what the trials show about what helps, the subject of 6c.

6b. The Disorders

Disorder	Prevalence	What it is, and what the evidence says
Depression	About 1 in 6 adults in a lifetime; about 1 in 12 in a given year; twice as common in women	Persistent low mood, loss of pleasure, and disturbed sleep and appetite, for weeks or more; treatable in most cases, recurrent in half
Anxiety disorders	About 1 in 5 adults in a year, the most common category	Generalized anxiety, panic, phobias, and social anxiety; cognitive-behavioral therapy (CBT) the best-evidenced treatment; selective serotonin reuptake inhibitors (SSRIs) effective
Post-traumatic stress disorder (PTSD)	About 6% in a lifetime; far higher in veterans, refugees, and survivors of abuse	Re-experiencing, avoidance, and hyperarousal after trauma; trauma-focused therapies effective; the trials of MDMA (methylenedioxymethamphetamine, sold as ecstasy) in 6e
Bipolar disorder	About 3% of adults in a year	Cycles of depression and mania; lithium, the oldest psychiatric drug still in use, remains the best-evidenced

Disorder	Prevalence	What it is, and what the evidence says
Schizophrenia	Well under 1%	Psychosis (delusions, hallucinations, disorganized thought), typically beginning in the late teens or twenties; antipsychotics effective for the psychosis, less so for the withdrawal and cognitive loss; life expectancy 15-20 years shorter, mostly from heart disease
Eating disorders	About 1-3% of young women for anorexia and bulimia; rising	Anorexia carries among the highest mortality of any psychiatric disorder; family-based treatment the best-evidenced for adolescents
Attention-deficit/hyperactivity disorder (ADHD) and autism	ADHD: about 1 in 9 children with a current diagnosis (2024). Autism: about 1 in 31 eight-year-olds (2022)	Neurodevelopmental conditions; stimulants effective for ADHD; the rise in diagnosis is real, and its cause (awareness, thresholds, or incidence) is disputed
Substance use disorders	About one American in six aged 12 and older in a year (2024), most involving alcohol	The addiction of 6f, and the most lethal category by far, through overdoses and alcohol

NIMH; the National Survey on Drug Use and Health; CDC; WHO. Prevalence figures depend on the thresholds discussed in 6a and differ across surveys.

6c. What Helps

The treatments work modestly and work better together, and the trials are unusually clear about the sizes. Antidepressants beat placebo by a margin that is small in mild depression and substantial in severe depression, and about half of patients respond to the first drug. How many more improve as drugs are switched is disputed: the largest such trial reported two-thirds reaching remission over four steps, and a 2023 reanalysis by the trial's own rules put the figure nearer a third. The placebo response is large, since a third to a half of patients improve on nothing, which is the reason the trials are needed and the reason the drugs look better in the clinic than in the data.

Psychotherapy, of which CBT is the most-trialed form, matches the drugs for mild and moderate depression and most anxiety disorders, and its effects outlast them, since a skill persists when a prescription ends. Therapy and drugs together beat either alone, and in trials of mild and moderate depression, exercise rivals both. Lithium prevents suicide in bipolar disorder more effectively than any other drug in psychiatry, and antipsychotics (6b) carry metabolic costs that shorten lives. Electroconvulsive therapy, the field's most stigmatized treatment, is its most effective for severe depression that nothing else has touched, with response rates near 70%.

The gap is not in the tools but in their delivery. Only about half of American adults with a mental illness received any treatment in 2024, the wait for a therapist often runs to months, and most antidepressants are prescribed by primary-care doctors without the therapy the evidence says should accompany them.

The digital tools that promised to close the gap remain unproven. About one American adult in ten used an AI chatbot for emotional support or advice in early 2026, and one in five under 30. A 2026 review of 39 randomized trials of chatbots found small benefits for depression and anxiety, but the eight trials of chatbots built on large language models did not show a significant effect as a group, and most of the trials did not systematically monitor safety. Regulators have begun to move: the Federal Trade Commission opened an inquiry into companion chatbots in September 2025, an FDA advisory committee weighed therapy chatbots that November, and Illinois and several other states have restricted AI therapy or companion bots.

6d. The Adolescent Decline

Two developments define the decade, and the first is the adolescent mental-health decline that began around 2012 in the data of many rich countries. In the CDC's Youth Risk Behavior Survey, the share of American high-school girls reporting persistent sadness or hopelessness rose from about 36% in 2011 to 57% in 2021, and emergency visits for self-harm among girls doubled. Then the trend turned: the survey released in September 2026 put the share at 53% in 2023 and 43% in 2025, and at 33% among all students in 2025.

The argument over screens

The case that screens did it, as its advocates make it. The social psychologist Jonathan Haidt and others point to the timing, since the decline began as smartphones and social media saturated adolescence between 2010 and 2015, and to its pattern, which appeared across the rich world at once and was sharpest in girls, for whom social comparison online is heaviest. Heavy users fare worst, some experiments that cut social-media use have improved mood, and a study of Facebook's staggered arrival at American colleges in the 2000s found that students' mental health worsened where it came. On this reading, a phone-based childhood displaced sleep, play, and face-to-face friendship.

The case that they did not, or not mainly. Researchers such as Candice Odgers, Amy Orben, and Andrew Przybylski answer that the correlations are small, explaining a sliver of the variation in teenagers' wellbeing, and that the direction is unclear, since distressed teenagers may use phones more rather than the reverse. Experiments that remove social media show small and mixed effects, and other causes fit parts of the record: academic pressure, the opioid era's toll on families, changing thresholds for what counts as distress, and, for the later years, the pandemic.

The evidence between them. The decline was real, and it has partly reversed since 2021 while phone ownership stayed near universal, so both sides can claim the reversal. It fits a recovery from the pandemic, and it also coincides with the spread of school phone restrictions, which at least 39 states and the District of Columbia required by mid-2026, while the trials remain small and short.

The course's reading. Screens are a plausible contributor and the leading suspect, but the case is not proven, and the partial recovery suggests they are not the whole story. The phone restrictions now in force across most states are the largest natural experiment yet, and their results should settle more than another survey can.

6e. The Returning Drugs

The second development is the arrival of fast-acting and psychedelic drugs for depression. Ketamine, an anesthetic since 1970, relieves severe depression within hours in a way no other drug does, and a nasal form, esketamine, has been approved since 2019, and since January 2025 as a treatment on its own; it is modestly effective and expensive.

Psilocybin, the active compound of 'magic mushrooms' and one of the psychedelics the field abandoned in the 1970s, is the closest to approval. Two late-stage trials by Compass Pathways in treatment-resistant depression succeeded, in June 2025 and February 2026, and the benefit held at 26 weeks. After an April 2026 executive order on psychedelics, the FDA granted the drug a rolling review and a priority voucher, and, as of October 2026, the company expected to complete its filing by the end of 2026 and to launch in the first half of 2027, if the Drug Enforcement Administration reschedules the drug.

MDMA for post-traumatic stress was the field's most anticipated therapy until the FDA rejected it in August 2024 over trial quality and unblinding, since the drug's effects were obvious to everyone in the room. Its developer, since renamed, was reported in August 2026 to have refiled without a new trial.

6f. Addiction and the Overdose Turn

Addiction is the reward system captured. Substances and behaviors that flood the dopamine circuits of Module 5 reset the brain's baseline, so that ordinary rewards fade and the substance becomes necessary rather than pleasant, with withdrawal and craving persisting long after use stops. Addiction is about 50% heritable and begins overwhelmingly in adolescence, and it is a chronic, relapsing condition rather than a failure of will, the evidence that turned the field from punishment toward treatment.

The American overdose epidemic was the reward system meeting a supply: prescription opioids in the 1990s and 2000s, heroin when prescriptions tightened, and from 2013 fentanyl, about fifty times stronger than heroin and cheap to make. Overdose deaths rose from about 17,400 in 2000 to about 108,000 in 2022, more Americans in a year than died in the whole Vietnam War.

The turn came in 2023. On the CDC's provisional counts, deaths fell about a quarter in 2024 and a further 13% in 2025, to about 70,700, back to the level of 2019, and the twelve months to April 2026 brought about 67,000. The field is still sorting the reasons: naloxone sold over the counter since 2023, wider treatment with buprenorphine and methadone, a weaker fentanyl supply, fewer new users, and the grim arithmetic of a vulnerable population already lost. Buprenorphine and methadone halve mortality, yet most people with opioid addiction still do not receive them.

Alcohol, the legal substance, kills about 178,000 Americans a year through liver disease, cancer, accidents, and violence, more than all the illegal drugs together. If larger trials confirm the GLP-1 drugs' signal against heavy drinking (Module 3), they would be the first new addiction treatment in a generation.

6g. Suicide

Suicide took 48,824 American lives in 2024 and about as many in 2025 on provisional data, when it fell from tenth to eleventh among the causes of death as influenza returned, and worldwide it takes about 727,000 lives a year. In the United States it is the second cause of death among people aged 10 to 14 and 25 to 34, and about four times more common in men, with the highest rates among older men, in rural areas, and among American Indians and veterans.

Most people who die by suicide have a diagnosable disorder, most were not in treatment, and many acted within an hour of deciding. That finding underlies the strongest evidence in the field: restricting access to lethal means during a crisis saves lives, because the crisis passes, and most people who survive an attempt do not go on to die by suicide. Screening, safety planning, follow-up contact after emergency visits, and lithium (6c) and ketamine in specific groups have trial evidence, and the crisis lines are the front door, in the United States the 988 line since 2022, with millions of contacts a year. This is a subject where a reader may be closer to the material than to the statistics, and where that front door is the right first call.

Module 6 Key Points

Mental Health

• Mental illness is measured by symptom, not test, so rising diagnoses cannot be read as rising illness without argument.

• Treatments work modestly and better together; about half of ill adults get none, and the placebo response is why trials matter.

• Teenage girls' persistent sadness rose from 36% to 57% by 2021, then fell to 43% in 2025.

• Screens are the leading suspect for the decline, but unproven; school phone restrictions in 39 states are the largest test.

• Overdose deaths fell from about 108,000 in 2022 to about 70,000 in 2025; alcohol kills more Americans than all illegal drugs.

• Suicide's strongest evidence is restricting lethal means during a crisis that passes.

Module 6 Quiz

Check Your Understanding

1. What share of American high-school girls reported persistent sadness or hopelessness in 2025?

A) About 57%, unchanged since 2021
B) About 65%, a new record
C) About 30%, back to the level of 2011
D) About 43%

2. What does the module say about the placebo response in depression trials?

A) A third to a half of patients improve on nothing, which is why trials are needed.
B) It is negligible, so antidepressant trials can be small and short.
C) It occurs only among patients who correctly guess that they are taking the placebo pill.
D) Active placebos have eliminated it from most trials since 2010, so the drug effects are now clean.

3. Which psychedelic does the module describe as closest to approval in 2026?

A) MDMA, for post-traumatic stress
B) Ketamine, for chronic pain
C) Psilocybin, for treatment-resistant depression
D) Ayahuasca, for addiction

4. What happened to American overdose deaths after 2022, according to the module?

A) They held near 100,000 a year.
B) They rose to a record of about 125,000 as fentanyl spread west.
C) They fell below 20,000 for the first time since the start of the century.
D) They fell from about 108,000 to about 70,000 in 2025.

5. What is the strongest evidence in suicide prevention?

A) Universal screening at checkups
B) Restricting lethal means during a crisis
C) Antidepressants at the first sign
D) Long hospital stays

Module 7 — Hormones

The Body's Messaging System

Recommended Reading / Reference

Book: Randi Hutter Epstein, *Aroused: The History of Hormones and How They Control Just About Everything*

Reference: The Endocrine Society's clinical practice guidelines and the Menopause Society's 2022 position statement on hormone therapy, the references for 7b and 7c

7a. The System

A hormone is a chemical released by one tissue into the blood to change the behavior of another, and the endocrine system is the set of glands that make them, run by the pituitary, a gland at the base of the brain that also makes growth hormone, under the instruction of the hypothalamus above it. The thyroid sets the metabolic rate, and the adrenal glands make cortisol and adrenaline for stress and aldosterone for salt. The pancreas makes insulin and glucagon (Module 3), and the ovaries and testes make estrogen, progesterone, and testosterone, while fat, gut, bone, and kidney, which were not counted as glands until recent decades, turn out to be among the busiest.

The system works by feedback: the hypothalamus signals the pituitary, the pituitary signals the gland, the gland's hormone rises, and its rise switches the signal off. It is a thermostat in three tiers, which is why a disorder can sit at any of the three levels, and why a hormone given as a drug suppresses the body's own production.

Most hormones circulate in billionths or trillionths of a gram per milliliter, and small shifts have large effects. A dozen common conditions are hormonal, among them thyroid disease (7b), polycystic ovary syndrome in about one woman in ten, and diabetes (Module 3).

7b. Cortisol, Thyroid, and the Stress Response

Cortisol is the hormone of the long emergency. It rises in the early morning and under stress, raises blood sugar, suppresses inflammation and immunity, and mobilizes the body for a threat that, in the original design, was a predator and is now a deadline. Its short-term action saves lives, but its chronic elevation corrodes, bringing higher blood pressure and blood sugar, abdominal fat, suppressed immunity, and disturbed sleep. That is one mechanism behind the well-replicated finding that chronic stress, poverty, and isolation raise disease risk, and the reason for caution about the supplement market's claims for 'adrenal fatigue', a condition the Endocrine Society says does not exist.

Too little thyroid hormone, hypothyroidism, affects about one adult in twenty, mostly women and mostly from autoimmune disease, and brings fatigue, weight gain, sensitivity to cold, and slowed thought, which a daily pill reverses by replacing the missing hormone exactly; too much brings the reverse. The condition is the model of endocrinology's success, a blood test, a replacement, and a normal life, and the model of its temptation, since the wish to explain fatigue and weight with a gland produces far more thyroid tests than thyroid disease.

7c. The Sex Hormones Across a Life

• **Puberty** — the hypothalamus wakes the gonads between about 10 and 14, earlier in girls than in boys, and about a year earlier than a century ago, a shift tracked to better nutrition and, in recent decades, to obesity. Estrogen and testosterone build the adult body over about four years and reshape the adolescent brain in ways that explain both its appetite for risk and its plasticity.

• **The reproductive years** — the menstrual cycle's monthly rise and fall of estrogen and progesterone governs these years, and hormonal contraception, which suppresses the cycle's signals, is among the most studied medicines in history. Fertility's decline with age is the subject of Module 10.

• **Menopause** — the ovaries retire at a median age of 51, taking estrogen with them; three-quarters of women have hot flushes, many have disrupted sleep and mood, and over the following decades come the bone loss and cardiovascular risk that estrogen had held back. Hormone therapy relieves the symptoms decisively, and its balance of risk and benefit is the field's longest argument. In 2002 the Women's Health Initiative trial reported higher risks of breast cancer and blood clots and use collapsed. Later analysis found the heart risks concentrated in women who started long after menopause and the absolute risks small for women who started near it, while estrogen taken alone did not raise breast-cancer risk in the trial. In November 2025 the FDA moved to remove the boxed warnings on heart disease, breast cancer, and dementia, and the first relabeled products were approved in February 2026, while the warning on uterine cancer stays for estrogen taken alone. The reversal is the largest in the drug's history, and the course marks it as still contested at the margins.

• **Testosterone** — peaks in the twenties and declines about 1% a year after 30, a normal trajectory that the 'low T' industry has turned into a diagnosis. True deficiency is real and treatable, and a 2023 trial of 5,246 men aged 45 to 80 with low levels found that treatment did not raise the rate of heart attacks and strokes, though it brought more atrial fibrillation, blood clots in the lungs, and kidney injury. In February 2025 the FDA removed the cardiovascular warning from testosterone labels and added the trial's results, and evidence that testosterone helps men with normal levels is still absent.

• **The hormones that were found late** — leptin from fat was discovered in 1994, ghrelin from the stomach in 1999, and the gut hormone GLP-1 in the 1980s. Older hormones gained new roles in the same decades: vitamin D, made in the skin from sunlight and activated by the kidney, which acts as a hormone governing calcium and bone; melatonin from the pineal gland, which signals night to the body clock; and oxytocin. Each is now a drug, a supplement, or both.

7d. GLP-1: Physiology Before It Was a Drug

Glucagon-like peptide-1 is a hormone the gut releases within minutes of a meal, telling the pancreas to release insulin, the stomach to empty more slowly, and the brain that the meal is enough. The natural hormone lasts about two minutes in the blood, which kept it from becoming a useful drug for two decades, and the answer came in steps: a twice-daily version in 2005, a daily one in 2010, weekly injections from 2012, and the potent weekly semaglutide in 2017, followed by pills. Tirzepatide, approved in 2022, also mimics a second gut hormone.

The lesson is the endocrine system's. The drugs do not add a foreign mechanism but hold a natural signal on, and the body responds as if every meal were larger and every craving quieter. Because the same signal acts on the brain's reward circuits and on the organs behind the trial results of Module 3, a hormone of satiety is turning out to be a hormone of restraint across systems. Not every reach has held: the Alzheimer's trials of Module 3 failed, a reminder that a signal in observational data is not yet a result.

Module 7 Key Points

Hormones

• The endocrine system runs on feedback loops, which is why a hormone taken as a drug suppresses the body's own.

• Cortisol saves life in the short term and corrodes over years; 'adrenal fatigue' does not exist.

• In November 2025 the FDA moved to drop menopause hormone therapy's boxed warnings, reversing two decades of caution.

• Testosterone declines about 1% a year after 30 by design; the 'low T' industry turned the trajectory into a diagnosis.

• GLP-1 is a satiety signal that lasts two minutes, held on for a week by the drugs: a hormone of restraint.

Module 7 Quiz

Check Your Understanding

1. Why does a hormone given as a drug suppress the body's own production?

A) The gland withers once the drug has been in the blood for a week
B) The synthetic hormone binds the receptors more tightly than the natural one
C) The feedback loop switches the gland off
D) The liver breaks down the natural hormone faster when a drug is present

2. What did the FDA do about menopausal hormone therapy in November 2025?

A) It moved to remove the boxed warnings on heart disease, breast cancer, and dementia.
B) It withdrew the therapy from the market over new breast-cancer data.
C) It made hormone therapy available without a prescription.
D) It added a new boxed warning for dementia after a study of women who began the therapy late in life.

3. What did the 2023 testosterone trial of 5,246 men find?

A) A doubling of heart attacks in men over 65
B) Better memory and mood in men with normal levels
C) No effect of any kind, so regulators withdrew the drug for men over 45 with low or normal levels
D) No rise in heart attacks or strokes, but more atrial fibrillation

4. How long does natural GLP-1 last in the blood?

A) About two minutes
B) About a week, like the drugs that copy it
C) About six hours, through the digestion of a meal
D) Roughly a day, until the next large meal

5. What does the module say about 'adrenal fatigue'?

A) It is the early stage of Addison's disease.
B) It is a condition the Endocrine Society says does not exist, sold by the supplement market.
C) It is a recognized result of chronic stress.
D) It is cortisol depletion after years of poor sleep.

Module 8 — The Immune System

The Defense and Its Misfires

Recommended Reading / Reference

Book: Philipp Dettmer, *Immune: A Journey into the Mysterious System That Keeps You Alive*

Reference: The CDC's vaccination-coverage and measles data, and the Global Research on Antimicrobial Resistance (GRAM) estimates published in *The Lancet*

8a. Two Systems

The immune system is two systems in one. The innate system is old, fast, and general: the skin and mucous membranes as barriers, the white cells that swallow anything foreign, the complement proteins that punch holes in bacteria, and inflammation, the heat, redness, swelling, and pain of blood vessels opening to flood a site with defenders. Inflammation resolves an infection in days, and when it does not resolve, it becomes the chronic inflammation of 8b.

The adaptive system is young in evolution, slow, and specific. B cells make antibodies shaped to one target out of billions, T cells kill infected cells or coordinate the response, and memory cells keep the shape for decades, so that the second encounter with a pathogen is over before it begins.

Vaccines are the adaptive system taught in advance, a harmless piece or version of the pathogen prompting the antibodies and memory without the disease. Their record is the largest in medicine after clean water: smallpox eradicated, polio nearly so, measles deaths down 88% between 2000 and 2024, and an estimated 154 million lives saved in fifty years. The messenger RNA (mRNA) platform behind the COVID-19 vaccines (8d) has since produced the first personalized cancer vaccines (Module 12).

8b. The Misfires

- **Allergy** — the adaptive system's response to a harmless target, such as pollen, peanuts, or penicillin, affecting about a third of people and rising in every rich country. The leading explanation, though a contested one, is the 'hygiene hypothesis', that fewer early infections and microbes leave the system poorly trained. Anaphylaxis can kill, and in 2015 a trial found that feeding peanuts early in infancy prevents peanut allergy, reversing a generation of advice.
- **Autoimmunity** — the system attacking the self, in type 1 diabetes, rheumatoid arthritis, lupus, multiple sclerosis, celiac disease, Hashimoto's thyroiditis, and about a hundred other conditions that together affect about one person in ten, women nearly twice as often as men. Biologic drugs that block specific immune signals, such as tumor necrosis factor (TNF) and the interleukins, arrived in the late 1990s and changed rheumatoid arthritis from a crippling disease to a managed one.
- **Immunodeficiency** — the system's absence, inherited or acquired. The human immunodeficiency virus (HIV) destroys the T cells that coordinate the response; it has killed about 44 million people, and 41 million live with it, about 32 million of them on treatment. Drugs that hold the virus at undetectable levels turned a death sentence into a chronic condition in a single generation, the field's proudest achievement, and a twice-yearly injection that prevents infection, lenacapavir, was approved in June 2025. In the same year international funding for HIV programs fell 18%, prevention work was cut, and new infections rose in 21 countries.

• **Cancer and immunity** — the system's failure to see, since tumors evade it by displaying 'do not attack' signals. The checkpoint inhibitors, drugs that block those signals, are Module 12's treatment revolution, and their discovery won a Nobel Prize in 2018.

• **Inflammation as the common thread** — the innate system's failure to stand down. Chronic inflammation, measured by C-reactive protein in the blood, tracks heart disease, diabetes, dementia, and frailty, and because obesity, smoking, inactivity, and stress raise it while their opposites lower it, the mechanism lies behind half of Module 14.

8c. Infection, Antibiotics, and Resistance

Tuberculosis kills about 1.23 million people a year, more than any other single pathogen, while malaria kills about 610,000, mostly African children, HIV about 570,000, and the pneumonias and diarrheal diseases of childhood about a million more.

Antibiotics, in use since 1942, cut the death rate from bacterial infection by an order of magnitude and made modern surgery, chemotherapy, and intensive care possible, but their misuse in medicine and agriculture has bred resistance faster than new antibiotics have been found. Resistant infections directly caused 1.14 million deaths in 2021, contributed to 4.71 million, and are forecast to cause 39 million deaths between 2025 and 2050, rising fastest among the old. Deaths from methicillin-resistant *Staphylococcus aureus* (MRSA) more than doubled between 1990 and 2021, and the frontier is hospital bacteria that resist the carbapenems, the drugs of last resort.

New classes of antibiotic have been rare for decades, a handful at most, because the economics do not work: a drug that is used sparingly and briefly cannot repay its development. In 2025 the FDA approved two more first-in-class oral antibiotics, gepotidacin for urinary-tract infections and gonorrhea and zoliflodacin for gonorrhea, the first new classes for those infections in decades, but both serve narrow uses and the economics have not changed. The responses are stewardship, vaccines that prevent the infections that would need antibiotics, and payment models that reward a drug's existence rather than its sales, which Britain has pioneered.

8d. What COVID-19 Taught and Left

The pandemic killed about 7 million people by official count, and the WHO estimates excess deaths in 2020-23 at about 22 million, the largest toll since 1918. It left the immune system's lessons in plain view. A novel virus finds a population without memory, and a vaccine built in eleven months, on a platform decades in development, cut deaths among the vaccinated by about 90% in its first months.

The residue in 2026 has three parts. Symptoms that persist for months after infection affected about 3% of American adults in 2024, with mechanisms under study and no treatment established. Trust fell, and vaccination with it, the subject of 8e. And the capacity for the next pandemic, built in 2020-22, has been partly dismantled: in August 2025 the federal government canceled about $500 million of research on mRNA vaccines, and in January 2026 the United States completed its withdrawal from the WHO.

The next pandemic is a matter of when. The bird-flu strain H5N1 (a subtype of influenza A) has circulated in American dairy cattle since 2024, reaching about 1,180 herds by October 2026, when Washington reported its first, and H5 bird flu has caused 71 known human cases in the United States since 2024. The lesson the course records is that the immune system worked and the institutions around it did not.

8e. The Vaccine Schedule Fight

The fall in trust (8d) set up the policy fight of 2025-26. Kindergarten vaccination coverage has fallen every year since 2020, and in the 2025-26 school year exemptions reached a record 4.2%, while coverage for the measles, mumps, and rubella (MMR) vaccine was 92.4%, below the 95% that stops measles spreading. Measles, declared eliminated in the United States in 2000, has returned, with 2,289 cases in 2025 and 3,887 by October 1, 2026, the most in more than three decades. Canada lost its elimination status in November 2025, and the Pan American Health Organization (PAHO) postponed its review of the American status to November 2026.

Federal policy changed in the same months. In June 2025 the health secretary, Robert F. Kennedy Jr., replaced every member of the Advisory Committee on Immunization Practices (ACIP), which sets the schedule, and in December the new committee ended the universal hepatitis B dose at birth for babies whose mothers test negative. On January 5, 2026, the Department of Health and Human Services (HHS) cut the vaccines recommended for every child from those against 17 diseases to 11, moving the vaccines against COVID-19, influenza, hepatitis A and B, meningococcal disease, and rotavirus to individual decisions. On March 16, 2026, a federal court stayed the change and the new committee's votes, restoring the earlier schedule, and the government's appeal was set for argument in early October 2026.

The case for the changes, as the administration and its supporters make it. The American schedule had grown larger than those of peer countries; Denmark, for one, recommends vaccines against far fewer diseases. Several vaccines protect against risks that depend on circumstances, since a newborn whose mother tests negative for hepatitis B faces little risk at birth and a healthy child faces little from influenza or COVID-19, and individual decisions fit such cases better than blanket recommendations. Its advocates also argue that the vaccines' safety was tested too narrowly, with few placebo-controlled trials and little study of the schedule as a whole. On this view, the pandemic's mandates broke public trust, and a smaller core schedule with more choice is the way to rebuild it.

The case against, as the American Academy of Pediatrics and most immunologists make it. The schedule's vaccines are safe and effective on decades of data. The hepatitis B birth dose catches infections that a mother's test misses or that come from others in the home, and an infection acquired at birth usually becomes lifelong. Peer countries' schedules sit inside systems of universal care and prenatal screening, so they do not transfer intact, and moving a vaccine to individual decision lowers its uptake. The process bypassed the committee's own evidence reviews, and outbreaks follow coverage, as measles shows.

The evidence between them. Most scientists regard the vaccines' safety and effectiveness as settled by decades of trials and surveillance, which the administration's advisers dispute, while the size of the schedule is a policy choice on which rich countries differ. Coverage was already falling before the 2026 changes, so trust was eroding before the policy moved, and under the court's stay the new schedule is not in force.

The course's reading. The question that matters for children's health is uptake, and any change that lowers it further carries a cost that the measles count will show first.

Module 8 Key Points

The Immune System

• The immune system is two: the innate, fast and general, and the adaptive, slow and specific, whose memory vaccines teach in advance.

• Vaccines saved about 154 million lives in fifty years; measles deaths fell 88% between 2000 and 2024.

• Resistant infections killed 1.14 million people directly in 2021, and new antibiotic classes stay rare: two arrived in 2025.

• COVID-19 caused about 22 million excess deaths; the vaccines worked, and the institutions around them did not.

• American kindergarten exemptions hit a record 4.2% in 2025-26, and measles reached 3,887 cases by October 2026.

• The 2026 cut to the childhood schedule is stayed in court; uptake is the question that matters for children.

Module 8 Quiz

Check Your Understanding

1. What is a vaccine, in the module's account?

A) A drug that kills viruses in the blood
B) An antibody made in a laboratory and injected to fight an infection
C) The adaptive system taught in advance, without the disease
D) A weakened pathogen that gives immunity by causing a mild case of the disease each time it is given

2. What did the FDA approve in 2025 for urinary infections and gonorrhea?

A) A vaccine against gonorrhea
B) Two oral antibiotics from new classes, the first for those infections in decades
C) A twice-yearly preventive injection
D) A drug that reverses resistance to old antibiotics

3. What did a federal court do on March 16, 2026?

A) It upheld the new schedule
B) It ordered measles vaccination for every schoolchild
C) It stayed the cut to the childhood schedule and the new committee's votes
D) It ruled that states may no longer grant exemptions from school vaccination for religious or personal reasons

4. What share of American kindergartners had vaccine exemptions in 2025-26?

A) About 1%, unchanged since 2019
B) About 10%, double the 2020 level
C) About 2.5%, close to where it stood before the pandemic began in 2020
D) A record 4.2%

5. Which pathogen kills the most people of any single infection?

A) Tuberculosis
B) HIV
C) Seasonal influenza
D) The malaria parasite

Module 9 — Muscles, Bones, and Movement

What Exercise Does to Every System

Recommended Reading / Reference

Book: Daniel Lieberman, *Exercised: Why Something We Never Evolved to Do Is Healthy and Rewarding*

Reference: The US *Physical Activity Guidelines for Americans* (2018) and the 2025 *Lancet Public Health* meta-analysis of daily steps in 57 studies

9a. The Machinery

The body's bones are living tissue, remodeled continuously by cells that lay bone down where it is stressed and remove it where it is not, so that the whole skeleton is replaced about every ten years. That is why astronauts lose 1-2% of their bone a month in weightlessness, and why weight-bearing exercise builds bone.

Bone mass peaks around 30 and declines after, faster in women after menopause, toward osteoporosis, which will break a bone in one woman in two and up to one man in four over 50, most often the hip, spine, or wrist. About a quarter of older patients who break a hip die within a year, and falls are the leading cause of injury death in the old, which makes balance a matter of life.

Skeletal muscle, some 600 muscles in all, is the body's largest tissue by mass and its largest consumer of glucose, so muscle is metabolic as well as mechanical: it stores glycogen and takes up sugar under insulin's instruction. Its loss with age, called sarcopenia, runs at 3-8% a decade after 30 and accelerates after 60, and it is the reason old people become frail, insulin-resistant, and unable to recover from illness. Muscle responds to load at any age, with people in their eighties and nineties gaining strength within a few months of resistance training, and its fiber types, fast for power and slow for endurance, and the mitochondria within them are what the exercise of 9b trains.

9b. What Exercise Does

Exercise is the closest thing medicine has to a universal drug, and its mechanisms are known. It raises the heart's output and the vessels' flexibility, lowers blood pressure and LDL cholesterol, raises high-density lipoprotein (HDL), and improves insulin sensitivity for a day or two after each session while building muscle that takes up glucose. It also reduces visceral fat and inflammation, builds bone, releases growth factors that support the hippocampus, the brain's memory center, improves sleep and mood (Module 6), and is associated with lower rates of thirteen cancers.

The dose is the question the evidence answers with unusual consistency. The largest gains come from the first steps, going from nothing to a little, and the returns then diminish (9c).

Aerobic fitness, measured as maximal oxygen uptake (VO2 max), is the single strongest predictor of mortality in the studies that measure it, stronger than smoking, diabetes, or blood pressure, and the least fit fifth of the population dies at three to four times the rate of the fittest. Strength comes second, with grip strength predicting survival in the old better than most blood tests. The design's lesson, in Daniel Lieberman's account, is that the body evolved to move because it had to and to rest because energy was scarce, so it is not lazy but efficient, and the sedentary environment removed the necessity without removing the need.

9c. The Dose-Response

Worked example — the dose-response of exercise

Take the evidence as it stands in 2026 and read the curves, starting with steps. A 2025 analysis of 57 studies found that 7,000 steps a day, against 2,000, was associated with 47% lower mortality from all causes and with lower rates of heart disease, cancer death, dementia, depression, and falls, and that most of the curves bend at 5,000-7,000 steps, with only modest gains above 7,000. A 2022 pooling of fifteen cohorts found mortality leveling off at 6,000-8,000 steps for adults over 60 and at 8,000-10,000 for younger ones, and a 2023 analysis of seventeen found each additional thousand steps a day associated with about 15% lower mortality across the range where the curve still falls. The 10,000 figure began as a Japanese pedometer slogan in 1965, and it turns out to be more than most people need.

Then minutes. The guidelines' 150 minutes a week of moderate activity, or 75 of vigorous, is where the curve has captured most of its gain, with mortality roughly a quarter to a third lower than with none, and three hundred minutes captures a little more. Beyond about 600 the curve is flat, so the extra benefit is zero, but it is never negative in any large cohort, and the worry about 'too much exercise' is confined to heart-rhythm problems in a small number of lifelong endurance athletes.

Then strength and intensity. Any resistance training, against none, is associated with about 15% lower mortality, with the benefit peaking at roughly 30-60 minutes a week, about two sessions, and combined with aerobic activity the association is stronger than either alone, at about 40% lower mortality. For a given volume, vigorous activity outperforms moderate, and short bursts count: in accelerometer studies, a minute or two of vigorous effort several times a day, such as climbing stairs, tracks much of the benefit of formal exercise.

The arithmetic for a sedentary 50-year-old is short. Thirty minutes of brisk walking five days a week, plus two 25-minute strength sessions, takes under four hours and sits where the curves have delivered most of what they will, and about a quarter of American adults report doing that much. About half meet the aerobic guideline alone, on a 2024 CDC survey. The caveat applies to all of it: these are cohorts, not trials, and the fit differ from the unfit in ways the statistics cannot fully remove. The randomized trials, which exist for blood pressure, blood sugar, mood, and cognition, show real effects that are smaller than the cohorts imply, so the evidence is settled for direction and contested for size.

9d. Injury, Pain, and the Back

Musculoskeletal disorders are the largest cause of disability in the world, among them low back pain, which affected about 619 million people in 2020, neck pain, osteoarthritis, and fractures. Their medicine is a case study in the evidence turning against the intervention. Most back pain resolves in weeks without treatment, while imaging finds 'abnormalities' in most pain-free adults and leads to surgery that trials show is no better than exercise for most cases, and opioids were prescribed for back pain in the quantities that fed the overdose epidemic (Module 5). The treatment the evidence supports, movement, strength, and time, is the one the system is least organized to provide.

Osteoarthritis, the wearing of joint cartilage, affects most people over 65, is accelerated by weight, and has no drug that changes its course. Its treatments are weight loss, exercise, and, when the joint is gone, replacement, and Americans receive more than a million hip and knee replacements a year.

Module 9 Key Points

Muscles, Bones, and Movement

• Bone is built by load; about a quarter of older hip-fracture patients die within a year, which makes falls a killer.

• Skeletal muscle is the body's largest tissue and largest glucose consumer, and it responds to training at any age.

• Aerobic fitness is the strongest single predictor of mortality in the cohorts that measure it, stronger than smoking.

• About 7,000 daily steps captures most of the mortality benefit, and any strength training is linked to about 15% lower mortality.

• Most back pain resolves alone, imaging misleads, and surgery rarely beats exercise: the evidence against intervention.

Module 9 Quiz

Check Your Understanding

1. What did a 2025 analysis of 57 studies associate with 7,000 daily steps, against 2,000?

A) No measurable benefit
B) 10% lower mortality
C) 47% lower mortality from all causes
D) More falls among the old

2. What is the strongest single predictor of mortality in the cohorts that measure it?

A) Resting heart rate.
B) Body-mass index, with the leanest living longest.
C) Daily step count, with 10,000 the threshold for any benefit at all.
D) Aerobic fitness, measured as VO2 max.

3. What share of older patients who break a hip die within a year, according to the module?

A) About a quarter of them
B) Under 5%
C) About one in ten
D) Just over half of them, mostly from blood clots and pneumonia in the first months

4. What caveat does the module apply to the exercise evidence?

A) Most of the studies were funded by the fitness industry.
B) These are cohorts, not trials.
C) The evidence applies only to adults under 60 years old.
D) The benefits vanish once diet and body weight are accounted for.

5. What treatment does the evidence support for most back pain?

A) Early imaging
B) Spinal surgery
C) Movement, strength, and time
D) Opioid painkillers

Module 10 — Reproduction, Development, and Aging

The Body Across a Life

Recommended Reading / Reference

Book: Andrew Steele, *Ageless: The New Science of Getting Older Without Getting Old*

Reference: The CDC's fertility and maternal-mortality reports and the Interventions Testing Program of the NIH's National Institute on Aging, the reference for which longevity compounds have worked in animals

10a. Fertility

A woman is born with all the eggs she will have, one to two million, falling to about 300,000 at puberty and a few hundred by menopause, and she releases about one a month for 35 to 40 years. Fertility peaks in the early twenties, declines gently from 30, and declines steeply from 35, as the chance of conceiving in a given cycle falls from about 25% at 25 to about 5% at 40 with both the number and the quality of the eggs.

A man makes sperm continuously from puberty, at a rate that declines slowly with age and with a quality that falls with age, weight, heat, and smoking. On contested evidence, sperm counts in rich countries have also fallen over fifty years, for reasons the studies have not identified.

Infertility, defined as a year of trying without conception, affects about one person in six worldwide, with the causes lying with men and women in roughly equal shares, and its treatment has become an industry. In-vitro fertilization (IVF), in use since 1978, now produces about 2.8% of American births, more than 100,000 babies in 2024, and 5-10% of births in some European countries. Success runs at roughly 40% per egg retrieval for women under 35 and under 10% over 42, while egg freezing, whose success rates the clinics that sell it rarely quote, is the decade's growth product.

The demographic consequence is a subject of its own. The physiological one is that the biology has not moved while the age at first birth has, from 21.4 in 1970 to 27.6 in 2024 in the United States, and the industry sells the gap.

10b. Pregnancy and Childhood

Pregnancy is the body's largest physiological project. Blood volume rises by about half and the heart's output by 40%, the immune system tolerates a half-foreign organism for nine months, and the placenta, an organ the fetus builds, runs the exchange.

Pregnancy's dangers, once the largest killer of young women, are now rare in rich countries and common elsewhere. American maternal mortality was 17.9 deaths per 100,000 live births in 2024, the worst among rich countries, and 44.8 for Black women, about three times the rate for white women, against a few per 100,000 in the Nordic countries. Worldwide, about 260,000 women died of pregnancy and childbirth in 2023, mostly from hemorrhage, infection, and high blood pressure in the poorest countries.

Infant mortality tells the same story, at about 1.8 deaths per 1,000 births in Japan and 5.5 in the United States in 2024, and above 50 in parts of sub-Saharan Africa. The first thousand days, from conception to the

second birthday, are when nutrition and infection set the trajectory of the brain, of growth, and of lifetime disease.

Childhood vaccination (Module 8) is among the largest determinants of whether a child reaches five. Adolescence, the reorganization of brain and body between about 10 and 25, is when most lifetime mental illness begins and when most lifetime habits are set, from smoking and drinking to activity, which is why prevention aimed at teenagers has the longest payoff of any.

10c. The Aging Trajectory

System	What declines, and when	What slows it
Muscle and bone	Both from 30, at the rates in Module 9	Resistance training, the best-evidenced intervention in aging; protein; vitamin D for the deficient
Heart and vessels	Arteries stiffen; maximum heart rate falls about one beat a year; VO2 max down about 10% a decade	Aerobic exercise; blood pressure and lipid control (Module 4)
Brain	Processing speed from the twenties; volume about 5% a decade after 40; memory retrieval slows, knowledge holds	Exercise, hearing correction, blood pressure, engagement; the modifiable risks of Module 5
Immune	The thymus shrinks after adolescence; response to new pathogens and vaccines weakens; inflammation rises	Vaccination, with higher-dose flu vaccines for the old; the anti-inflammatory levers of Module 14
Metabolism	Adjusted for body size, energy use holds steady from 20 to 60, then falls about 0.7% a year; insulin sensitivity falls; fat shifts to the abdomen	Muscle, weight control, sleep
Senses	Presbyopia at about 45; hearing loss in half of those over 75; smell and taste dull	Hearing aids, against a dementia risk (Module 5)
Kidneys, liver, lungs	Kidney filtration falls about 1% a year after 40; lung capacity as in Module 4	Not smoking; the cardiovascular levers
Skin, hair, sleep	Collagen loss; graying; deep sleep shrinks and waking increases	Sun protection; the sleep habits of Module 5

Population averages; individual trajectories vary widely, and the variance itself grows with age.

10d. The Longevity Science, and the Longevity Industry

In thirty years the science of aging has produced a set of interventions that extend healthy life in animals, a handful now in human trials, and an industry built on them. Calorie restriction (2e) is the model the rest imitate. Rapamycin, a drug that mimics restriction through the nutrient-sensing pathways, gives the strongest animal result in the field: in the Interventions Testing Program it extended mouse lifespan even when started late in life, by about 9-14% at first and by about a quarter at higher doses. Its first human aging trial, published in 2025, found low doses safe over 48 weeks but missed its main goal, a fall in visceral fat, and modest gains in women's lean mass were the only signal.

Metformin, the diabetes drug, showed longevity signals in observational data, but the trial designed to test it, Targeting Aging with Metformin (TAME), has waited a decade for full funding. Senolytics, the drugs that clear senescent cells, reversed frailty in mice, but in people the results are mixed: a 2024 trial in older women found no effect on bone overall, and one company's lead senolytic failed in 2025. Precursors of NAD raise its level in the blood and have shown nothing in human outcomes, and young-blood transfusions and most 'biohacking' have shown nothing in humans.

Epigenetic reprogramming, resetting cells' marks to a younger state, drew billions of dollars of investment from 2022 and reached people in June 2026, when the first trial began treating patients with diseases of the optic nerve, glaucoma and a kind of stroke of the optic nerve. The first data, on three patients and released in October 2026, showed the treatment tolerated, with improved visual fields in two, which is a first step and not a result. The GLP-1 drugs, which cut deaths from all causes in their largest heart trial (Module 3), may turn out to be the first longevity drug to reach the population, by accident.

The industry sells the frontier's promise on the evidence of its weakest studies: supplements with mouse data, clinics with none, and tests that report a 'biological age' from the epigenetic clocks of Module 2, which are real research tools but not yet a guide to anything a person should do. The course's standard is that an intervention counts when a randomized human trial shows a health outcome, and as of October 2026 no product sold for longevity meets it. What meets it is the settled list of Module 14, with the metabolic drugs for those who need them.

Module 10 Key Points

Reproduction, Development, and Aging

• Female fertility falls steeply from 35, while the age at first birth rose from 21 to 27.6; an industry sells the gap.

• American maternal mortality, 17.9 per 100,000 births in 2024, is the rich world's worst, and about three times higher for Black women.

• Every system declines on a schedule, muscle from 30 and the brain from 40, and each decline can be slowed.

• Rapamycin's mouse results are the field's strongest; its first human aging trial, in 2025, missed its main goal.

• The first human trial of epigenetic reprogramming began in June 2026; no longevity drug yet has a trial outcome.

Module 10 Quiz

Check Your Understanding

1. Where does American maternal mortality stand among rich countries?

A) It is among the best, near Norway's.
B) It is the worst, at 17.9 per 100,000 births in 2024.
C) It sits in the middle of the group, level with France and Germany.
D) It is just below the average for rich countries, after falling sharply since 2021.

2. What did the first human trial of rapamycin for aging find in 2025?

A) A 20% gain in lifespan
B) Fewer infections in men
C) Large falls in visceral fat in every participant
D) Safe, but it missed its main goal

3. What is the course's standard for a longevity intervention to count?

A) A randomized human trial showing a health outcome
B) A published mechanism and supportive studies in mice and monkeys
C) Lifespan extension in at least two different species of mammal
D) A measurable fall in biological age on a validated epigenetic clock, confirmed in a second laboratory

4. How much does the chance of conception per cycle fall between ages 25 and 40, according to the module?

A) From about 25% to about 5%
B) From about 50% to about 25%, mostly from sperm quality
C) It holds near 20% until menopause, then falls very abruptly
D) From about 10% to about 2%, because of declining frequency of intercourse rather than biology

5. What happened in June 2026 in the longevity field?

A) Rapamycin was approved for aging
B) The metformin trial reported
C) Japan approved a senolytic drug for frailty in the elderly after a successful trial in 2025
D) The first human trial of epigenetic reprogramming began

Module 11 — How the Body Fails

The Causes of Death and Disability

Recommended Reading / Reference

Book: Atul Gawande, *Being Mortal: Medicine and What Matters in the End*

Reference: The CDC's *Mortality in the United States: Provisional Data, 2025* (July 2026) and the WHO's Global Health Estimates (updated October 2026)

11a. What People Die Of

The cause-of-death table is the health of a population on one page, and its shape changed more in the twentieth century than in all the centuries before. In 1900 the leading American causes were pneumonia, tuberculosis, and diarrhea, and a third of deaths were of children under five, but by 1950 heart disease and cancer led, and they have led every year since.

The 2025 table, from provisional data published in July 2026, counts 3.09 million American deaths and the lowest age-adjusted death rate ever recorded, and it carries four lessons. The top two causes, the diseases of Modules 4 and 12, account for more than two deaths in five. The third, unintentional injury, is mostly drug overdoses, falls, and road deaths, and it is the leading cause of death between ages 1 and 44. Alzheimer's disease, absent from the table in 1950, is sixth because people now live long enough to get it, and influenza and pneumonia returned to the top ten, in eighth place, after a severe flu season, while COVID-19, which left the top ten in 2024, stayed out of it.

Rank	United States, 2025 (provisional)	Deaths
1	Heart disease	694,708
2	Cancer	622,832
3	Unintentional injuries (overdoses, falls, road deaths)	184,265
4	Stroke	About 170,000
5	Chronic lower respiratory diseases	About 150,000
6	Alzheimer's disease	About 115,000
7	Diabetes	About 95,000
8	Influenza and pneumonia	56,511
9	Kidney disease	About 55,000
10	Chronic liver disease and cirrhosis	About 52,000

CDC National Center for Health Statistics, provisional data (July 2026). Ranks 4-7 are rounded; the counts for ranks 9 and 10 are approximated from 2024's final figures. Unintentional injuries are undercounted in provisional data (197,449 in 2024's final count).

The world's table is similar at the top and different below it. On the WHO's estimates for 2023, released in October 2026, the leading causes were ischemic heart disease (9.5 million deaths), stroke (6.8 million), COPD (3.6 million), lower respiratory infections (2.7 million), Alzheimer's and other dementias (2.1 million), diabetes (2.0 million), and lung cancer (1.8 million). COVID-19, the first cause in 2021, had fallen to fourteenth. In the poorest countries, seven of the top ten causes are still infections, as lower respiratory infections, diarrhea, malaria, tuberculosis, and HIV kill there as infections killed everywhere in 1900.

The 'epidemiological transition', the shift from infectious to chronic disease, is the single fact that most distinguishes one country's health from another's, and most of the world is in the middle of it, carrying both burdens at once.

11b. How Death Arrives

The mechanism of dying is nearly always the same at the end, as the heart stops or the breathing does, and what differs is the path. The sudden paths are the clot (heart attack, stroke, or a clot in the lungs), the rhythm, the injury, and the overdose, and sudden cardiac arrest outside the hospital strikes more than 350,000 Americans a year, often as the first symptom of heart disease.

The gradual paths are the organ failures, in which a damaged heart cannot keep up, or the kidneys, the liver, or the lungs of COPD fail the same way. The systemic paths are cancer's spread and the frailty of the very old, in which no single organ fails but all of them run down together.

Sepsis, the body's overwhelming response to infection, is the final common pathway for many of these deaths. At least 1.7 million American adults develop it each year and at least 350,000 of them die in the hospital or are discharged to hospice, and sepsis is involved in more than a third of hospital deaths, most of them among people who were already ill. It is the reason infection remains a leading killer of the old even in rich countries, and the reason antibiotic resistance (Module 8) is a question of mortality rather than convenience.

Where people die has changed as much as what they die of. A century ago nearly everyone died at home, by 1980 most Americans died in hospitals, and since 2017 home has again been the most common place of death in the United States. Hospice, care aimed at comfort at the end of life, was used by about 53% of Medicare patients who died in 2024, replacing much of the intensive-care death that most people say they do not want and that many still get without the conversations Atul Gawande's *Being Mortal* is about.

11c. The Chronic Burden

Death is the wrong measure for most of what ails people. Counted in years lived with disability, the leading causes are low back pain, depression, headache disorders, diabetes, anxiety, hearing loss, and osteoarthritis, conditions that kill rarely and disable for decades, and the world's disability burden has shifted toward them as people survive the diseases that used to kill.

About three American adults in four report at least one chronic condition and about half report two or more (2023). The CDC says 90% of the nation's health spending goes to people with chronic and mental-health conditions, a figure that counts all their care rather than only the care for those conditions (Module 15). The pattern is the mismatch of Module 1, which is why the largest gains available are not in the hospital but before it.

On the disability-adjusted life year (1c), which captures the whole burden, the world's leading burdens are heart disease, stroke, newborn conditions, COPD, lower respiratory infection, diabetes, back pain, depression, and road injury, the double burden of 11a.

Behind every line of the table runs the demography. The population grows older every year, so the count of chronic conditions rises even as the rate of each one falls, and the diseases of the very old, dementia, frailty, and falls, take a growing share of the table whatever medicine does.

Module 11 Key Points

How the Body Fails

• Heart disease and cancer have led the American table since 1950; 2025 had the lowest age-adjusted death rate ever recorded.

• The epidemiological transition, from infectious disease to chronic, is the single fact that most distinguishes a country's health.

• Death arrives suddenly by clot, rhythm, injury, or overdose, or gradually by organ failure; sepsis features in a third of hospital deaths.

• Home has been the most common place of death since 2017; about 53% of Medicare patients who die use hospice.

• Three American adults in four have a chronic condition, and the leading causes of disability kill rarely but last decades.

Module 11 Quiz

Check Your Understanding

1. What has led the American cause-of-death table since 1950?

A) Accidents
B) Infections
C) Heart disease, then cancer
D) Stroke and diabetes

2. Where has the most common place of death in the United States been since 2017?

A) Hospitals
B) Home, as in 1900
C) Nursing homes, for most over 85
D) The intensive-care unit, as it has been since about 1980 for most Americans

3. What is the 'epidemiological transition'?

A) The replacement of hospital care by outpatient medicine in rich countries
B) The movement of disease surveillance from paper records to digital systems
C) The rise of drug overdoses to become the leading cause of death among Americans under 45 since 2020
D) A shift from infectious to chronic disease

4. What role does sepsis play in American hospital deaths, according to the module?

A) It is confined to surgical patients.
B) It is involved in more than a third of them.
C) It causes fewer than one hospital death in a hundred.
D) It causes about two-thirds of all deaths in intensive care, but few elsewhere.

5. Why does the module call death the wrong measure for most of what ails people?

A) The leading causes of disability kill rarely and disable for decades
B) Death certificates are usually wrong
C) Most deaths now come after 85
D) Death data lag by two years

Module 12 — Cancer

Two Hundred Diseases, One Mechanism, and a Treatment Revolution

Recommended Reading / Reference

Book: Siddhartha Mukherjee, *The Emperor of All Maladies: A Biography of Cancer*

Reference: The American Cancer Society's *Cancer Statistics, 2026* (January 2026) and the WHO cancer agency's global estimates for 2024 (September 2026), the sources for the figures in this module

12a. What Cancer Is

Cancer is not one disease but about two hundred, sharing the mechanism of Module 2, a cell whose mutations let it divide without limit and spread. They differ in everything else: where they start, how fast they grow, what drives them, and what stops them.

The mutations come from three sources, in proportions that vary by cancer. The first is the copying errors of ordinary division (2c). The second is inherited variants, which account for 5-10% of cases, such as BRCA1 and BRCA2 (genes named for 'breast cancer') in breast and ovarian cancer, and Lynch syndrome in colorectal cancer. The third is the environment, with tobacco leading, followed by obesity, alcohol, infections, ultraviolet light, radiation, and a short list of chemicals; the infections include human papillomavirus (HPV) in cervical and throat cancers, hepatitis B and C in liver cancer, and *H. pylori* in stomach cancer. On the American Cancer Society's estimate, about 40% of cases and nearly half of cancer deaths are attributable to modifiable risks.

A cancer is named for its tissue and staged by its extent, from a localized tumor to regional spread to distant metastasis, and the stage at diagnosis determines survival more than any other factor. That is the case for screening in 12c, and the reason the same word describes a curable skin lesion and a fatal pancreatic tumor.

12b. The Numbers

About 2.1 million Americans will be diagnosed with cancer in 2026 and about 626,000 will die of it, roughly 1,720 a day, while about 18.6 million Americans are alive after a diagnosis. Worldwide, the WHO's cancer agency estimates about 20.6 million new cases and 9.8 million deaths in 2024; about one person in five develops cancer before 75, and the burden is projected to rise by more than half by 2050 as populations age.

Lung cancer kills more Americans than colorectal and pancreatic cancer combined, and most of it traces to smoking (Module 4). In the United States, prostate and breast cancer are the most common diagnoses. Worldwide, lung and breast cancer lead and colorectal cancer is the third most common and the second deadliest, while pancreatic, liver, and brain cancers remain the ones where treatment has moved least.

The two trends that define the era run in opposite directions. The first is falling mortality: the American cancer death rate fell 34% between its 1991 peak and 2023, averting about 4.8 million deaths, thanks to smoking's decline, screening, and treatment, and five-year survival reached 70% for diagnoses made in 2015-21, against 49% in the mid-1970s. Some of the largest gains came in the deadliest cancers, with survival rising from 16% to 35% for metastatic melanoma, from 32% to 62% for myeloma, and from 2% to 10% for metastatic lung cancer.

The second trend is rising incidence in the young. Colorectal cancer under 50 has been rising by about 2-3% a year, alongside breast, kidney, uterine, and pancreatic cancers in adults under 50, for reasons that are under investigation and unresolved: obesity, diet, the microbiome, or something in the environment of people born after 1960. The rise is why colorectal screening, which began at 50, now begins earlier (12c).

12c. Screening

Screening finds cancer before it shows, and its value depends on the arithmetic of Module 13 and on whether early detection changes the outcome. Five programs have trial evidence or strong support, on the American guidelines in force in 2026.

- **Colorectal** — from 45 to 75, by colonoscopy every ten years or stool tests every one to three, the most effective screening in medicine, because it removes polyps before they become cancer. A blood test approved in 2024 is an option, which the American Cancer Society's May 2026 guideline recommends only for people who decline or do not complete the preferred tests.
- **Cervical** — by testing for human papillomavirus every five years from 25, now including samples people collect themselves, in a cancer that vaccination against HPV is on course to eliminate.
- **Breast** — by mammography every two years from 40 to 74, which prevents about one death per thousand women screened over a decade, at the cost of several hundred false alarms and some overdiagnosis.
- **Lung** — by low-dose computed tomography (CT) scans in heavy smokers from 50 to 80, which prevents about three deaths per thousand people screened.
- **Prostate** — by the prostate-specific antigen (PSA) blood test, where the trials show a small mortality benefit against a large overdiagnosis and the guidelines call for an informed decision rather than a default.

The newest tests are blood tests that look for fragments of tumor DNA from many cancers at once, and their first large trial reported in May 2026. In 142,000 people in England's National Health Service (NHS), the leading test did not meet its main goal, which was to reduce the number of cancers found at the late stages, III and IV. It did reduce stage IV cancers by 14%, and about half of its positive results proved to be cancer. Deaths have not yet been reported, and in September 2026 an FDA advisory panel voted 6-4 that the test is effective, with the agency's decision pending. Whole-body scans have no such evidence, and both are sold, meanwhile, on promises their trials have not yet delivered.

12d. Treatment

- **Surgery** — the oldest tool and, for localized solid tumors, still the most curative, removing the tumor with a margin of healthy tissue, guided by imaging that shows its extent, with minimally invasive techniques that have turned months of recovery into weeks.
- **Radiation** — focused energy that damages the DNA of dividing cells, now delivered with millimeter precision by proton beams and focused radiosurgery that spare the tissue around; about half of all patients receive it.
- **Chemotherapy** — drugs, from the 1940s onward, that kill dividing cells and so harm the hair, gut, and marrow too. Chemotherapy is still the backbone for many cancers, and its toxicity is what the newer classes were built to escape.
- **Targeted therapy** — drugs matched to a tumor's specific mutations, beginning with imatinib, which turned chronic myeloid leukemia from a fatal disease into a managed one in 2001. Tumors are now

sequenced at diagnosis and drugs chosen by the tumor's genetics rather than its organ, with dozens of targets and a resistance problem, since the tumor evolves around the drug.

• **Immunotherapy** — the checkpoint inhibitors of Module 8, which since 2011 have produced durable remissions in metastatic melanoma, lung, kidney, and bladder cancers, helping about a fifth to a third of patients in the cancers where they work, for reasons still under study. Chimeric antigen receptor T-cell (CAR-T) therapy goes further, removing a patient's T cells, engineering them to recognize the cancer, and returning them. It has cured some blood cancers that nothing else could, and in 2025 a randomized trial in advanced stomach cancer showed a CAR-T therapy delaying the disease, a first for a solid tumor.

• **The vaccines** — the mRNA platform applied to a patient's own tumor, in which sequencing finds the tumor's mutations and a personalized vaccine encodes them. Combined with immunotherapy, the leading vaccine cut melanoma recurrence or death by about half over five years in a mid-stage trial, and in August 2026 its late-stage trial, in 1,137 patients, met its main goal, though detailed results have not yet been released. It would be the first personalized vaccine to treat cancer.

• **The cost** — the new drugs are among the most expensive in medicine, at $150,000-500,000 a course.

Cancer	US new cases (2026, est.)	US deaths (2026, est.)	Five-year survival
Lung	About 229,000	About 125,000	28%
Breast (female)	About 322,000	About 42,000	92%
Prostate	About 334,000	About 36,000	98%
Colorectal	About 159,000	About 55,000	65%
Pancreatic	About 68,000	About 53,000	13%
Melanoma	About 112,000	About 8,500	95%
Liver	About 42,000	About 31,000	22% (from 7%)

American Cancer Society, Cancer Statistics, 2026 (estimates rounded); survival for diagnoses in 2015-21.

Module 12 Key Points

Cancer

• Cancer is two hundred diseases with one mechanism, a cell that divides without limit; nearly half its deaths trace to modifiable risks.

• About 2.1 million Americans will be diagnosed in 2026; the death rate is down 34% since 1991, and survival reaches 70%.

• Incidence is rising in the young, colorectal cancer under 50 by about 2-3% a year, for reasons unresolved.

• Colorectal, cervical, breast, and lung screening prevent deaths; the first big multi-cancer blood-test trial missed its main goal in 2026.

• Immunotherapy, targeted drugs, CAR-T, and a personalized mRNA vaccine that succeeded in 2026 are the revolution, at some of the highest prices in medicine.

Module 12 Quiz

Check Your Understanding

1. What share of cancers come from inherited variants such as BRCA1 and BRCA2?

A) About half
B) Nearly all of them
C) About 5-10% of cases
D) Under 1%, confined to the rare cancers of childhood

2. What did the first large trial of a multi-cancer blood test find in May 2026?

A) A 50% cut in cancer deaths
B) A halving of late-stage cancers, which led to its immediate approval
C) No fall in late-stage cancers, its main goal
D) That nine in ten of its positive results were false alarms, so the test was withdrawn

3. Why is colorectal screening called the most effective in medicine?

A) It removes polyps before they become cancer
B) Colorectal cancer is the most common cancer among American adults
C) Its new blood test finds the disease earlier than any other screening test
D) It is the only screening that every insurer must cover in full, so nearly all eligible adults are screened

4. What happened to the American cancer death rate between 1991 and 2023?

A) It rose 10% as the population aged
B) It fell 34%, averting about 4.8 million deaths
C) It held flat despite new drugs
D) It fell by more than two-thirds, mostly because of the new immunotherapies of the last decade

5. What did the personalized mRNA melanoma vaccine achieve in 2026?

A) It was approved for all melanoma patients.
B) Its late-stage trial was stopped for safety reasons.
C) It prevented melanoma in high-risk people who never had it.
D) Its late-stage trial met its main goal of reducing recurrence alongside immunotherapy.

Module 13 — Medicine's Toolkit

How Medicine Knows What It Knows

Recommended Reading / Reference

Book: Ben Goldacre, *Bad Science*

Reference: The Cochrane Library (cochranelibrary.com), the standard collection of systematic reviews of medical evidence, and the FDA's list of AI-enabled medical devices

13a. The Evidence Hierarchy

Medicine's central problem is that the body heals itself, symptoms fluctuate, and people who take a treatment differ from people who do not, so almost any treatment appears to work to the person giving it. That is why bloodletting lasted two thousand years.

The tools that solved the problem form the ladder the course has been climbing. At the bottom are anecdote and expert opinion, then case series, and above them are observational studies that follow cohorts and compare exposures, which can establish association and, when they meet the tests of 1d, make a strong case for causation. But such studies are confounded by everything that differs between the exposed and the unexposed, which is why the course marks the cohort evidence on exercise (Module 9), diet (Module 14), and hormones (Module 7) as it does.

At the top is the randomized controlled trial, formalized in 1948, which assigns treatment by chance so that the groups differ in nothing else, blinds both sides so that expectation cannot act, and measures an outcome that matters. It is the invention that separates modern medicine from everything before it, and above the single trial sits the systematic review, which pools all the trials on a question.

The hierarchy's limits are real. Trials are expensive, so most questions have none, and they test what a sponsor will pay to test, in populations narrower than the patients who later get the drug. About half of the trials ever run went unpublished, a bias that the registration reforms of the 2000s only partly fixed. But the rule stands: where a randomized trial exists, it outranks everything below it, and where none exists, the claim is marked as unsettled, which is the standard of this course.

13b. Diagnosis

Diagnosis converts a story, an examination, and tests into a name, and the tests are the era's abundance. Blood chemistry measures a hundred substances for a few dollars, and imaging shows the interior at millimeter resolution through X-rays, ultrasound, CT, and magnetic resonance imaging (MRI). Sequencing reads a whole genome for about $200, and new blood tests for Alzheimer's disease (Module 5) and cancer (Module 12) are arriving.

The arithmetic of 13c governs all of them. Every test has a sensitivity, the share of the sick it catches, and a specificity, the share of the well it clears, and the meaning of a result depends on how common the condition is in the person tested.

AI entered diagnosis in earnest in 2024-26. By mid-2026 the FDA had authorized more than 1,600 AI-enabled devices, about three-quarters of them in radiology, reading mammograms, chest X-rays, retinal scans, and skin lesions, and language models now draft clinical notes and answer patient messages in many large American health systems. The strongest randomized evidence comes from a Swedish trial of

AI-supported mammography in about 106,000 women, in which the AI-supported arm found 29% more cancers with no rise in false positives and cut radiologists' reading workload by 44%. Its final results, published in January 2026, showed no increase in the cancers that surface between screenings.

The rule of 13a applies to the tool as to the drug. In the Swedish design, the software decided which scans needed two radiologists and which needed one, and a radiologist still read every scan.

13c. The Arithmetic of a Positive Test

Worked example — the arithmetic of a positive test

Take a screening mammogram in a woman of 50 and use realistic numbers. The prevalence of undetected breast cancer in her age group is about 5 in 1,000, and the test's sensitivity is about 90%, so it catches 9 cancers in 10, while its specificity is also about 90%, so it correctly clears 9 healthy women in 10. Now screen 1,000 women. Of the 5 with cancer, the test finds about 4 or 5, and of the 995 without cancer, it correctly clears about 895 and wrongly flags about 100, so there are about 105 positive results, of which about 5 are cancer. A woman with a positive mammogram therefore has roughly a 5% chance of having breast cancer and a 95% chance that the result is a false alarm, a chance that surveys show most doctors, and nearly all patients, overestimate by a factor of ten.

The lesson is not that the test is bad but that the base rate governs. Use the same test in a woman with a lump, where the prevalence is perhaps 1 in 5, and a positive result is right about 70% of the time. In a woman of 30, where the prevalence is about 1 in 2,000, a positive result is right less than 1% of the time, about once in every 220 positives. That is why screening is recommended by age and risk, and why every screening program carries a cost, in false alarms, biopsies, and anxiety, that must be weighed against the deaths it prevents.

The second piece of arithmetic is overdiagnosis. Some of the cancers screening finds would never have caused harm, from 10% to 30% of the breast cancers detected by screening on current estimates and more of the prostate cancers found by PSA testing, and treating them is all cost and no benefit. The trials' net effect for each program is in 12c.

The arithmetic is why the course asks of every test not 'how accurate is it?' but 'in whom, and to what end?'

13d. Drugs and Surgery

- **How a drug works** — nearly every drug binds a receptor, blocks an enzyme, or mimics a signal, and most have one intended target and several unintended ones, which are the side effects. The dose that helps and the dose that harms are separated by a margin that varies from wide, as for penicillin, to narrow, as for warfarin and lithium, and the body's processing, through absorption, the liver's metabolism, and the kidneys' clearance, is why doses differ by age, weight, and organ function.
- **Placebo and nocebo** — an inert treatment produces real improvement in pain, nausea, depression, and any outcome the patient reports, and real side effects, the 'nocebo' effect, when the patient expects them. That is why trials are blinded, and it explains most of the statin aches of Module 4.
- **The number needed to treat** — the measure that converts a trial into a decision: a statin prevents one heart attack for every 20-40 high-risk patients treated for five years, but only one for every 200 or more low-risk patients. Aspirin for preventing a first heart attack was once nearly universal, until most guidelines withdrew it in 2019-22, when the bleeding it caused matched the events it prevented.

• **Surgery** — the toolkit's oldest branch, transformed by anesthesia (1846), antisepsis, blood banking, imaging, and the minimally invasive and robotic techniques of the last thirty years. Joint replacement, cataract removal, and opening a blocked artery during a heart attack are among the highest-value procedures in medicine, while operations never tested against sham surgery, such as arthroscopy for knee arthritis, vertebroplasty for spinal fractures, and several spine operations, failed when they finally were.

• **The new tools** — monoclonal antibodies, the '-mabs', are among the best-selling drugs in the world, and gene therapies treat sickle cell disease and spinal muscular atrophy in a single dose, at $2-4 million a patient. With mRNA and the GLP-1 class, they make up the toolkit's most expensive shelf.

Module 13 Key Points

Medicine's Toolkit

• The body heals itself and the treated differ from the untreated, so the randomized trial separates medicine from bloodletting.

• Where a randomized trial exists, it outranks everything below it; where none exists, the claim is unsettled.

• A test result's meaning depends on how common the condition is in the person tested, not only on the test's accuracy.

• A positive screening mammogram at 50 is cancer only about 5% of the time; the base rate governs.

• AI-supported mammography found 29% more cancers without more false alarms in Sweden's randomized trial of about 106,000 women.

Module 13 Quiz

Check Your Understanding

1. What problem does the randomized controlled trial solve?

A) Slow recruitment
B) The treated differ from the untreated
C) The cost of studies
D) Following large cohorts for decades at a lower cost

2. In the worked example, what is the chance that a woman of 50 with a positive mammogram has cancer?

A) About 90%, the test's sensitivity
B) About 50%, a coin toss
C) About 5%, because the base rate governs
D) About 30%

3. Why was aspirin for preventing a first heart attack withdrawn from most guidelines in 2019-22?

A) Its bleeding matched its benefit
B) Statins made it redundant for everyone
C) It raised blood pressure in older patients
D) Makers withdrew the low-dose formulation

4. What happened when arthroscopy for knee arthritis was finally tested against sham surgery?

A) It worked
B) It worked in the young but failed in the old
C) The trial was stopped because sham surgery was judged unethical
D) The sham did as well

5. In Sweden's randomized trial, what did AI-supported mammography achieve?

A) 29% more cancers found, with no rise in false positives
B) Fewer cancers found, but faster
C) It replaced radiologists entirely
D) It cut false positives by half while finding the same number of cancers as before

Module 14 — What the Evidence Says

The Claims, Graded

Recommended Reading / Reference

Book: Tim Spector, *Spoon-Fed: Why Almost Everything We've Been Told About Food Is Wrong*, a useful corrective whose own enthusiasms the module grades

Reference: The US Preventive Services Task Force recommendations (uspreventiveservicestaskforce.org) and the Cochrane Library, the two sources whose grading this module follows

14a. The Grading

Health advice is where the weakest evidence attracts the loudest claims, because the questions matter to everyone, the studies are mostly observational, and the market for answers is unlimited. Nutrition science is the worst case. Its evidence base is largely food-frequency questionnaires that people fill in wrongly and cohorts in which the people who eat well also exercise more, earn more, and smoke less, and it has only a handful of trials, which are expensive, short, and hard to blind. One is the Mediterranean-diet trial PREDIMED (Prevención con Dieta Mediterránea, Spanish for 'prevention with the Mediterranean diet').

The module therefore grades. **Settled** means randomized trials, or evidence so consistent across mechanism, dose-response, and populations that no serious researcher disputes it, and **probable** means consistent observational evidence with a plausible mechanism and no trial that contradicts it. **Contested** means the evidence points in more than one direction or is too weak to say, and **marketing** means the claim exceeds the evidence, usually because someone is selling something. The grades below are the module's judgment as of October 2026, and the reader should expect some of them to move.

Claim	Grade	The evidence
Smoking causes lung cancer, heart disease, COPD, and a dozen other cancers; quitting at any age helps	Settled	The strongest causal evidence in epidemiology; about 480,000 US deaths a year; heart-attack risk drops sharply within one to two years of quitting
Regular exercise lowers mortality and the risk of heart disease, diabetes, depression, dementia, and cancer	Settled (direction); contested (size)	Large, consistent cohorts; smaller effects in trials (Module 9)
Lowering blood pressure and LDL cholesterol prevents heart attacks and strokes	Settled	Dozens of trials; the numbers needed to treat are known (Modules 4 and 13)
Vaccination prevents the diseases it targets and their deaths	Settled	The trials and the eradications (Module 8)
Obesity raises the risk of diabetes, heart disease, and cancer	Settled	Consistent cohorts and genetic studies; the mechanisms of Modules 3 and 4
Losing weight lowers those risks	Settled for diabetes; probable for heart disease and cancer	The Diabetes Prevention Program; the GLP-1 drugs cut cardiovascular events, but intensive lifestyle weight loss did not (14b)
A Mediterranean-pattern diet (vegetables, legumes, fish, olive oil, nuts, little processed meat) lowers cardiovascular events	Probable, with trial support	PREDIMED (14b); consistent cohorts
Ultra-processed food raises weight and disease risk beyond its calories and nutrients	Probable	Consistent cohorts; two small trials (14b); the mechanism is debated

Claim	Grade	The evidence
Replacing saturated fat with unsaturated fat lowers cardiovascular events	Probable, with trial support	Trials of two years or more: about 17% fewer cardiovascular events, no clear effect on deaths (Cochrane, 2020); LDL is the mechanism (Module 4)
Adults need 1.2-1.6 grams of protein per kilogram a day, well above the old 0.8	Contested; probable for older adults who train	The 2026 guidelines' figure (14d); no outcome trials for the general population
Seven hours of sleep is optimal; less raises cardiometabolic risk	Probable (short sleep); contested (the details)	Cohorts and short trials (Module 5)
Red and processed meat raise colorectal cancer risk	Probable (processed); contested (red meat, and the size)	WHO classification; the absolute risk is small; a 2019 review that reversed the advice was itself disputed
Moderate alcohol is good for the heart	Contested, trending to marketing	The J-curve is mostly confounding and 'sick quitters' (14b); cancer risk rises from the first drink
Coffee is protective	Probable, modest	Consistent cohorts for mortality, liver disease, and diabetes; no outcome trial; the effect is small
Vitamin D supplements prevent cancer, heart disease, or fractures in people who are not deficient	Marketing	Large trials null; correcting a measured deficiency is a different, settled question
Fish oil supplements prevent heart disease	Contested, mostly negative	Most trials null; one prescription formulation helped patients with high triglycerides; the supplement market's evidence does not transfer
Multivitamins prevent disease	Marketing	Large trials null (14b); a modest cognitive signal in one
Antioxidant supplements prevent cancer	Marketing, and harmful	Beta-carotene and vitamin E raised cancers in trials (14b)
Intermittent fasting outperforms ordinary calorie restriction	Contested; probably equivalent	Trials show equal weight loss when calories match; metabolic claims beyond weight unproven in humans
Stress and isolation raise disease risk; social connection lowers it	Probable	Large, consistent cohorts; the cortisol mechanism (Module 7); trials of interventions weak
Probiotics improve general health in healthy people	Marketing	Narrow settled uses; general claims unsupported (Module 3)
Detoxes, cleanses, alkaline diets, and most 'wellness' products do anything	Marketing	No mechanism and no trials; the liver and kidneys are the detox (Module 3)

Grades are the module's judgment from the sources cited; 'settled' means beyond serious dispute, not beyond all revision.

14b. The Trials Behind the Grades

The grades rest on a small number of trials that anyone reading health news should know by name, because they are the evidence and the headlines usually are not.

On diet, four trials carry most of the weight. PREDIMED (Spain, 2013, 7,447 people at high cardiovascular risk) found about 30% fewer heart attacks, strokes, and cardiovascular deaths on a Mediterranean diet supplemented with olive oil or nuts, against a low-fat diet. It is the largest diet trial to show fewer cardiovascular events, and its result survived retraction and republication in 2018 after randomization errors at some sites. The trial of Dietary Approaches to Stop Hypertension (DASH, 1997) showed in a controlled-feeding study that a diet of vegetables, fruit, and low-fat dairy lowers blood pressure about as much as a drug. The Diabetes Prevention Program (2002) showed that diet and exercise cut progression from prediabetes to diabetes by 58%, more than metformin's 31%. Look AHEAD (Action for Health in

Diabetes, 2013) complicated the story, finding that intensive lifestyle change in people with diabetes produced lasting weight loss and better function, but not fewer cardiovascular events over a decade.

Two trials stand behind the grade on ultra-processed food. In a 2019 NIH study, 20 people living on a metabolic ward ate about 500 kilocalories a day more on an ultra-processed diet than on an unprocessed one matched for nutrients. In a 2025 British trial, 55 adults who ate two home-delivered diets for eight weeks each, both following national guidelines, lost about twice as much weight on the minimally processed one. The trials are small and short, which is why the grade is 'probable' rather than settled.

On salt, the Salt Substitute and Stroke Study (China, 2021, about 21,000 people) found that a potassium-enriched salt substitute cut strokes by 14% and deaths by 12%, trial evidence for the oldest dietary advice.

On supplements, the trials were decisive. Two trials in the 1990s, one in Finland and one in the United States, found that beta-carotene raised lung cancer in smokers, by 18% and 28%, ending the antioxidant hypothesis in its strongest form. A 35,000-man trial of selenium and vitamin E (2011) found that vitamin E raised prostate cancer by 17%. The Vitamin D and Omega-3 Trial (VITAL, 2018, about 26,000 people) found that vitamin D and fish oil prevented neither cancer nor cardiovascular disease, and the Physicians' Health Study II found that multivitamins did nothing for mortality or heart disease over a decade.

On alcohol, no long-term trial exists, and the grade rests instead on Mendelian randomization, a natural experiment in which people who carry gene variants that make them drink less show no cardiovascular benefit at any level of drinking, and lower cancer risk. That finding undid the J-curve, the old pattern in which moderate drinkers seemed healthier than abstainers. In January 2025 the US Surgeon General called alcohol a leading preventable cause of cancer, behind about 100,000 American cancer cases and 20,000 cancer deaths a year, and asked for a cancer warning on labels.

On exercise, the trial of Lifestyle Interventions and Independence for Elders (LIFE, 2014) found that a structured program cut major mobility disability among 1,635 older adults by 18%. Norway's Generation 100 trial (2020) found no clear difference in mortality between supervised exercise and advice over five years, a null result to read against the cohorts' large effects. The trials on mood, blood pressure, and blood sugar are in 9c, and on sleep the restriction and insomnia trials of 5c carry the weight.

The lesson of the list is Module 13's. The field's most famous reversals, hormone therapy (Module 7), antioxidants, aspirin, vertebroplasty, and arthroscopy, were all cases where a trial finally tested what observation had assumed.

14c. How to Read a Health Claim

- **Ask what kind of study** — place it on the ladder of 13a, where a mouse study, a mechanism, or a survey sits at the bottom and most headlines come from.
- **Ask for the absolute number** — 'reduces risk by 30%' from what to what (1d), and what is the number needed to treat (13d)?
- **Ask who was studied** — a trial in patients with heart disease does not transfer to the healthy, and a supplement that helps the deficient does nothing for the replete. The GLP-1 trials enrolled people with obesity, or with overweight and a related illness, not people who want to lose ten pounds.
- **Ask what was measured** — a blood marker, a scan, or a score is a surrogate, while a heart attack, a fracture, or a death is an outcome, and drugs that improved the surrogate and worsened the outcome have been approved and withdrawn. In 2026 a drug that cut lipoprotein(a) substantially failed to cut heart attacks (Module 4).

- **Ask who paid** — sponsorship does not make a result wrong, but industry-funded trials of a product find that it works more often than independent trials do, and the effect is measurable.
- **Ask whether it has been replicated** — a single study is a hypothesis, and many claims the field later reversed rested on one study believed too soon. A claim reaches 'settled' in the table above only when trials, or evidence too consistent for serious dispute, have confirmed it.
- **Ask whether someone is selling something** — in the marketing tier of the table the answer is yes, and the wellness market is organized to make the question hard to ask.

14d. The 2026 Dietary Guidelines

The federal Dietary Guidelines for Americans are revised every five years and shape school meals, food programs, and food labels, and the 2025-2030 edition, released on January 7, 2026, by HHS and the Department of Agriculture, broke with forty years of advice. It replaced the plate graphic with an inverted pyramid under the slogan 'eat real food', told Americans for the first time to avoid highly processed foods, recommended no amount of added sugar, and raised the protein target (graded in 14a). It endorsed full-fat dairy without added sugar and named butter and beef tallow among cooking fats while keeping the long-standing cap of 10% of calories from saturated fat, and it dropped the numeric limits on alcohol in favor of advice to drink less.

The case for, as the guidelines' authors make it. The low-fat, grain-heavy advice coincided with rising obesity and diabetes, and on this view the real culprits were processed food and sugar, not fat. Whole foods, including meat, eggs, and full-fat dairy, are nutrient-dense and satisfying, and protein preserves muscle, which matters more with age and with weight loss on GLP-1 drugs. Telling people to avoid highly processed food targets what the newest evidence suggests drives overeating.

The case against, as the American Heart Association and many nutrition researchers make it. Saturated fat raises LDL cholesterol, LDL causes atherosclerosis (Module 4), and trials that replace saturated fat with unsaturated fat cut cardiovascular events, so promoting butter, tallow, and red meat while keeping the cap is contradictory and will push many people over the cap. The protein target exceeds what most adults need, dropping the alcohol limits ignores the cancer evidence the Surgeon General had just summarized, and the process set aside the report of the guidelines' own scientific advisory committee.

The evidence between them. Both sides agree on sugar and on highly processed food, where the cohorts and the recent trials point the same way. Both links in the chain from saturated fat to heart disease, that saturated fat raises LDL and that LDL causes atherosclerosis, are settled, and the replacement trials support the conclusion, which the table grades probable because those trials are few and old. Cohort studies of dairy fat itself are mostly neutral, and the benefit of extra protein is clearest for older adults who also do resistance training.

The course's reading. The guidelines are right where the evidence is newest and strongest, in telling people to eat less sugar and less highly processed food. Their praise of butter, beef tallow, and red meat sits uneasily with the saturated-fat cap they kept, and the cap, not the praise, is the evidence's verdict.

14e. What the Grades Add Up To

Read together, the table says something the wellness market does not. The interventions with settled evidence are few, cheap, and old, not smoking, moving, controlling blood pressure and cholesterol, vaccinating, and keeping weight in range, and they account for most of the preventable difference in how long and how well people live. The probable tier is the diet-and-sleep tier, where the direction is clear and

the details are not, so the honest advice is a pattern rather than a prescription: plants, fish, less processed food, and enough sleep. The contested tier is where the reader should hold claims loosely, alcohol above all, where the twentieth century's 'a glass a day' has not survived the genetics, and the marketing tier is where the money is.

The module's last grade is on the claims of the course itself. The body's evidence base is deep on the things that kill and shallow on the things that merely trouble, and a person who does the settled list and ignores the rest has, on the evidence, done nearly everything the evidence supports.

Module 14 Key Points

What the Evidence Says

• Health advice is where the weakest evidence meets the loudest claims, so the course grades claims settled, probable, contested, or marketing.

• Settled: not smoking, exercise, blood pressure and LDL control, vaccination, and weight in range; few, cheap, and old.

• Probable: the Mediterranean pattern, less ultra-processed food, less saturated fat, seven hours of sleep, coffee, and connection.

• Moderate drinking's heart benefit did not survive the genetics; vitamin D, fish oil, and multivitamins in the replete are marketing.

• The 2026 guidelines are right on sugar and processed food; their praise of butter and tallow strains the saturated-fat cap they kept.

• Read any claim by asking what kind of study, what absolute number, who was studied, what was measured, and who paid.

Module 14 Quiz

Check Your Understanding

1. What undid the alcohol J-curve, in the absence of a long-term trial?

A) A French cohort's retraction
B) A cohort of a million drinkers followed for thirty years in three countries
C) Mendelian randomization, using genes that cut drinking
D) A meta-analysis that excluded every study funded by the wine, beer, and spirits industries since 1990

2. How does the module grade vitamin D supplements for people who are not deficient?

A) Settled benefit
B) Marketing
C) Probable, modest
D) Contested, mostly positive

3. What does the 2026 lipoprotein(a) result show, in the module's reading?

A) Lipoprotein(a) is not inherited after all
B) Statins lower lipoprotein(a) as well as LDL
C) The drug prevented heart attacks only in people with the highest lipoprotein(a) levels
D) A drug can move a marker substantially and still fail to prevent heart attacks and strokes

4. What did the 2025 British trial of processed food find?

A) Weight loss was identical on both diets once calories and nutrients were matched to the guidelines.
B) People on the ultra-processed diet lost more weight because their portions were smaller.
C) People lost about twice as much weight on minimally processed food.
D) The trial was stopped early because participants would not eat the minimally processed meals.

5. What is the course's reading of the 2026 Dietary Guidelines?

A) Right on every point, ending forty years of error
B) Right on sugar and processed food, but its praise of butter and tallow strains its own saturated-fat cap
C) Wrong on every point, and harmful to children
D) Right on saturated fat and protein, but wrong to tell people to avoid processed food

Module 15 — Health Systems and the Cost of Care

What the Money Buys

Recommended Reading / Reference

Book: Elisabeth Rosenthal, *An American Sickness: How Healthcare Became Big Business and How You Can Take It Back*

Reference: The National Health Expenditure Accounts and projections of the Centers for Medicare & Medicaid Services (CMS), June 2026, and the Commonwealth Fund's *Mirror, Mirror* international comparison

15a. What the United States Buys

The United States spent $5.3 trillion on health in 2024, 18.0% of GDP and about $15,500 a person, and the total reached about $5.7 trillion in 2025, with CMS projecting about $9 trillion, 20.6% of GDP, by 2034. That is about one and a half times the share of the other rich countries, which spend 10-12% of GDP, and about twice as much per person, and they get more by every population measure: longer lives, lower infant and maternal mortality, and fewer avoidable deaths. In the Commonwealth Fund's 2024 comparison of ten rich countries, the United States ranked last, as it has for two decades.

The money does not go where intuition puts it. Americans do not see doctors more often or stay in hospitals longer than Europeans, but they pay more for everything: physicians' salaries, hospital days, imaging, and drugs, which cost two to three times as much as abroad. They also pay for administration, which a 2020 study put at about a third of American health spending, twice Canada's share, in the billing, coding, and claims negotiation that a system of a thousand payers requires.

The system's structure explains the rest. Employer insurance covers about half the population, with a tax subsidy that hides its cost, while Medicare covers the old and Medicaid the poor, together about 40% of spending and rising with the demography, and a marketplace created by the Affordable Care Act (ACA) covers much of the rest. In 2025, 26.7 million Americans, 7.9% of the population, were uninsured all year.

That number is set to rise. The enhanced ACA subsidies expired at the end of 2025, and net premiums for marketplace customers rose by more than half in 2026, while the 2025 budget law requires many adults on Medicaid to document work, school, or volunteering from January 1, 2027, a rule Nebraska began enforcing in May 2026. The Congressional Budget Office (CBO) projects 30 million uninsured in 2026 and about 35 million by 2028.

The system's results are the prices, the paperwork, and medical debt, which about four American adults in ten carried in some form in a 2022 survey.

15b. What Other Countries Buy

- **Britain** — a single public system, the NHS, free at the point of use and funded by taxes, among the most efficient systems by cost and among the worst for waiting. In August 2026, 7.4 million cases were on England's waiting list, below the record 7.7 million of 2023 but far above target, and its outcomes for cancer and heart disease lag its peers', the model of what a system starved of capital looks like.
- **Germany, France, the Netherlands, and Switzerland** — insurance-based systems with universal mandates, regulated prices, and competing insurers, with the highest satisfaction in the rich world and

choice without American prices. They are the model that most reform proposals in the United States quietly resemble.

• **Canada and the Nordic countries** — public single-payer or regional systems, with long waits for elective care and strong primary care and outcomes.

• **Japan and South Korea** — universal insurance with national fee schedules, among the world's longest lives, the most hospital beds and scans per person of any countries, and the fastest-aging populations, whose costs are the next decade's question.

• **Singapore** — compulsory savings accounts, catastrophic insurance, and public hospitals, at about 4.5% of GDP, with outcomes among the best: the system economists cite and no democracy has copied.

• **The middle-income countries** — China's public insurance covers about 95% of its 1.4 billion people, at about 6% of GDP, while India spends about 3-4% of GDP, about two-fifths of it out of pocket. The global picture is a transition, with every country moving toward universal coverage on a curve where spending rises with income and outcomes rise with spending until, near the American level, they stop.

15c. The GLP-1 Bill and the Drug Prices

The GLP-1 drugs are the health-system question of the decade in one drug class. They list at $1,000-1,350 a month, and the evidence says they prevent the diseases that cost the system most, but at list price, treating everyone eligible would have cost more than the entire Medicare drug budget.

The response has been price. Under agreements announced in November 2025, Medicare and Medicaid pay $245 a month for the leading injections, and cash prices on the federal TrumpRx website, launched in February 2026, start at $149 for the Wegovy pill and run $299-349 for most injection doses. Medicare began covering the drugs for obesity on July 1, 2026, through a temporary program with a $50 copay that runs to the end of 2027. Semaglutide's patents expired in 2026 in India, Canada, and Brazil, where generic versions have launched or been approved, though American generics are not expected before the early 2030s, and at the new price the case that the drugs pay for themselves in avoided disease is far stronger than it was at list price.

The broader price story is the attempt in 2025-26 to end the American premium. A 'most favored nation' executive order in May 2025 led to deals with Pfizer, AstraZeneca, Novo Nordisk, Eli Lilly, and others that pegged some prices to those abroad. A September 2026 analysis found that of 32 brand-name drugs on TrumpRx, 17 cost less than the average in peer countries and 15 cost more. Separately, Medicare's negotiated prices under the Inflation Reduction Act took effect for the first ten drugs on January 1, 2026, fifteen more, semaglutide among them, follow in 2027, and as of October 2026 the prices for a third round were due by November 30.

The argument over prices and innovation

The case for high prices, as the industry makes it. American prices fund a large share of the world's drug research, so lower prices mean fewer new drugs. Negotiation already shifts investment, since the law lets Medicare negotiate the price of a pill nine years after approval but a biologic drug only after thirteen, and companies say that gap steers money away from pills. New drugs also launch first, and more often, in the United States. The patients who would have benefited from drugs never developed bear the cost, invisibly.

The case against, as reformers make it. Americans pay the premium of 15a for the same drugs, much of the basic science comes from public funding through the NIH, and companies spend heavily on marketing and on buying back their own shares. Countries that pay less have not stopped receiving new drugs.

The evidence between them. The CBO estimated that negotiation would reduce the number of new drugs by about 13 of some 1,300 expected over thirty years, about 1%, while other economists, such as Tomas Philipson of the University of Chicago, have estimated losses many times larger. Reports of shifted research pipelines are early and mostly anecdotal.

The course's reading. Lower prices will cost some drugs at the margin, by the best estimate a small share, and the larger question is who pays for innovation, which at present is mostly the American patient.

15d. The Gains and the Losses

Life expectancy rose in most of the world in the 2020s, after the pandemic's dip, but in the United States it fell further in 2020-21 than in any peer before recovering to a record (Module 1). Britain's gains stalled for a decade before the pandemic, Russia's and parts of Eastern Europe's fell, and sub-Saharan Africa gained about thirteen years between 1990 and 2024, from 50 to 63. The countries that gain most are the ones that spend on the settled list of Modules 1 and 14 before they spend on anything else.

Country	Health spending, % of GDP (2024)	Per person (US$, at purchasing-power parity)
United States	17.2% on this measure (CMS's broader one is in 15a)	About $14,900
Switzerland	11.8%	About $10,000
Germany	12.3%	About $9,400
France	11.5%	About $7,400
Canada	11.3%	About $7,300
United Kingdom	11.1%	About $6,700
Japan	10.6%	About $5,800
South Korea	8.4%	About $4,800

Organisation for Economic Co-operation and Development (OECD), Health at a Glance 2025 (2024 data, some provisional). The figures for Singapore and China in 15b are WHO estimates for 2023.

Module 15 Key Points

Health Systems and the Cost of Care

• The United States spent $5.3 trillion on health in 2024, 18% of GDP and about twice its peers per person, and gets less.

• The premium is higher prices for everything plus administration, about a third of spending, not more visits or longer stays.

• The uninsured, 26.7 million in 2025, are projected to reach about 35 million by 2028 as subsidies lapse and work rules start.

• Medicare and Medicaid now pay $245 a month for the leading GLP-1 drugs, against list prices above $1,000.

• Negotiation may cost about 1% of future new drugs, by the budget office's estimate; Americans pay most of the world's innovation bill.

Module 15 Quiz

Check Your Understanding

1. Where does the American premium in health spending come from, according to the module?

A) More doctor visits per person
B) Longer hospital stays
C) A larger and sicker population that needs far more care per person than European populations do
D) Higher prices for everything, plus heavy administration

2. What do Medicare and Medicaid pay for the leading GLP-1 drugs under the 2025 agreements?

A) $245 a month
B) $50 a month
C) $1,000 a month
D) About $599 a month

3. Which system does the module describe as starved of capital?

A) Germany's social insurance system.
B) Singapore's model of savings accounts.
C) Japan's universal insurance.
D) Britain's National Health Service, with 7.4 million cases on England's waiting list.

4. How many Americans were uninsured for all of 2025?

A) 9 million
B) About 45 million
C) 26.7 million
D) Roughly 60 million

5. What did the Congressional Budget Office estimate drug-price negotiation would cost in new drugs?

A) About 13 of some 1,300 over thirty years
B) About 130 of 1,300, a tenth
C) Half of all new drugs
D) About a third of the pipeline, ending most research on pills

Module 16 — Where Things Stand, and What to Watch

The Argument, the Contradictions, and What Moves Next

Recommended Reading / Reference

Reference: The WHO's *World Health Statistics* and the CDC's provisional mortality releases, the two annual documents that will show whether the trends in this module hold

16a. The Argument

The course's argument fits on a page. The body is a feedback machine tuned for scarcity, and most of what now kills and disables people in rich countries is that tuning running in abundance: fat stored against famines that never come (Module 3), a reward system that met cheap opioids (Module 6), and inflammation that does not stand down (Module 8).

The century's great gains came from removing threats from outside the body, such as dirty water, infection, and tobacco (Modules 1 and 4). The defenses against the threats from within are old, cheap, and proven, and they are badly delivered, as the fifth tension below shows.

The decade's frontier has mostly brought ways to see disease sooner: amyloid and tumor DNA in the blood, biological age read from an epigenetic clock, and cancers flagged by software. Its one great therapeutic success, a drug class that acts on appetite, is the first of the tensions below.

16b. The Contradictions

Read across the modules, the course's evidence leaves five tensions that no single module states.

• **The cause is the environment, and the cure that worked is a drug.** The evidence puts obesity's cause in the food environment (Module 3), yet the lifestyle trial that produced lasting weight loss did not cut heart attacks (Module 14), and most dieters regain what they lose. The remedy that has worked at scale, the GLP-1 class, acts on the body instead, by holding one of its own signals on (Module 7).

• **Seeing sooner is not living longer.** The frontier's tests find disease earlier than ever, but its trials keep finding a marker that moves while the outcome stays put: the lipoprotein(a) drug (Module 4), the multi-cancer blood test (Module 12), and the amyloid antibodies, whose large effect on plaque buys a small effect on decline (Module 5). Early detection also carries the cost worked out in Module 13, in false alarms and in disease that would never have mattered.

• **The strongest predictor has the weakest proof.** Fitness predicts survival better than smoking or blood pressure in the cohorts that measure it (Module 9), but the course's one exercise trial with mortality as its outcome found no clear difference (Module 14). By the rule of Module 1, part of what fitness predicts may be illness already present, which lowers fitness the way illness lengthens sleep (Module 5).

• **The trial decides, but someone has to read it.** The course ranks the randomized trial above everything else (Module 13). Yet several of its biggest stories turned on how a trial was read rather than on a new trial: the reanalysis of the hormone-therapy trial behind the 2025 reversal (Module 7), the reanalysis that halved a depression trial's remission rate (Module 6), and the dispute over pooling two working antibodies with five that failed (Module 5).

• **The cheapest proven care is the worst delivered.** The interventions the course grades settled are cheap (Module 14), yet it keeps finding them in short supply, from mental-health care and the drugs for opioid addiction (Module 6) to exercise and back care (Module 9) and childhood vaccines (Module 8). The system that spends the most delivers them least (Module 15), so the gap is in delivery, not in knowledge.

16c. What to Watch

What	When	Why it matters
The GLP-1 era: the pills, generics abroad, Medicare's coverage and negotiated price, and long-term data on stopping and on muscle	2026-28	Whether the drugs end the stall in cardiovascular deaths that Module 4 blames on obesity and diabetes, and whether measured obesity confirms the self-reported decline
The Alzheimer's prevention trials in people with amyloid and no symptoms; the blood tests in primary care	Readouts 2027-28	Success would make healthy people with amyloid candidates for costly treatment on a blood test, putting the base-rate arithmetic of Module 13 and the spending question of Module 15 on the same patient
Cancer: the FDA's decision on the first multi-cancer blood test, and the mRNA melanoma vaccine's full results and filing	2026-27	Approving the test would accept fewer late-stage cancers in place of fewer deaths, the surrogate step Module 14 warns about; the vaccine's full data will show the size of its benefit
Lipoprotein(a): the failed trial's full results, and the rival drugs' outcome trials	2026-29	Whether the failure belongs to one drug or to the target; a second failure would leave an inherited risk with no treatment that prevents its events
Psychedelics: the FDA's decisions on psilocybin for depression and on the refiled MDMA application	2026-27	Psilocybin's effects are as obvious to patients as MDMA's were, in a disease with a large placebo response, so approval would show how far the FDA will accept trials that cannot be fully blinded
Longevity: rapamycin's human trials, TAME's funding, and the reprogramming trial's next data	2026-30	The readouts in this window measure safety and markers, not health, so they can produce leads but not the verdict the course's standard requires (Module 10)
Antimicrobial resistance: the new antibiotic classes in use, the payment models, the vaccines	Ongoing	Whether paying for an antibiotic's existence rather than its sales produces new classes; sepsis (Module 11) is where resistance turns into deaths
Vaccination: PAHO's measles review, the appeal over the childhood schedule, and kindergarten coverage	November 2026; 2026-27	Losing elimination would show a settled intervention undone by falling uptake rather than by new evidence: the vaccine's grade has not changed, only its coverage
The next pandemic: H5N1 in cattle and birds, and American surveillance outside the WHO	Any time	How much of the capacity built in 2020-22 survives the cuts of Module 8, since detection and vaccine supply, not immunity, set the toll
American spending and coverage: the spending projection, the uninsured, Medicaid's work requirements, and the third round of negotiated drug prices	2026-28	Prices are falling while coverage shrinks: whether the lower prices reach the people losing insurance, and whether the record-low death rate of Module 11 survives the loss
The measures: US life expectancy, the death rate, measured obesity, and overdose deaths	Annual	Each series tests a reading in the course: obesity the GLP-1 decline (Module 3), overdoses whether the fall outlasts a weaker fentanyl supply (Module 6), and life expectancy the recovery (Module 1)
AI in medicine: FDA authorizations, randomized trials beyond mammography, and the rules for chatbots	2026-28	The evidence is strongest where use is narrowest: one randomized trial supports AI in mammography (Module 13), while the chatbots many adults confide in showed no clear effect in trials (Module 6)

16d. The Last Word

Most of this course's figures will date within a few years, and some of its grades will move, as Module 14 warned when it dated them. What will not date is the arithmetic used to reach them: risks multiply (Module 4), a positive result means what the base rate allows (Module 13), and a marker can move while the outcome does not. A reader who keeps that arithmetic can grade the next decade's claims without this course.

The harder test of that decade is delivery, not discovery. The treatments with the strongest evidence, from buprenorphine to the measles vaccine, already exist, and the counts on the watch list, of overdoses, measles cases, and the uninsured, will show whether they reach the people the system now misses.

Module 16 Key Points

Where Things Stand, and What to Watch

• The argument: a body tuned for scarcity now lives in abundance, and that mismatch drives most of what kills in rich countries.

• The century's gains came from removing outside threats; the proven defenses against inside threats are cheap but badly delivered.

• The frontier mostly sees disease sooner, while its trials keep finding markers that move without outcomes following.

• Obesity's cause is environmental, yet the remedy that has worked at scale, the GLP-1 class, acts on the body.

• What will not date is the arithmetic: risks multiply, base rates govern, and a marker is not an outcome.

• The watch list's counts of overdoses, measles, and the uninsured will show whether proven care reaches the people it misses.

Module 16 Quiz

Check Your Understanding

1. What is the course's argument, as Module 16 states it?

A) Genes set most of a person's risk, and medicine can change little of it.
B) A body tuned for scarcity now lives in abundance.
C) The body wears out on a fixed schedule that the newest drugs have begun to reverse.
D) Most disease in rich countries comes from infections the body has not yet adapted to.

2. Which tension does Module 16 draw from the obesity evidence?

A) The drugs work only alongside a diet
B) Lifestyle programs cut more heart attacks than the drugs
C) The cause is environmental, but the remedy that worked at scale acts on the body
D) Obesity is rising fastest where the drugs are most used

3. What is scheduled for November 2026 on the module's watch list?

A) PAHO's review of the United States' measles elimination status.
B) The FDA's decision on the first GLP-1 pill.
C) The results of the Alzheimer's prevention trials.
D) The start of Medicaid work requirements in every state, under the 2025 budget law.

4. What does Module 16 say the frontier's trials keep finding?

A) Early tests too costly for most systems
B) Blood tests less accurate than scans
C) Patients who rarely act on an early result, so that detection changes nothing in their care
D) Markers moving without outcomes

5. In its last word, what does Module 16 say will outlast the course's figures?

A) Its grades
B) The arithmetic
C) The trials it names
D) The watch list's dates

Answer Sheet

Answers to every module's Check Your Understanding quiz.

Module	Answers
Module 1 Quiz	1. A 2. B 3. C 4. D 5. A
Module 2 Quiz	1. C 2. B 3. D 4. B 5. D
Module 3 Quiz	1. A 2. C 3. B 4. C 5. D
Module 4 Quiz	1. A 2. C 3. B 4. A 5. D
Module 5 Quiz	1. D 2. A 3. B 4. C 5. B
Module 6 Quiz	1. D 2. A 3. C 4. D 5. B
Module 7 Quiz	1. C 2. A 3. D 4. A 5. B
Module 8 Quiz	1. C 2. B 3. C 4. D 5. A
Module 9 Quiz	1. C 2. D 3. A 4. B 5. C
Module 10 Quiz	1. B 2. D 3. A 4. A 5. D
Module 11 Quiz	1. C 2. B 3. D 4. B 5. A
Module 12 Quiz	1. C 2. C 3. A 4. B 5. D
Module 13 Quiz	1. B 2. C 3. A 4. D 5. A
Module 14 Quiz	1. C 2. B 3. D 4. C 5. B
Module 15 Quiz	1. D 2. A 3. D 4. C 5. A
Module 16 Quiz	1. B 2. C 3. A 4. D 5. B