

Fall 2026

**ENGINEERING A NEW ERA OF
HUMAN HEALTH**

The BRIDGE

LINKING ENGINEERING AND SOCIETY

**Platform Technologies for Precision Diagnostics
and Therapeutics**

*Rashid Bashir, Gang Bao, Mehmet Toner, Enrique Valera,
So Hyun Park, Murat Karabacak, Jon F. Edd, and Avanish Mishra*

**Advances in Immunoengineering: Designing the
Context of Immunity**

Erica Budina and Jeffrey A. Hubbell

The Future of Digital and Computational Pathology

*Andrew H. Song, David Brenes, Andrew M. Sohn, Faisal Mahmood,
and Jonathan T.C. Liu*

Engineering Cell Therapies as Living Medicines

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**Engineering Therapeutic Cancer Vaccines: Teaching
the Immune System to Fight Cancer**

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**A Unifying Engineering Framework for Trustworthy
AI Clinical Decision Systems: Lessons from Cervical
Cancer Imaging in Global Healthcare Settings**

Nimmi Ramanujam and Jessica de Souza

**Predictive AI, Personalized Prevention, and the
Future of Health**

Daniel K. Sodickson, Daniel Rueckert, and Marzyeh Ghassemi

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Mission Statement of *The Bridge*

The Bridge publishes articles on engineering research, education, and practice; science and technology policy; and the interface between engineering and technology and society. The intent is to stimulate debate and dialogue both among members of the National Academy of Engineering (NAE) and in the broader community of policymakers, educators, business leaders, and other interested individuals. *The Bridge* relies on its editor in chief, NAE members, and staff to identify potential issue topics and guest editors. Invited guest editors, who have expertise in a given issue's theme, are asked to select authors and topics, and independent experts are enlisted to assess articles for publication. The quarterly has a distribution of about 7,000, including NAE members, members of Congress, agency officials, engineering deans, department heads, and faculty, and interested individuals all over the country and the world. Issues are freely accessible at www.nae.edu/TheBridge.

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The **National Academy of Sciences** was established in 1863 by an Act of Congress, signed by President Lincoln, as a private, nongovernmental institution to advise the nation on issues related to science and technology. Members are elected by their peers for outstanding contributions to research. Dr. Neil Shubin is president.

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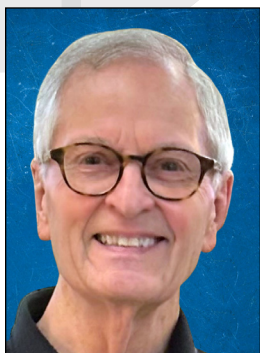
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Editor in Chief's Note

Engineering and Health Care: A Personal Perspective



Ronald M. Latanision (NAE) is the Neil Armstrong Distinguished Visiting Professor at Purdue University, and editor in chief of *The Bridge*.

In 2017, I underwent quadruple coronary artery bypass surgery. My cardiologist was from Korea, my surgeon from Chile, and the nurses who cared for me came from Haiti and the United States. As I waited for surgery to begin, I met my anesthesiologist and discovered, much to my surprise, that she had once been a student in my freshman solid-state chemistry class at MIT. It was a remarkable convergence of people, expertise, and experience, brought together in service of a single patient.

My surgeon and cardiologist were, and remain, internationally recognized both as practitioners and researchers. The care I received from the entire team was exceptional, and I continue to benefit from it today. That experience gave me a deeply personal appreciation for the value of research, engineering, medicine, and international collaboration. I remain profoundly grateful.

I have long preferred the view that science makes the unknown known, while engineering makes the known useful. At its best, that usefulness serves the public need and interest. Few areas demonstrate this more powerfully than the intersection of engineering and medical science. Advances in prevention, diagnosis, therapeutics, treatment, medical technologies, and healthcare systems show what can happen when scientific discovery is coupled with the engineering discipline required to translate knowledge into practical benefit.

Over the years that I have served as editor in chief, *The Bridge* has returned frequently to this intersection. We have published issues on *Convergence of Engineering and the Life Sciences* (Fall 2013), guest edited by Phil-

ip A. Sharp and Robert Langer; *Technologies for Aging* (Spring 2019), guest edited by Jeffrey A. Kaye; *Engineering for Women's Health* (Spring 2022), guest edited by Marta Villarraga; and *Advanced Biomanufacturing for Medicines* (Summer 2025), guest edited by Barry C. Buckland and Kelvin H. Lee. Each explored, from a different perspective, how accomplished teams of researchers and practitioners are applying engineering to address fundamental human needs.

Much has changed since our Fall 2013 issue examined the convergence of engineering and the life sciences. In the years since, biomedical engineering has advanced remarkably, while the boundaries separating engineering, biology, medicine, computing, and other disciplines have become increasingly permeable. That convergence continues to generate new capabilities and new approaches to improving human health.

This issue of *The Bridge*, skillfully shepherded by Guest Editors Roderic I. Pettigrew of the Texas A&M University School of Engineering Medicine and Rebecca Richards-Kortum of Rice University, carries that conversation forward. It examines how the systems thinking that fundamentally underpins engineering is continuing to inform and transform medical science and healthcare. Pettigrew and Richards-Kortum have assembled a distinguished group of authors whose work spans education, practice, invention, and discovery. Collectively, their contributions offer a view of how engineering can help shape not only the future of healthcare, but also how we understand and pursue a healthy human lifespan.

I am also pleased to open this issue with messages from NAE President Tsu-Jae Liu and National Academy of Medicine (NAM) President Monica Bertagnolli. Both speak to an issue that is essential to realizing the promise described throughout these pages: public trust.

NAM President Bertagnolli observes that “the future of engineering health will depend not only on technical excellence, but also on public trust.” It is a subject on which I have commented previously in this column and one that I believe deserves our continued attention. In today’s technologically intensive world, I am concerned that technologists can, whether inadvertently or knowingly, put that trust at risk. Technical achievement alone is not enough. The public must have confidence that innovation is being pursued responsibly and in service of society.

President Liu reminds us of the extraordinary reach of that responsibility: “Like physicians, engineers help people, often in ways that reach far beyond any single individual. Through innovations that save lives, strengthen communities, enhance security, and improve quality of life, engineering can have an extraordinary impact on society.”

I could not agree more. The work presented in this issue provides compelling evidence of what engineering can accomplish when that responsibility remains at its core. The advances described here in prevention, diagnosis, therapeutics, treatment, education, and healthcare

delivery are technologically impressive, but their ultimate importance lies in the people they serve. At the interface of engineering and medicine, perhaps more clearly than almost anywhere else, making the known useful means improving lives. My own life is one example.

With this issue of *The Bridge*, I am pleased to introduce our new editor, Adrienne Young, who joined us in April of this year. While at the EFI Foundation, prior to joining us, Adrienne served, among other responsibilities, as a media liaison for EFIF executive leadership, including former US Secretary of Energy Ernest J. Moniz and expert researchers. She is a superb writer and editor who has quickly become a valued contributor to our stellar Communications Team. I have enjoyed working with her enormously. I hope that you will have an opportunity to meet Adrienne at our Annual Meeting in October. I do also want to thank David Butler, J. Herbert Hollomon Scholar of the National Academy of Engineering, for stepping in as interim editor during this transition.

Finally, we are happy to introduce a new feature to *The Bridge* in this issue: Member Perspective. This column gives contributors a space to explore ideas and issues of interest to them, share perspectives, and invite readers into the conversation. We welcome submissions from NAE members and look forward to sharing your voices.

As always, I welcome your comments. Feel free to reach out to me at rlatanision@alum.mit.edu.

Guest Editors' Note

Convergence Advanced: Pursuing 22nd Century Healthcare Today



Roderic I. Pettigrew



Rebecca Richards-Kortum

Roderic I. Pettigrew (NAE; NAM) is the Robert A. Welch Professor of Medicine, former Vice Chancellor for Health, and Inaugural Dean at the School of Engineering Medicine at Texas A&M University. Pettigrew also served as Founding Director of the National Institute of Biomedical Imaging and Bioengineering at the National Institutes of Health from 2002 to 2017. Rebecca Richards-Kortum (NAE; NAS; NAM) is the Malcolm Gillis University Professor, a Professor of Bioengineering, and Co-Director of Rice360 Institute for Global Health Technologies at Rice University.

One of the great opportunities for tomorrow's medicine is not simply to extend life, but to extend health. That means enabling people to live longer with sustained physical, intellectual, and emotional well-being. The goal is to be healthy throughout the entirety of life with a great human healthspan as the norm. Reaching that goal will require us to think well beyond diagnosing and treating disease. It requires a more complete understanding of illness and the use of that deeper knowledge to develop solutions to health challenges immediately. In this pursuit, engineering is increasingly shaping how we understand, preserve, and ultimately engineer health at every stage of our lives.

Achieving this vision will require more than advances in medicine alone. It calls for the purposeful and robust integration of engineering, medicine, the life sciences, the physical sciences, and the behavioral and social sciences to address complex problems that exceed the reach of any single discipline.

The need for convergence is not new. More than a decade ago, the Fall 2013 issue of *The Bridge* (guest edited by Phillip A. Sharp and Robert Langer) explored the emerging concept of convergence and its promise for transforming biomedical science. Today, that promise is being realized. Many of the most significant advances in health now stem from the dynamic interplay between fundamental science and engineering. Discovery informs invention, invention enables new discovery, and together

they accelerate progress in ways that neither could achieve independently.

The articles in this issue illustrate how far that dynamic convergence has progressed and what this projects for the future. They span molecular engineering, advanced imaging, regenerative medicine, biomedical devices, artificial intelligence, computational biology, precision diagnostics, and novel therapeutic strategies. Together, they point toward a broader transformation: from engineering solutions for disease to engineering the elements and systems for better health across the lifespan. The progress in recent decades provides reason for optimism. Advances in basic discovery science have revealed the molecular, cellular, and physiological foundations of health, aging, and disease. Engineering has translated those discoveries into practical innovations that improve lives. New imaging technologies allow us to observe biology with unprecedented resolution in space and time. Materials science has produced sophisticated approaches to drug delivery and tissue regeneration. Advances in genomics, computation, and bioengineering continue to transform diagnostics and therapeutics. Wearable sensors and connected technologies increasingly allow continuous health monitoring. On the horizon are now predictive artificial intelligence, quantum computing for complex multifactorial problems, and quantum sensors for even more sensitive detection of disease at its earliest stage. Together,

these developments are reshaping our understanding of what medicine can become, and our work to achieve it.

As convergence-based innovators, we appreciate that health is determined not only by the life sciences, physical sciences, and engineering therein, but also by behavior, environment, education, economics, and the design of health systems that shape access to care. A breakthrough diagnostic has limited value if it never reaches the populations that need it. A remarkable therapy cannot achieve its intended impact if affordability, trust, infrastructure, or cultural barriers prevent its adoption. The most elegant engineering solutions succeed only when they reach and improve lives in the real world. The communities where these advances are to be used impose engineering design parameters that should be incorporated from the outset.

Engineers have long designed within constraints such as performance, reliability, safety, manufacturability, and cost. As we strive for the greatest advances in the future of health, like those envisioned for the 22nd century, our design criteria should also include accessibility, equity, usability, cultural relevance, and scalability. Solutions that benefit only a fraction of society cannot fully realize their potential. By intentionally designing for diverse populations in varied settings, engineering can help democratize access to innovation and improve health across whole communities, countries, and globally.

Ultimately, it is the application of systems thinking that will allow teams to develop and scale transformative ideas. The need for systems approaches extends to one for new partnerships that bridge academia, industry,

government, and clinical practice. No single institution or discipline can accomplish this transformation alone. These approaches should also integrate advances in artificial intelligence and quantum technologies. These recent progressions promise to reveal biological relationships that have remained hidden within extensive datasets that are becoming increasingly comprehensive.

Today, we can envision and pursue innovations likely to be mainstream in the 22nd century—technologies that predict disease long before symptoms appear, detect the first cell that becomes cancerous, regenerate damaged tissues, restore lost function, prevent the progression of acute injury into chronic illnesses, correct abnormalities at the molecular and cellular levels, and in time eliminate diseases that remain beyond our current therapeutic reach.

We believe that engineering's greatest contribution to medicine may ultimately extend beyond the next diagnostic, device, or therapy. It may be helping us redefine what health can be. By embracing convergence in its fullest sense, we can move to a system that is increasingly capable of sustaining health throughout life.

The contributions in this issue of *The Bridge* offer compelling advances that are components of that future already taking shape. They remind us that the path forward lies in the thoughtful integration of all of life's constituent disciplines. Through convergence, engineering has an unprecedented opportunity to help create a future in which healthy longevity is not the exception, but the expectation. Few challenges are more worthy of our collective imagination, or our collective effort.

President's Perspective

Engineering a Healthier Future



Photo: Christopher Michel

Tsu-Jae Liu is President of the National Academy of Engineering.

In high school I thought about becoming a physician, drawn by the opportunity to directly help people; however, I quickly discovered that I had no stomach for biology and anatomy labs. Fortunately, my interest in medicine led me to engineering, inspired by medical technologies used by healthcare workers to diagnose, monitor, and treat diseases and injuries. Like physicians, engineers help people, often in ways that reach far beyond any single individual. Through innovations that save lives, strengthen communities, enhance security, and improve quality of life, engineering can have an extraordinary impact on society.

Engineering became the foundation of my career, from advancing semiconductor research and educating future engineers to developing technologies with far-reaching applications. My professional journey ultimately led me to the presidency of the National Academy of Engineering, where I now have the privilege of helping to strengthen US engineering leadership and shape a better future for the nation and global society.

The complex challenges we face in health, energy, infrastructure, national security, and other areas demand innovation and collaboration across disciplines. The NAE plays an important role in convening experts to

develop practical, evidence-based solutions. We also have an opportunity and an obligation to improve public understanding of engineering. People benefit every day from engineering achievements without always recognizing the ingenuity behind them or the engineers who made them possible. By sharing the stories behind their innovations to benefit people and society, we can inspire more young people to pursue engineering and help build the technically skilled workforce needed to meet tomorrow's challenges.

Few domains illustrate engineering's human impact more clearly than health. Engineers create and continually improve tools, devices, and systems used for diagnosis and treatment, to expand access to medical care, and enable people to live longer, healthier lives. Increasingly, the most significant advances emerge at the intersection of engineering, medicine, and public health.

This issue of *The Bridge*, developed in collaboration with the National Academy of Medicine (NAM), reflects that important convergence. Several guest authors are members of both the NAE and NAM, and some have been elected to all three National Academies. Their achievements demonstrate what is possible when expertise crosses traditional boundaries and disciplines unite around a shared purpose.

I extend a warm welcome to Monica M. Bertagnolli, who recently began her tenure as president of the National Academy of Medicine. I look forward to working with her to strengthen collaboration between our academies and advance the innovations, partnerships, and ideas that can improve health and well-being for all.

I hope this issue inspires readers to reflect on how profoundly engineering has transformed health and to imagine how much more we can accomplish together.

Foreword

The Engineering Mindset in Medicine



Photo: Christopher Michel

Monica M. Bertagnolli is President of the National Academy of Medicine and Vice Chair of the National Research Council.

When I was elected to lead the National Academy of Medicine (NAM), I knew that a priority of my presidency would be not only to celebrate what each Academy uniquely contributes to the fields of science and research, but also to strengthen what becomes possible when science, engineering, and medicine work together.

As a surgical oncologist and physician-scientist, I have relied for decades on the lessons from my undergraduate training at Princeton, where I earned a Bachelor of Science in Engineering. In my first communication to NAM members this July, I shared my belief that our work in health and biomedical research can benefit enormously from an engineering mindset: one that defines problems clearly, designs practical solutions, tests them rigorously, learns from each iteration, and scales successful approaches thoughtfully and responsibly.

In 2014, the National Research Council of the National Academies released a landmark report, *Convergence: Facilitating Transdisciplinary Integration of Life Sciences, Physical Sciences, and Engineering and Beyond*, which described convergence as a way of solving complex problems by bringing together knowledge, tools, and ways of thinking from multiple fields. The report highlighted transformational opportunities at the intersection of health and engineering, from engineering the microbiome to treat disease to using three-dimensional printing to customize medical devices and advance the possibility of bioprinted tissues and organs.

Today, the vision articulated in the 2014 National Research Council report is increasingly becoming reality. The articles in this issue of *The Bridge* demonstrate the

breadth of progress made possible by the convergence of medicine and engineering: precision diagnostics, immunoengineering, spatial transcriptomics and AI-enabled digital pathology, engineered cell therapies, cancer vaccines, medical imaging and predictive AI, and technologies designed for under-resourced settings.

These advances are powerful in their own right. But their full promise will depend on whether we can design health systems capable of evaluating them rigorously, integrating them responsibly, and delivering them equitably. That is where the convergence of engineering and medicine becomes not only a source of innovation, but a strategy for transformation.

Many of the most vexing problems we see today in health and healthcare are not scientific mysteries, but systems challenges. How do we connect fragmented data? How do we translate discoveries into everyday clinical practice more quickly? How do we design clinical trials that are faster, more inclusive, and better integrated into care? How do we responsibly harness AI to improve decision-making? And how do we ensure innovation reaches every patient and community that stand to benefit?

Addressing these challenges requires more than new technologies. It requires designing a health system capable of continuous learning, adaptation, and improvement. More than a decade ago, the Institute of Medicine and the National Academy of Engineering made this point clearly in *Engineering a Learning Healthcare System: A Look at the Future*, which emphasized that engineering principles are central to a system that keeps the patient in focus while continuously improving quality, safety, knowledge, and value.

That goal remains urgent. In a learning health system, data, evidence, and real-world experience are dynamically integrated to improve care.¹ Patients, families, and communities are active participants. New knowledge is generated as an integral part of the care experience, and that knowledge is applied to improve outcomes for the next patient. Like any well-designed system, it learns from

¹ Institute of Medicine. 2013. [Best care at lower cost: the path to continuously learning health care in America](#). Washington, DC: The National Academies Press.

feedback, refines itself over time, and becomes stronger with each cycle.² Engineering provides the architecture that transforms disconnected data into a trusted engine for continuous learning, innovation, and better health.

Ultimately, engineering health is not about technology for its own sake. It is about ensuring every scientific advance translates quickly and reliably into better care for patients and healthier communities. It is about designing systems that are safer, more effective, more equitable, and more responsive to the people they serve.

The future of engineering health will depend not only on technical excellence, but also on public trust. Patients and communities must have confidence that their data will be used responsibly, that innovation will reflect their needs, and that the benefits of scientific progress will be shared broadly. Trust is not separate from innovation; it is one of its essential design requirements.

No single discipline can accomplish this alone. Engineers, clinicians, scientists, data scientists, public health leaders, patients, industry, and policymakers each bring essential perspectives. The most important advances in the coming decades will emerge not from one field working in isolation, but from purposeful collaboration across disciplines.

The articles you will read in this issue demonstrate what that collaboration looks like in practice. Together they illustrate how engineering is reshaping diagnosis, treatment, prevention, and health care delivery, while opening entirely new possibilities for improving health. If we continue to embrace this convergence, we will not simply build better technologies. We will build better systems of health, capable of learning continuously and delivering better outcomes for every person and every community. That is the promise of engineering health, and it is one of the greatest opportunities before us.

² Agency for Healthcare Research and Quality. 2019. [Learning health systems: making the case against business as usual](#).

By integrating diagnostics and therapeutics around shared molecular and cellular targets, there is great potential to improve treatment efficacy, minimize unnecessary interventions, accelerate therapeutic development, and advance precision medicine.

Platform Technologies for Precision Diagnostics and Therapeutics

Rashid Bashir, Gang Bao, Mehmet Toner, Enrique Valera, So Hyun Park, Murat Karabacak, Jon F. Edd, and Avanish Mishra



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Introduction

Precision medicine rests on two coupled technology pillars: diagnostics that resolve a patient's molecular and cellular state, and therapeutics that act on the disease mechanism revealed by diagnostics. Nucleic acid amplification, next-generation sequencing, immunoassays, mass spectrometry, and electrochemical sensing now extend from reference laboratories to wearable devices, each embodying distinct trade-offs among sensitivity, multiplexing, turnaround time, and deployment setting. Complementing these measurements of soluble analytes, cellular diagnostics interrogates the intact cells in diseased tissues that

are shed into the bloodstream: microfluidic enrichment recovers circulating tumor and endothelial cells present at a few copies among billions of blood cells, and single-cell genomic profiling has converted them from enumerated biomarkers into mechanistic readouts of tissue injury, therapeutic target expression, and treatment response. In parallel, genome editing, RNA-based medicines, engineered cell therapies, and the vehicles that deliver them have moved from concept to approved products for treating inherited, malignant, and infectious diseases. We envision that the convergence of these platform technologies into a closed-loop theranostic workflow defines the next phase of precision medicine, in which data generated can be used to advance machine learning and artificial intelligence (AI) for improved disease stratification, prediction of severity, and new drug development.

Precision Molecular Diagnostics

A targeted therapy is only as valuable as the test that identifies the patients who will benefit from it. Precision medicine therefore rests on a diagnostic layer capable of detecting and quantifying nucleic acids, proteins, metabolites, or cells in complex specimens—blood, urine, saliva, swabs, and tissue biopsies—with high sensitivity, specificity, and speed. The field has shifted from phenotypic methods based on culture, microscopy, and enzyme activity toward assays that quantitatively report the sequence, abundance, or presence of defined molecules. The platform families that now dominate clinical practice are shown in Figure 1, and each embodies distinct trade-offs among sensitivity, multiplexing, turnaround time, cost, and footprint that determine whether a test runs in a reference laboratory, a clinic, or a patient's home.

Nucleic Acid Amplification Tests

The polymerase chain reaction (PCR) remains the workhorse of molecular diagnostics: exponential amplification of a defined target, monitored in real time by fluores-

cence, detects a few copies of DNA or RNA per reaction and supports viral load measurement, oncogenic mutation detection, and transplant monitoring. Digital PCR partitions a sample into thousands of nanoliter compartments scored as positive or negative, giving absolute quantification without a calibration curve and resolving allele fractions below 0.1%, the regime required for circulating tumor nucleic acid and molecular residual disease. Isothermal chemistries such as loop-mediated isothermal amplification (LAMP) eliminate thermal cycling, enabling battery-powered cartridge devices, and CRISPR-based detection couples Cas12 or Cas13 collateral cleavage to a fluorescent or lateral-flow readout for single-nucleotide discrimination near ambient temperature (Kaminski et al. 2021; Lim et al. 2025). The engineering challenges lie in sample preparation, inhibitor tolerance, and cold-chain-free reagent stability with push toward an ideal test for rapid point-of-care testing (Table 1).

Sequencing-Based Tests

Next-generation sequencing reads millions of DNA fragments in parallel, and the collapse in cost—from roughly \$3 billion for the first human genome to a few hundred dollars today—has moved sequencing into routine care (Shendure et al. 2017; Smedley et al. 2021). Exome and genome sequencing resolve many previously undiagnosed inherited disorders, and rapid whole-genome sequencing can return actionable results for critically ill newborns within days. In oncology, comprehensive genomic profiling panels identify driver mutations, tumor mutational burden, and microsatellite instability, linking diagnosis directly to therapy selection. Sequencing of cell-free DNA in plasma underlies noninvasive prenatal screening and, as liquid biopsy, enables tumor genotyping, resistance monitoring, and residual disease detection (Pantel and Alix-Panabières 2025). Metagenomic sequencing identifies pathogens without culture, and long-read platforms resolve structural variants and repeat expansions that

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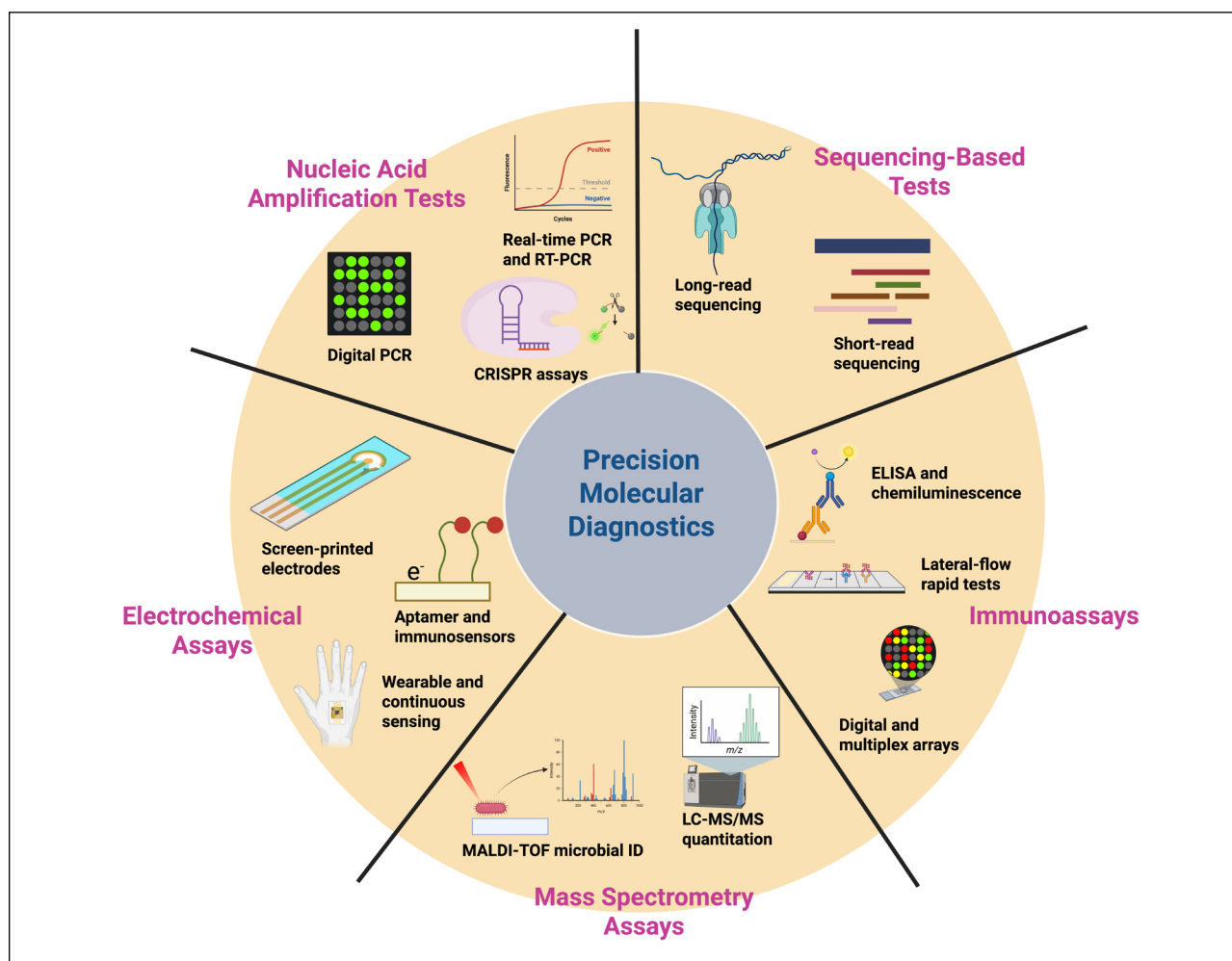


FIGURE 1 The five platform families that underpin precision molecular diagnostics. Nucleic acid amplification tests copy a target sequence until it can be detected. Sequencing-based tests read the order of bases directly, by short-read sequencing or long-read sequencing. Immunoassays use antibodies to capture protein analytes. Mass spectrometry assays identify molecules by mass-to-charge ratio. Electrochemical assays convert binding or catalysis into an electrical signal. ELISA = enzyme-linked immunosorbent assay; LC-MS/MS = liquid chromatography-tandem mass spectrometry; MALDI-TOF = matrix-assisted laser desorption/ionization time-of-flight; m/z = mass-to-charge ratio; PCR = polymerase chain reaction; RT-PCR = reverse transcription polymerase chain reaction. Created with www.BioRender.com.

short reads miss. The bottleneck has shifted from data generation to interpretation: variants of uncertain significance, ancestral bias in reference databases, and pipeline validation.

Immunoassays

Antibody-based protein detection remains the highest-volume format in laboratory medicine, spanning lateral-flow strips used for self-testing, enzyme-linked immunosorbent assays, and automated chemiluminescent platforms processing hundreds of samples per hour. Sensitivity has been extended by orders of magnitude:

digital immunoassays that count individual immunocomplexes captured on beads in femtoliter wells reach sub-femtomolar detection limits (Kan et al. 2020), making brain- and heart-derived proteins measurable in blood. High-sensitivity cardiac troponin assays permit rapid rule-out of myocardial infarction, and in 2025 the US Food and Drug Administration cleared the first blood-based test to aid Alzheimer's disease diagnosis, a plasma p-tau217/amyloid- β 1-42 ratio substituting for lumbar puncture or amyloid imaging. Antibody variability, cross-platform harmonization, and matrix interference remain limiting.

Feature	Real-Time PCR	RPA	LAMP	CRISPR-Dx	Ideal Assay
Temperature Requirement	Denaturation: 95°C Annealing: 55-65°C Extension: 72°C	Isothermal: 37-42°C	Isothermal: 60-65°C	Isothermal: 25-42°C	Isothermal: 25-35°C
Time to Results	1-2 hours	20-30 minutes	30-60 minutes	30-60 minutes (might need pre-amplification)	<10 minutes
Sensitivity	High	High	High	High	High
Specificity	High	Moderate-to-High	Moderate-to-High	High	Very high
Equipment Required	Thermal cycler with fluorescence detection	Portable heating block	Portable heating block	Portable heating block	Minimal equipment
Cost	High initial capital investment	Low initial capital investment	Low initial capital investment	Low initial capital investment	Low
	High per individual test	Low-to-moderate running cost	Low-to-moderate running cost	Low running cost	
Multiplexing	Primer design complexity, primer-dimer formation, prone to nonspecific amplification—would need new labeling techniques			Yes/No for large, pooled panels (exclusive OR)	Pooling or high degree of multiplexing

TABLE 1 Nucleic acid amplification tests. The engineering challenges lie in sample preparation, inhibitor tolerance, and cold-chain-free reagent stability with push toward an ideal test for rapid point-of-care testing.

Mass Spectrometry Assays

Mass spectrometry identifies analytes by mass-to-charge ratio and therefore needs no target-specific binding reagent. Matrix-assisted laser desorption/ionization time-of-flight (MALDI-TOF) mass spectrometry has transformed clinical microbiology: a colony is co-crystallized with a matrix, ionized by a laser pulse, and its largely ribosomal protein fingerprint is matched against a reference library. This gives species-level identification in minutes at a few cents per sample, in place of biochemical panels requiring a day or more (Idelevich and Becker 2021). Applied directly to positive blood cultures, it shortens time to targeted antimicrobial therapy. Beyond microbiology, liquid chromatography-tandem mass spectrometry underpins newborn screening for dozens of inborn errors of metabolism from a single dried blood spot. Constraints include incomplete spectral databases for uncommon organisms, capital cost, and the expertise required.

Electrochemical Assays

Electrochemical sensors convert a molecular recognition or catalytic event directly into a current, potential, or impedance change, dispensing with optics and enabling miniaturized, low-power devices. The archetype is the

amperometric glucose strip and its descendant, the continuous glucose monitor—an implanted enzymatic electrode reporting interstitial glucose every few minutes, by far the most widely deployed biosensor in medicine. The same architecture supports immunosensors, aptamer-based sensors, and nucleic acid sensors, while nanostructured electrodes and field-effect transistor transducers lower detection limits. Screen printing yields disposable electrodes costing cents apiece that a smartphone can read. Wearable formats, including sweat patches and microneedle arrays sampling interstitial fluid, are under development for lactate, electrolytes, hormones, and therapeutic drugs (Kim et al. 2019). Biofouling, calibration stability, and the uncertain relationship between sweat and blood analyte levels are the central obstacles.

Converging and Future Trends

Advances in these platforms could be used individually or combined with others to capture information across the genome, transcriptome, proteome, and cellular phenotype. For example, CRISPR-based recognition for rapid syndromic panels can eliminate amplification steps; exosomes could be used for sampling the intracellular content such as nucleic acid molecules inside or

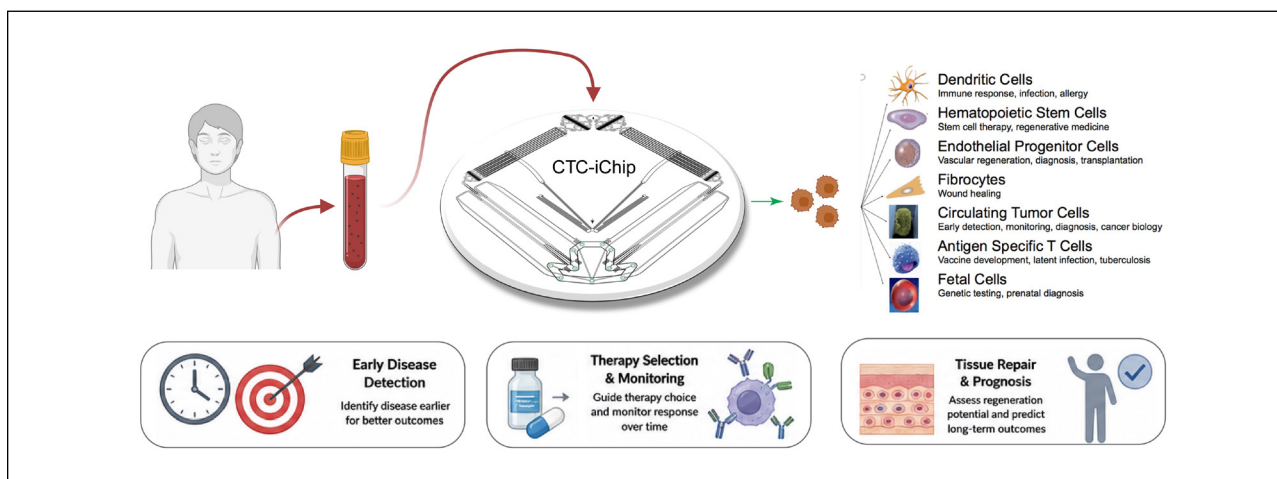


FIGURE 2 Cellular diagnostics from a routine blood sample. A single peripheral blood draw contains rare cells released into the circulation from tissues throughout the body; recovering them intact provides a minimally invasive window into organs that would otherwise require biopsy. Whole blood is processed through the CTC-iChip, a microfluidic device that sorts cells by size, aligns them by inertial focusing, and magnetically depletes antibody-labeled leukocytes, so that rare nucleated cells are enriched without labeling the target cells themselves and are recovered viable for downstream genomic, transcriptomic, proteomic, and functional analysis. CTC = circulating tumor cell; CTC-iChip = circulating tumor cell inertial focusing chip. Source: Original figure created by the authors.

the surface proteins; sequencing is paired with liquid biopsy; mass spectrometry and sequencing together give both organism identification and resistance genotyping; and wearable sensors in flexible electronics are linked to molecular assays for continuous monitoring. Machine learning applied to these multimodal datasets identifies biomarker signatures that no single platform resolves alone.

Cellular Diagnostics and Analysis

Modern medicine relies largely on indirect measurements of disease. Imaging, laboratory testing, and physiological monitoring provide valuable clinical information, but they often reflect tissue injury after significant biological changes have already occurred. An important goal in precision medicine is to identify disease-associated cellular programs at their earliest stages, before significant biological changes have already occurred.

Reading Disease Through Circulating Cells

Cellular diagnostics addresses this challenge by directly interrogating cells circulating in the bloodstream. Unlike the soluble biomarkers described earlier, which in many cases provide only indirect evidence of disease, circulating cells carry rich molecular information about their tissue of origin and physiological state. They can be isolated from a routine blood sample and analyzed by genomic, transcriptomic, proteomic, and functional assays, provid-

ing a minimally invasive window into biological processes occurring throughout the body (Figure 2).

The field emerged from studies of circulating tumor cells (CTCs), which demonstrated that rare cells shed from diseased tissue into the bloodstream carry clinically relevant information about disease burden, progression, and therapeutic response, and that they preserve many of the genomic and transcriptional features of the tumors from which they originate (Allard et al. 2004; Pantel and Alix-Panabières 2019; Cristofanilli et al. 2004). That work changed how investigators viewed blood: not simply a transport medium, but a readily accessible source of disease-relevant cells that reflect the biology of otherwise inaccessible tissues.

The Needle-in-a-Haystack Problem

Disease-associated circulating cells are exceptionally rare, often only a few cells among the billions present in each milliliter of blood. Recovering them at high yield and purity has required advances in microfluidics that exploit differences in cell size, hydrodynamic behavior, and membrane protein profile to enrich viable cells from whole blood while preserving their molecular integrity. Inertial focusing and immunomagnetic depletion, among other strategies, laid the engineering foundation for many current liquid biopsy platforms (Nagrath et al. 2007). Because rarity argues for ever larger sample volumes, full leukapheresis products have recently been used to recover

CTCs from effectively the entire blood volume (Mishra et al. 2025), opening a path to CTC-based detection of early cancer.

CTCs for Guiding Therapy

Perhaps the most transformative application of CTCs is guiding targeted therapy selection. Therapies directed at tumor-cell surface proteins have transformed cancer treatment, but the diagnostic tools needed to guide patient selection have not kept pace. Antibody drug conjugates (ADCs), which deliver chemotherapy to epitope-expressing cancer cells, and bispecific T cell engager (BiTE) antibodies, which recruit CD3-positive T cells to those cells, both call for readily deployable biomarkers of initial and persistent target expression. Intact CTCs are well suited to this task: blood sampling is noninvasive, permits serial analysis, and captures tumor cells derived from multiple metastatic lesions. CTCs predict response to the DLL3-targeting bispecific antibody tarlatamab in small-cell lung cancer (SCLC) (Mishra, Meador, et al. 2026) and provide guidance on ADC design in metastatic breast cancer (Mishra, Abelman, et al. 2026).

These principles now extend well beyond cancer. Many tissues release cells into the circulation in response to injury, inflammation, regeneration, and pathological remodeling. Circulating endothelial cells (CECs), released following vascular injury, are among the best studied; because endothelial dysfunction contributes to cardiovascular disease, inflammatory disorders, infection, and cancer, CECs offer a window into vascular health and disease activity that is difficult to obtain through conventional laboratory measurements alone (Blann et al. 2005; Erdbruegger, Haubitz, and Woywodt 2006).

Genomics Advancing Cellular Diagnostics

Single-cell genomics has substantially expanded the utility of cellular diagnostics. While early rare-cell studies focused primarily on enumeration, individual circulating cells can now be profiled at genome-wide resolution. Single-cell RNA sequencing revealed extensive cellular heterogeneity and enabled characterization of distinct cellular states, signaling programs, and differentiation trajectories (Tang et al. 2009; Zheng et al. 2017). Rather than measuring the average behavior of large cell populations, investigators can now identify rare pathogenic subpopulations and the active biological programs within them (Stuart and Satija 2019), converting circulating cells from simple biomarkers into rich sources of mechanistic information about tissue injury, immune activation, and regeneration.

Converging Trends and Future Opportunities

Circulating cells may serve as dynamic indicators of biological activity occurring deep within tissues, reporting pathological programs as they emerge rather than after end-stage manifestations appear. Multimodal characterization integrating genomic, transcriptomic, proteomic, and metabolic information can generate comprehensive molecular portraits of disease (Collins and Varmus 2015), and machine-learning approaches applied to these datasets are increasingly capable of extracting clinically meaningful patterns that improve disease classification, prediction of outcomes, and assessment of therapeutic response.

Cellular diagnostics therefore represents more than a new class of biomarkers. By providing direct access to the cells actively participating in tissue injury, regenera-

Circulating cells may serve as dynamic indicators of biological activity occurring deep within tissues, reporting pathological programs as they emerge rather than after end-stage manifestations appear.

tion, and therapeutic response, it offers a route to earlier diagnosis, improved risk stratification, and more precise monitoring of treatment—information that would otherwise require invasive tissue biopsy.

Precision Molecular Therapeutics

The completion of the Human Genome Project, together with rapid advances in molecular biology, biotechnology, and computational sciences, has fundamentally changed drug discovery and therapeutic development. Traditional pharmacological agents primarily target proteins using small molecules, yet many disease-associated proteins remain inaccessible to conventional drugs. Precision molecular therapeutics has shifted the treatment paradigm from symptom management to interventions that directly target the molecular mechanism(s) underlying disease. Advances in genome editing, synthetic biology, protein engineering, and drug delivery have enabled high-

ly specific therapeutics, including gene editing therapy, messenger RNA (mRNA)-based and RNA-targeted medicines, cell therapies, and engineered antibody therapies (Figure 3; Doudna and Charpentier 2014; Collins and Varmus 2015), expanding the therapeutic landscape to include nucleic acids, engineered proteins, living cells, and genome editing technologies capable of addressing disease at its molecular origin. Molecular therapies can now be tailored to an individual's genetic and molecular profile, improving outcomes across inherited disorders, cancer, infectious diseases, and autoimmune conditions.

Precision Genome Editing

Genome editing represents one of the most transformative advances in molecular therapeutics (Wang and Doudna 2023). Programmable nucleases, including zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), and CRISPR-Cas systems, enable precise modification of genomic DNA, with CRISPR-Cas9 predominant because of its high efficiency, ease of design, and versatility. Conventional CRISPR-Cas9 editing relies on DNA double-strand breaks (DSBs), which can result in unintended large genomic alterations and other deleterious outcomes. Base editing and prime editing have substantially improved precision by enabling targeted nucleotide substitutions and small insertions or deletions without introducing DSBs (Anzalone, Koblan, and Liu 2020). Collectively, these technologies show tremendous promise for correcting pathogenic mutations underlying hematologic diseases, inherited retinal disorders, and other monogenic conditions (Levesque and Bauer 2025), culminating in the approval of Casgevy, the first CRISPR-based ex vivo gene-editing therapy, for sickle cell disease and transfusion-dependent β -thalassemia. Successful clinical implementation of in vivo genome editing will require substantial improvements in delivery systems as well as enhanced editing efficiency, specificity, and safety.

RNA Therapeutics

mRNA therapeutics have emerged as a versatile platform for transient protein expression without permanently altering the host genome (Wang, Weissman, and Dong 2025). The rapid development and global deployment of mRNA vaccines against COVID-19 demonstrated the clinical feasibility of this approach and established lipid nanoparticles (LNPs) as effective delivery vehicles for nucleic acid therapeutics. Beyond infectious diseases, mRNA therapeutics are being investigated for cancer

immunotherapy, cardiovascular disease, protein replacement, regenerative medicine, and rare metabolic disorders; key advantages include transient and controllable expression, rapid and flexible design, scalable manufacturing, and broad applicability. RNA-based therapeutics more broadly encompass microRNAs (miRNAs), small interfering RNAs (siRNAs), antisense oligonucleotides (ASOs), and RNA-editing technologies, enabling modulation of gene expression at multiple levels. Several RNA therapeutics have received FDA approval for spinal muscular atrophy, hereditary transthyretin amyloidosis, and other rare genetic disorders.

Cell-Based Therapies

Cell-based therapeutics that use engineered cells have the potential to address diseases that remain intractable to conventional treatment (Bashor et al. 2022). Extensive effort has focused on genetically engineering immune cells, including chimeric antigen receptor (CAR)-T cells, T-cell receptor (TCR)-engineered T cells, and natural killer (NK) cells, to enhance cancer immunotherapy through improved persistence, tumor specificity, and resistance to the immunosuppressive tumor microenvironment. Other applications include transplantation of hematopoietic stem cells and induced pluripotent stem cell (iPSC)-derived cells for hematologic malignancies and type 1 diabetes, and the use of stem cells to repair or replace damaged tissues. Major challenges remain: identifying optimal cell sources, generating safe, potent, and durable products tailored to individual patients and diseases, and developing scalable, cost-effective manufacturing. A major frontier is the development of stem cell-derived, off-the-shelf cellular therapeutics that provide a renewable source of therapeutic cells while minimizing immune rejection through targeted disruption of immune-recognition pathways.

Delivery of Therapeutic Nucleic Acids

Gene editing, RNA-, and cell-based therapies all require efficient delivery of nucleic acids into target cells with low toxicity, and in vivo applications additionally demand high tissue specificity with minimal off-target effects. The two major classes of delivery vehicles are non-viral and viral vectors. Most FDA-approved non-viral platforms are lipid- or polymer-based, with LNPs emerging as particularly powerful because of their ease of manufacturing, scalability, favorable safety profile, and ability to support repeated administration (Hou et al. 2021). Exosomes and extracellular vesicles

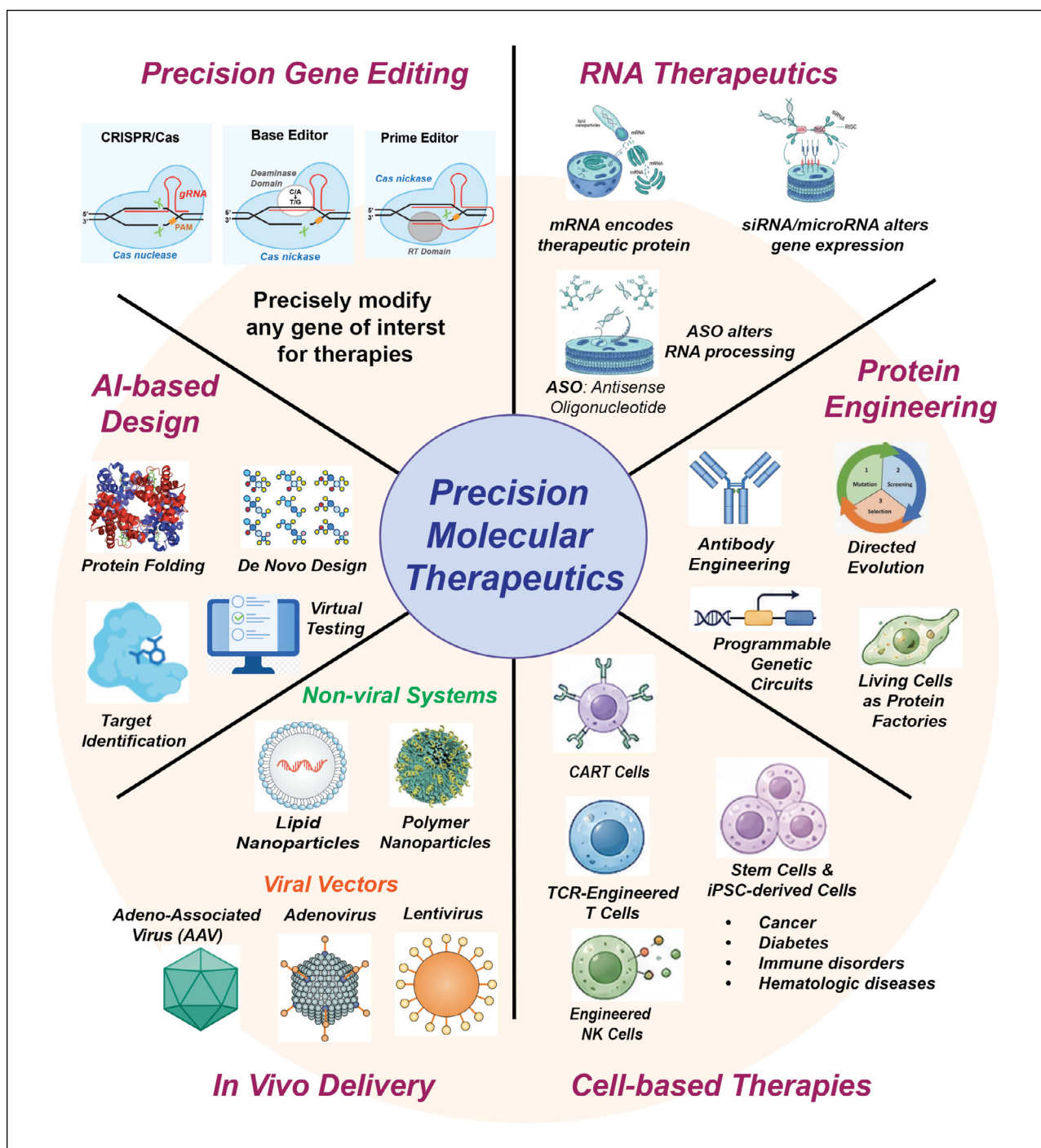


FIGURE 3 Major areas of molecular therapeutics. The six major areas that underpin precision molecular therapeutics are shown. Precision gene editing rewrites the genomic information, by CRISPR-Cas nucleases, base editors, and prime editors. RNA therapeutics, including that use mRNA, siRNA, microRNA, and antisense oligonucleotide, act on the transcript rather than DNA. Protein engineering creates new protein-based therapeutic agents, including engineered antibodies, through directed evolution (iterative rounds of mutation, screening, and selection), programmable genetic circuits, or using living cells as protein factories. Cell-based therapies use living cells as the therapeutic agent. Most molecular therapies require efficient and safe in vivo delivery, with vehicles carrying therapeutic payloads to target tissues by non-viral systems and viral vectors. AI-based design spans the discovery pipeline, from target identification and protein structure prediction to de novo molecular design and virtual testing. AAV = adeno-associated virus; AI = artificial intelligence; ASO = antisense oligonucleotide; CAR = chimeric antigen receptor; iPSC = induced pluripotent stem cell; NK = natural killer; PAM = protospacer adjacent motif; TCR = T-cell receptor. Source: Original figure created by the authors.

(EVs), both circulating and matrix bound, are natural nanoscale carriers that can be used to deliver proteins, lipids, and nucleic acids due to their high biocompatibility, ability to cross biological barriers, and low intrinsic immunogenicity (Ronan et al 2026). Viral vectors, particularly adeno-associated viruses (AAVs) and lentiviruses, remain predominant for gene therapy owing to their high transduction efficiency, and approved products have demonstrated efficacy in inherited retinal diseases, spinal muscular atrophy, hemophilia, and certain immunodeficiency disorders. Substantial challenges remain in improving delivery efficiency, tissue specificity, and safety. These include achieving higher payload capacity as well as enabling targeted delivery and efficient endosomal escape while minimizing immunogenicity.

Precision Medicine in the New Era

The emerging trend is to move beyond viewing diagnosis and treatment as separate stages of patient care. Major advances in molecular diagnostics, cellular characterization and analyses, targeted therapeutics, molecular imaging, and computational sciences have given rise

to precision molecular and cellular theranostics, an integrated approach that combines disease detection, patient stratification, therapeutic intervention, and treatment monitoring within a single framework (Aboagye, Haberkorn, and Barwick 2023). Molecular and cellular diagnostics and therapeutics have entered an era of unprecedented precision and therapeutic innovation. In particular, the convergence of genomics, transcriptomics, proteomics, metabolomics, and single-cell sequencing has accelerated the development of personalized precision medicine. Comprehensive molecular and cellular profiling and measurements enable clinicians to classify diseases with greater accuracy and select therapies based on each patient's unique molecular characteristics rather than clinical presentation alone. The generation of vast amounts of high-quality multi-omics data, combined with advances in artificial intelligence (AI) and machine learning, is transforming not only advanced diagnostics but also drug discovery and development by accelerating target identification, protein structure prediction, virtual drug screening, molecular optimization, and clinical trial design. These advances have the potential

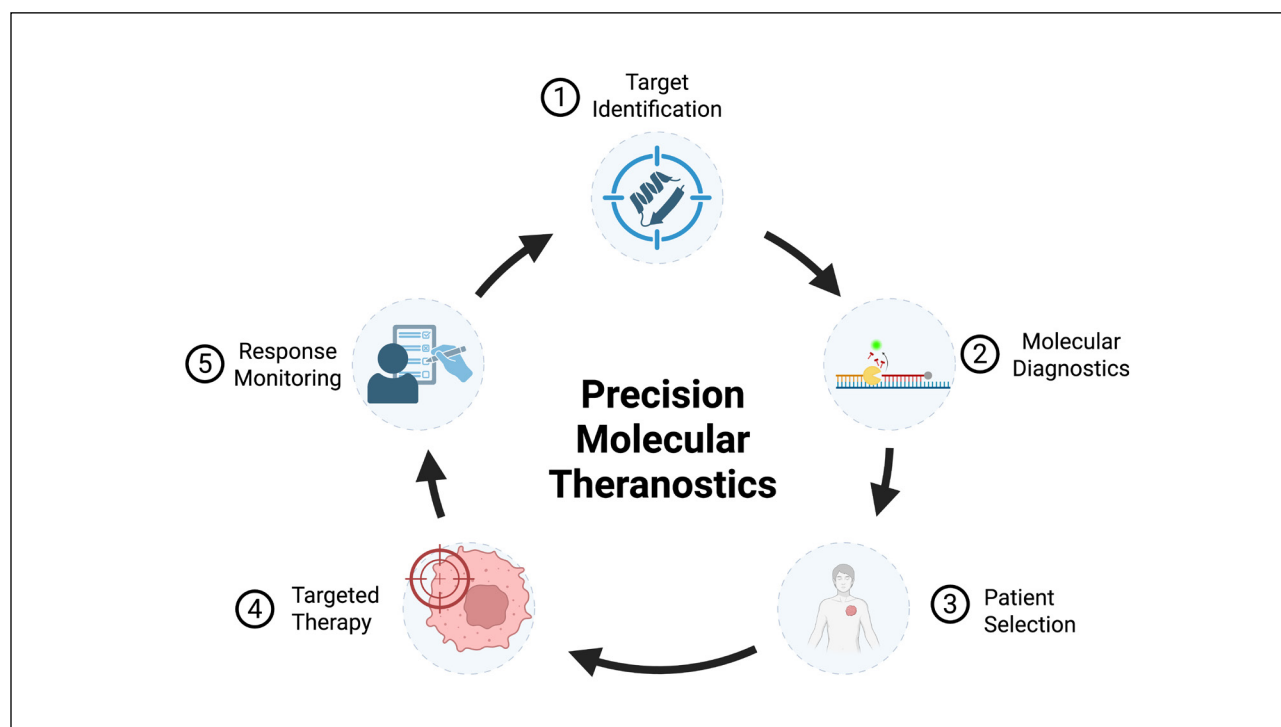


FIGURE 4 Continuous workflow of precision molecular theranostics. Precision molecular theranostics integrates molecular diagnostics and targeted therapeutics within a continuous, closed-loop framework for personalized disease management. Information generated during response monitoring feeds back into target reassessment and patient stratification, creating a continuous cycle, thereby enabling adaptive, data-driven clinical decision-making and highly personalized care. Created with www.BioRender.com.

to improve therapeutic efficacy, reduce adverse effects, and optimize treatment for individual patients. Hence, precision molecular theranostics establishes a continuous workflow in which molecular targets are identified and characterized, patients are stratified according to their molecular profiles, targeted therapies are selected and administered, and treatment response is assessed through molecular diagnostics and biomarker monitoring (Figure 4). This closed loop enables dynamic, data-driven clinical decision-making and supports highly personalized disease management (Herrmann et al. 2020).

By integrating diagnostics and therapeutics around shared molecular and cellular targets, there is great potential to improve treatment efficacy, minimize unnecessary interventions, accelerate therapeutic development, and advance precision medicine across cancer, sepsis, infectious diseases, autoimmune disorders, and other complex human diseases.

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With design rules directed toward tipping the balances between effector responses and tolerance, immunoengineering can yield advances in both therapy and promotion of health.

Advances in Immunoengineering

Designing the Context of Immunity



Erica Budina



Jeffrey A. Hubbell

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The human immune system serves many functions: some related to effector responses and others to tolerance. Through its effector functions, it defends human hosts against external pathogens that may result in an infectious disease; it protects us from cells with mutations that may result in cancer; and it may drive a rapid, even if fibrotic, healing response to injury that was necessary for us to survive in our evolutionary past. Through its regulatory and tolerogenic functions, it helps our bodies accept the foods we eat and the helpful commensal organisms that inhabit our gut and other body surfaces, as well as heal to a more fully functional state following damage in a modern world

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that affords time and protection to recover. Indeed, the healthy immune system exists in a détente between effector responses and tolerance, balancing how quickly and strongly to respond to danger while also promoting and maintaining homeostatic tolerance to self and the beneficial features of our environment, which could otherwise lead to autoimmunity and allergy, respectively.

The field of immunoengineering is based on understanding the design rules that govern this evolutionary balance between effector responses and tolerance. On the one hand, how can immunoengineers employ an antigen (a molecular structure that the adaptive immune system specifically recognizes) to prepare for defense against an infectious pathogen? And on the other, how can an antigen be utilized to prevent or even treat an autoimmune disease or allergy? How can they employ cytokines (immune signaling molecules) to induce inflammation in a tumor to lead to its rejection, and how can cytokines be employed to quiesce an inflamed tissue? How can they employ immunity to yield rapid tissue repair following trauma, surgery, or disease while ameliorating pain and restoring full tissue function? With design rules directed toward tipping that balance, immunoengineering can yield advances in both therapy and promotion of health.

Another feature of immunity that leads to design rules is that of memory. For example, when we experience an infection or receive a vaccine, we develop immunological memory that protects us for a prolonged period from that and sometimes related challenges. Likewise, when we develop tolerance to a food substance or molecular features of self, that tolerance is also lasting. This memory, of both effector responses and tolerance, holds promise for therapies that may be durable, having beneficial effects long after cessation of treatment. Examples of durable therapies being pursued include vaccines that direct the immune system to kill cancer cells and prevent cancer recurrence, and therapies to treat autoimmunity or allergy that would reestablish immune tolerance.

Given the breadth of immunoengineering, this perspective focuses on molecular and cellular approaches to modulating immune responses, in particular through the engineering of antigens, adjuvants, cytokines, metabolites, and immune cells. Additional areas of investigation in the field, including organoids and tissue-engineered models, organ-on-chip systems, and cell therapy manufacturing, are addressed in other excellent reviews (Dias et al. 2024; Ingber 2022; S. Kim et al. 2019; Lipsitz, Timmins, and Zandstra 2016).

Design: Tools of the Trade, From Immune Molecules to Immune Contexts

The tools of immunoengineering are both familiar and novel to the field of immunology. On the familiar side, there are antigens, adjuvants, cytokines, metabolites, and immune cells. These agents can exist in their native forms, but they can also be engineered to confer novel, super-physiological characteristics (Figure 1).

Antigens can be present in soluble form, or they may be arrayed on a biological (Keshavarz-Joud et al. 2023) or synthetic nanoparticle to induce immune responses that may show a broader antibody (humoral) repertoire (Marchitto et al. 2026; Steichen et al. 2026; Guenaga et al. 2026) or accentuated cellular immunity (Wilson, Hirose, et al. 2019). Adjuvant molecules, which are often synthetic analogs of molecular signals from pathogens that the immune system has evolved to sense, may be co-associated with antigens as well, or engineered to remain in a depot for prolonged exposure to enhance a vaccinal response (Soni et al. 2024; Wilson, Hirose, et al. 2019; Rakhra et al. 2021).

Cytokines are proteins from the immune and other systems that signal cellular processes, whether to induce proliferation, agonize inflammation, or drive tolerogenic processes. In their native forms, translation of cytokines to therapies has been challenging, which may relate to differences in the context of their natural function versus administration, in that they are typically produced locally to induce local signaling. Thus, immunoengineers have developed approaches to enhance their deposition in particular sites, such as tumors or inflamed tissues (Mansurov et al. 2020; Momin et al. 2019), or to provide them in inactive form such that they are locally activated within their site of desired action (Mansurov et al. 2021).

Living cells themselves have become part of the engineering toolkit. Chimeric antigen receptor (CAR)-T cells and related cellular therapies show that immune cells can be redesigned to recognize malignant cells, persist after infusion, and exert highly specific functions such as killing cells in blood cancers or solid tumors (Patel et al. 2025). Similar principles are being explored to kill immune cells that are effectors in autoimmunity (English et al. 2024; Vu et al. 2026) or even to redirect regulatory cells (Bluestone et al. 2025) in autoimmunity and transplantation. In addition to the engineered cells acting themselves, they can also locally express cytokines and other factors to further drive or quell inflammation (Sasaki et al. 2026).

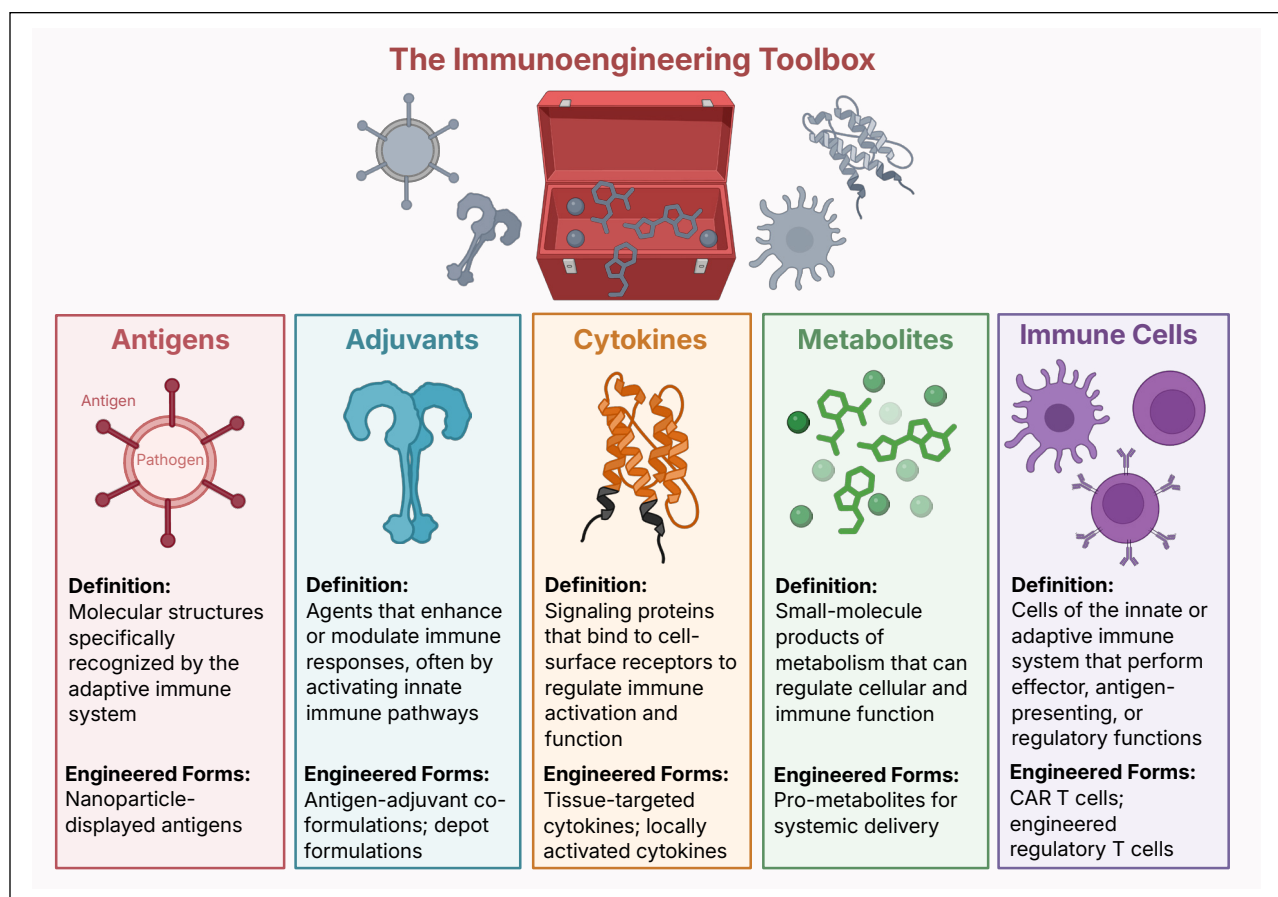


FIGURE 1 The immunoengineering toolbox. The tools of immunoengineering include antigens, adjuvants, cytokines, metabolites, and immune cells. These agents can exist in their native forms, but they also can be engineered to confer novel, super-physiological characteristics. Antigens may be incorporated into biological or synthetic nanoparticles; adjuvants may be co-associated with antigens or engineered to remain in a depot for prolonged exposure; cytokines may be engineered to increase their deposition at specific sites or to remain inactive until locally activated; metabolites may be delivered as pro-metabolites to control their release or enable systemic bioavailability; and immune cells may be engineered to recognize defined targets, kill pathogenic cells, or promote regulatory immune responses. Figure created using www.BioRender.com.

In the above, one can observe that the immune context by and in which the tool is provided is critical. In a vaccinal response, an objective is to direct antigen and adjuvant to the lymph nodes that drain the site of administration. There, antigen and adjuvant meet antigen-presenting cells, key members of the innate immune system that are activated by the adjuvant to present the antigen. Antigen-presenting cells then meet members of the adaptive immune system (adaptive, because it responds to these antigens), including B cells (that lead to antibody production to bind the antigen) and T cells (that help B cells, and that can also kill infected or malignant cells that express the antigen) (Reddy et al. 2007). Thus, the lymph node produces a context for immunological education

(Gammon et al. 2023; H. Liu et al. 2014; Moynihan et al. 2018).

A counterexample can be found in many solid tumors, where the immune microenvironment is often immune suppressive or even tolerogenic, based on metabolites, cytokines, and cell-surface checkpoint molecules, which can prevent immune response to tumor cells (which contain mutated antigens that could otherwise be recognized) and even drive regulatory immunity. Thus, the tissue context can sometimes be harnessed to favorable effect but in other use cases must be overcome and modified to achieve a desired outcome. These features further involve biophysical cues, in addition to molecular ones, including tissue mechanics (White et al. 2025; Ma et al. 2026;

Liu, Tan, and Loebel 2026), crosslinking state (Ahmed et al. 2025), and interstitial flow (Swartz and Lund 2012).

Antigen-Specific Therapies: From Vaccines for Infectious Disease and Cancer to Tolerance in Autoimmunity and Allergy

Antigen-specificity is perhaps the most precise approach of immunoengineering, yet it requires detailed knowledge of the target's antigens (Figure 2). In infectious disease, vaccination seeks to prepare the immune system to recognize molecular features of a pathogen before infection occurs. The design challenge is not simply to choose an antigen, but to choose one that is sufficiently conserved, accessible, and immunogenic, and then to present it in a way that induces the needed combination of antibodies, helper T cells, cytotoxic T cells, and immunological memory. For mutable pathogens (e.g., as in human immunodeficiency virus) and chronic infections (e.g., as sometimes occurs in hepatitis B virus infection), the problem becomes more difficult: the immune response must be focused on features that the pathogen cannot easily mutate and sometimes must be rescued from exhaustion or tolerance-like contexts that permit chronicity, respectively.

Cancer vaccines pose a related but distinct challenge. Tumor antigens may be mutated, overexpressed, developmentally restricted, or shared with normal tissues (Galliverti et al. 2018; Corgnac et al. 2020). The desired response is often cellular rather than purely humoral: cytotoxic T cells must enter the tumor, remain functional, and recognize malignant cells despite local immunosuppression provided by the tolerogenic context of many tumors (Galliverti et al. 2020). Here, antigen selection must be integrated with adjuvant choice, delivery vehicle, tissue localization and timing, and potentially combination with therapies that disable or overcome the inhibitory signals within the context of the tumor-immune microenvironment (Moynihan et al. 2018; Lucas et al. 2025). Stromal and vascular cells may also need to be considered, because the solid tumor is a tissue-like immune ecosystem rather than a collection of malignant cells alone (O'Melia, Rohner, and Thomas 2022).

Adjuvants are indispensable in this setting because antigens rarely induce a potent immune response on their own (Soni et al. 2024). Adjuvants also illustrate the importance of localization and context (Reddy et al. 2007). A danger signal that effectively stimulates an immune response in a draining lymph node may cause

undesirable inflammation were it to be distributed systemically. Linking antigen and adjuvant in the same particle, matrix, or molecular construct can help ensure that the immune system interprets the antigen in the intended way (i.e., to mimic a pathogen or malignant cell) (Soni et al. 2024). Immunoengineering therefore treats the antigen and its context as a coupled design problem, and researchers are pursuing combinations to guide the inflammatory response toward productive immunity and away from unhelpful inflammation (Kim JY et al. 2023; Poston et al. 2025).

With the objective to unwind an established pathogenic effector immune response rather than induce one, antigens are also being utilized and further developed to desensitize immunity and even induce tolerogenic immunity, with the goal not to provoke attack, but to induce antigen-specific tolerance (Gomez Medellin et al. 2025; Kim A 2023). In allergy and autoimmunity, one would like to present the relevant antigen within the context of a tolerogenic organ or cellular pathway, so that regulatory immunity is induced rather than effector immunity. Such approaches seek to generate T regulatory cells, delete or silence pathogenic clones, or establish durable antigen-specific non-responsiveness.

As to such tolerogenic contexts, the liver presents one such target, based on its natural function to drain antigens from food and commensal organisms in the gut and to clear debris in the blood arising from natural cell turnover (Gomez Medellin et al. 2025; Watkins et al. 2021). The antigen-presenting cells in the liver, and the processes for antigen collection there, provide a context that is conducive for development of regulatory immunity; as such, the liver is a target for tolerogenic interventions (Wilson, Damo, et al. 2019). It should be noted that T regulatory cells that home to a tissue based on their cognate antigen (e.g., a myelin antigen in nervous tissue) are able to regulate autoimmunity or allergy to other auto- or allergic antigens in the target tissue, and even to induce tissue repair (Ahn et al. 2025), via tolerogenic cytokines, enzymes, and metabolites that they produce; as such, if T regulatory cells can be induced, it may be unnecessary to know all of the antigenic features of the pathogenic target, only some of them (Tremain et al. 2023). If successful, such antigen-specific tolerogenic therapies may eventually replace broad immunosuppression with a therapy that restores the immune tolerance that failed and led to disease in the first place.

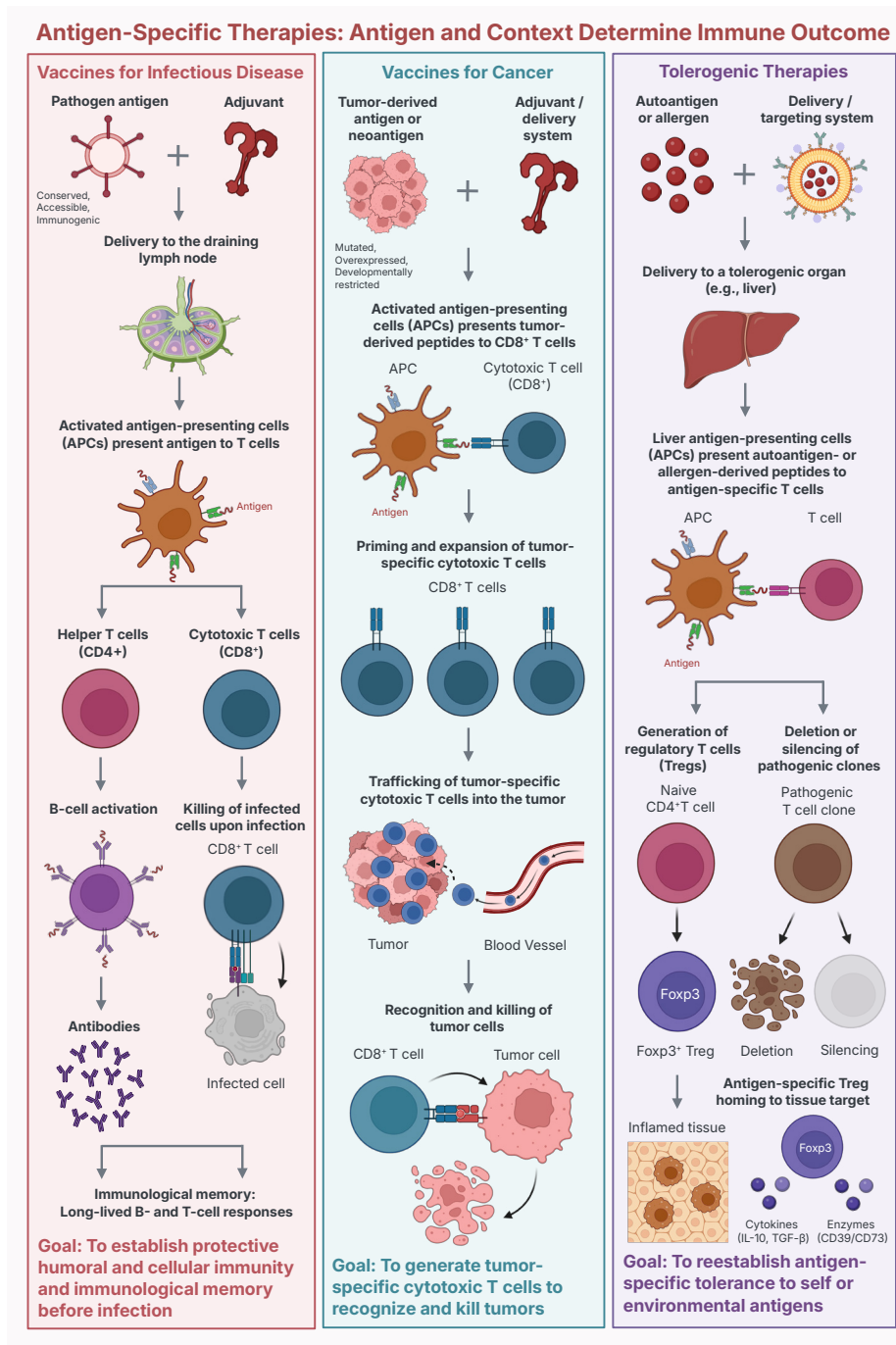


FIGURE 2 Antigen-specific therapies: antigen and context determine immune outcome. In infectious disease, vaccination prepares the immune system to recognize a pathogen prior to infection by presenting a sufficiently conserved, accessible, and immunogenic antigen in a context that induces antibodies, helper T cells, cytotoxic T cells, and immunological memory. In cancer, tumor-derived antigens or neoantigens can be used to prime and expand tumor-specific cytotoxic T cells that traffic into tumors, recognize malignant cells, and mediate tumor-cell killing. In autoimmunity or allergy, autoantigens or allergens can instead be presented through tolerogenic organs, such as the liver, to generate regulatory T cells (Tregs), delete or silence pathogenic clones, and restore immune tolerance to the disease-relevant antigen. Antigen-specific regulatory T cells can also home to inflamed target tissues and regulate local immune responses through the production of tolerogenic cytokines and enzymes. These approaches show how antigen and immune context can be engineered to direct either protective effector immunity or antigen-specific tolerance. Figure created using www.BioRender.com.

Cytokine Therapies: From Cancer Immunotherapy to Inflammatory Disease

Cytokines are among the immune system's most powerful signaling molecules. They can expand immune cells, polarize their functions, recruit them into tissues, promote inflammation, induce tolerance, or support repair. Modern medicine has already exploited cytokine biology, but largely by blocking harmful cytokines. Inhibitors of inflammatory cytokines including tumor necrosis factor alpha, interleukin-6, type 2 cytokines (interleukin-4, interleukin-5, and interleukin-13), interleukin-17, and related pathways have become transformative drugs. Yet these therapies generally work by suppressing an undesirable actor rather than by actively promoting a beneficial one to drive quiescence, repair, regulation, or durable tolerance.

As mentioned above, cytokines are usually active locally, thus an immunoengineering challenge is to modify or present cytokines as context-dependent medicines. In some cases, the same cytokine (e.g., interleukin-10) that can drive cytotoxic T cell proliferation, in another form or location, can quiet an inflamed tissue (Yuba et al. 2021). As another example, the type-2 cytokine interleukin-4 can push macrophages, cells of the innate immune system, toward a pro-regenerative state (Lauterbach et al. 2023), but under other conditions can also drive allergic responses.

Thus, the details of context matter, including localization, timing, and the presence of other immune signals and cells. A cytokine may be attenuated to reduce systemic toxicity; fused to another protein to prolong its residence in lymph nodes or target tissues (Budina et al. 2025); given affinity for extracellular matrix to retain it locally in tumors; or masked so that it becomes active only in a diseased microenvironment (Mansurov et al. 2022). Cytokines can also be targeted to the surfaces of specific cell populations to accentuate their effects (Santollani et al. 2024). Furthermore, cytokine-receptor affinity can be deliberately reduced, or “detuned,” so that signaling depends on simultaneous engagement of the cytokine receptor and a surface marker on the intended cell type. This can be achieved by fusing the detuned cytokine to an antibody against that marker, restricting the activity of a broadly acting cytokine to a specific cell subset (Moynihan et al. 2024). Cytokine engineering can also rewire intracellular signaling. For example, “Trikinases” are engineered to bring together three cytokine receptor chains at the cell surface, rather than the usual two, leading to signaling and gene expression programs distinct from those of native cytokines (Rodriguez et al. 2026). These strate-

gies change not only pharmacokinetics, but the biological interpretation of cytokine signaling: they alter where, when, to whom, and how the cytokine signals.

Matrix affinity may be especially attractive because many cytokines evolved to act locally. Binding to extracellular matrix can concentrate cytokines where immune signaling is desired and reduce exposure elsewhere. In cancer, this can help create inflammation within a tumor while limiting systemic toxicity (Mansurov et al. 2020; Momin et al. 2019). In autoimmunity or allergy, a complementary goal is to deliver regulatory cytokine activity to the disease sites or associated secondary lymphoid tissues and lymph nodes, where pathogenic immune programs are maintained. In both cases, cytokine engineering turns a broadly acting mediator into a more precise instruction within the desired context.

This approach also holds the potential to reframe therapy in inflammatory disease. Instead of inhibiting one pro-inflammatory pathway after another, one may be able to induce active regulatory programs that restore tissue homeostasis (Budina et al. 2025; Volpatti et al. 2026). Such therapies must preserve host defense, but they may point toward a more constructive immunology: not merely blocking inflammation but rebuilding the signals that allow inflammation to resolve and remain that way.

Microbiome and Related Therapies: From Gut to Systemic Immunity

The cellular targets in immunoengineering are not merely those of the person, but also of the person's microbiome. Indeed, we evolved in concert with our microbiota, and that co-evolution is central to immune health. The gut is not only a digestive organ; it is also one of the major sites at which the immune system learns the difference between danger, nourishment, and symbiosis with our commensal microbiome. Microbial communities help shape gut barrier function, modulate local inflammation, drive regulatory T cell development, and modulate systemic immunity. Disturbances in these commensal communities can therefore influence health and disease far from the gut, even in the brain, for example, via neurotransmitters such as serotonin produced in the gut (Hoffman and Margolis 2020; Lavoie et al. 2019).

Microbial metabolites provide one mechanistic bridge between the microbiome and immunity. Short-chain fatty acids, bile acid derivatives, tryptophan metabolites, and other microbial products can act locally on epithelial and immune cells, but they may also circulate and influence distant tissues. For immunoengineering, these molecules

are attractive because they are not foreign inventions imposed on the immune system; they are part of physiological immune regulation that may be engineered and rebalanced.

Engineering can intervene at several levels. Diet can be used to support beneficial metabolic pathways, and the connection between diet and the microbiome can be quantitatively determined and even predicted (Connors

Cytokine engineering also holds the potential to reframe therapy in inflammatory disease.

et al. 2026; Qian et al. 2026); specific dietary fiber feed-stocks can moreover be used to expand desirable microbial populations (Han et al. 2024). Microbial communities can be transferred or reshaped, for example to restore gut barrier function and prevent immune response even in the face of established food allergy (Hesser et al. 2024; Feehley et al. 2019). Specific organisms can be engineered to produce defined products, using methods of gene editing analogous to those employed to edit human cells in gene therapy (Gelsinger et al. 2025; Ronda et al. 2019). Alternatively, microbial metabolites can be delivered as pro-metabolites that control where and when they are released in the gut (Wang et al. 2023) or to escape the gut to become systemically bioavailable (Beckman et al. 2025; Cao et al. 2024).

Immunoengineering in the Clinic

Many of these immunoengineering design principles have been used to develop therapies that have reached the clinic. The licensed vaccine Shingrix represents an example of adjuvant design. The vaccine combines recombinant varicella-zoster virus glycoprotein E with the liposomal AS01_B adjuvant system. In a phase 3 trial, it showed 97.2% efficacy against herpes zoster, or shingles, in adults 50 years of age or older (Lal et al. 2015). As an example of engineered antigen presentation, the licensed vaccine Gardasil 9 consists of recombinant human papillomavirus proteins that self-assemble into virus-like particles, mimicking the outer structure of the virus. In a phase 2b-3 trial, the vaccine showed 96.7% efficacy against

high-grade cervical, vulvar, or vaginal disease caused by the five additional human papillomavirus types covered by the 9-valent vaccine compared to the quadrivalent vaccine (Joura et al. 2015). Intismeran autogene (intismeran) is a personalized messenger RNA-based cancer vaccine designed based on mutations identified in each patient's tumor and encapsulated within lipid nanoparticles. The vaccine was administered with pembrolizumab, an immune checkpoint-blocking antibody, to patients with high-risk, surgically resected stage IIIB to IV melanoma. At five years of follow-up, the combination was associated with a 49% lower risk of recurrence or death than pembrolizumab alone (Khattak et al. 2026).

Cellular engineering has also reached the clinic. In a phase 2 trial, the CAR T-cell therapy tisagenlecleucel (Kymriah), which recognizes CD19, a protein expressed on B cells, induced remission within three months in 81% of children and young adults with relapsed or refractory B-cell acute lymphoblastic leukemia (Maude et al. 2018). CAR T cells are also being used to kill immune cells that maintain autoimmune disease, for example, by targeting B cell maturation antigen that is present on plasma cells that produce antibodies that cause disease such as in the Descartes-08 trial in myasthenia gravis (Fedak et al. 2026; Vu et al. 2026).

Modulation of the microbiome has also entered clinical use. RBX2660, now approved as Rebyota, consists of a consortium of live microorganisms derived from human donor stool and is administered after antibiotic treatment to prevent recurrent *Clostridioides difficile* infection. In a phase 3 trial, 70.6% of patients who received RBX2660 remained free of recurrent infection for eight weeks compared with 57.5% of patients who received the placebo (Khanna et al. 2022).

Challenges in Development

The promise of immunoengineering is of course associated with challenges in development, and in many ways those challenges motivate engineering approaches to overcome them. With the objective to reestablish a healthy balance between inflammation and tolerance, an engineering objective is to navigate around immune-related adverse events; for example, to avoid inflammatory events associated with driving away from tolerance and toward inflammation in the tumor microenvironment, or to circumvent opportunistic infection when suppressing inflammation and driving tolerance in inflammatory disease. Localization, timing, dose, reversibility, and patient

selection are therefore not secondary details; rather they are central design requirements.

Combination therapy presents a second challenge. Immunity is controlled by networks, so combinations are often scientifically compelling: antigen plus adjuvant, cytokine plus checkpoint blockade, tolerogenic antigen plus regulatory cytokine, cell therapy plus conditioning. However, such scientifically rational combinations complicate attribution of cause and effect, dosing, manufacturing, and clinical trial design and regulation. In some cases, components may need to be developed first as monotherapies or modular products before they can be rationally assembled into combinations.

Routes and frequencies of administration impose additional constraints. A therapy that requires repeated infusions at a specialized center may be appropriate for some cancers and clinical care centers but unrealistic for chronic inflammatory disease or rural healthcare areas. Cold-chain requirements, infusion infrastructure, rural access, cost, and ease of administration thus will determine whether a therapy can become broadly useful. Such considerations drive features of simplicity of logistics and clinical use into aspects of technological elegance as questions of both engineering and public health.

Personalization also illustrates both the power and challenges of the field. Autologous CAR T-cell therapy shows that individualized immune engineering can produce dramatic clinical benefit, but it also brings complex manufacturing and delivery. In situ approaches that engineer immune cells inside the body, or universal cellular products that can be used across patients, are beginning to address these barriers (Parayath and Stephan 2021; Bot et al. 2026). For example, CAR T cells have been generated directly in patients by administering cell-targeted lipid nanoparticles that deliver messenger RNA encoding a CD19-directed chimeric antigen receptor, without requiring ex vivo cell manufacturing (Wang et al. 2025). The future will likely require a spectrum of approaches, from highly personalized living medicines to off-the-shelf molecular and material systems that achieve sufficient specificity by exploiting tissue context for targeting, activity, and duration of action.

These challenges do not diminish the field; they define its next phase. Immunoengineering will advance when design rules are linked to translational rules: how to manufacture, monitor, deliver, combine, and discontinue therapies that guide immune memory and immune balance. The goal is to reestablish immune homeostasis that protects self while fighting pathogens and malignancy,

rapidly promotes functional tissue repair, and creates immunological robustness in the face of diverse exogenous challenges.

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Pathology AI models combined with multi-dimensional and multimodal pathology data will enable better prediction of clinical outcomes.

The Future of Digital and Computational Pathology

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How Far Has Digital Pathology Come?

Tissue specimens obtained through biopsy or surgical procedures must undergo a series of steps—including tissue fixation, wax embedding, sectioning, mounting onto glass slides, and staining—before being viewed with an analog

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light microscope or digitized with a slide scanner. This complex tissue preparation protocol (i.e., histology) originated nearly 150 years ago and rapidly became the diagnostic cornerstone of medicine, informing many clinical decisions. However, the success and standardization of analog slide-based histopathology over the past century have made it difficult to transition to a digital era. Unlike the field of radiology, where physical X-ray films were rapidly replaced with digital detector panels, and where imaging modalities such as magnetic resonance imaging and positron emission tomography emerged entirely within a digital framework, histopathology in the clinic remains dependent on the production of thinly sliced tissue sections mounted on glass slides. Digitizing histology slides adds to an already complex process of slide preparation, increasing the burden for adoption.

Despite these challenges, easier data sharing for remote diagnosis and research, together with the deployment of artificial intelligence (AI), has made the broader adoption of digital pathology possible. A major inflection point was the US Food and Drug Administration's (FDA's) 2017 authorization of the Philips IntelliSite Pathology Solution (FDA 2017), the first whole-slide imaging system for primary surgical-pathology interpretation. Since then, the scanner ecosystem has broadened, along with advances in storage, networking, data infrastructure, and graphics processing unit (GPU) computing, which have made it more practical to ingest and analyze gigapixel whole-slide images (WSIs) within diagnostic workflows.

Software solutions for digital pathology have also matured. Open-source research platforms such as QuPath now support visualization and annotation (Bankhead et al. 2017) and newer frameworks such as TRIDENT (Mahmood Lab 2025) enable large-scale preprocessing of images for AI-integrated workflows. While interoperability remains incomplete due to heterogeneous data formats, efforts to establish DICOM (digital imaging and communications in medicine)-based pathology standards and enterprise-imaging approaches provide an increasingly clear path for connecting scanners, digital archives, software viewers, and laboratory information systems.

Numerous professional organizations have helped to leverage this technical progress to provide institutional legitimacy for early adopters. The College of American Pathologists (CAP) has issued evidence-based guidance for validating whole-slide imaging before diagnostic use, and the Digital Pathology Association (DPA) has promoted education, adoption, and regulatory clarity. Consequently, health systems increasingly recognize the value

of digital pathology for remote consultation, subspecialty collaboration, education, quality assurance, workload distribution, and AI integration.

The remaining challenges are primarily financial and logistical. From a financial standpoint, digital pathology is an enterprise clinical service that goes beyond just purchasing a scanner. Institutions must support recurring costs for storage, networking, image management, cybersecurity, and technical support. While benefits accrue across the health system, pathology and IT departments bear most of the costs for implementation and maintenance. Moreover, reimbursement for digitization and AI tools remains limited. Operationally, FDA authoriza-

Health systems increasingly recognize the value of digital pathology for remote consultation, subspecialty collaboration, education, quality assurance, workload distribution, and AI integration.

tion of digital pathology solutions does not obviate the need for local intended-use validation, downtime contingency procedures, and continuous monitoring. AI systems additionally require model-version control, drift surveillance, and explicit human oversight. Logistically, most institutions are still transitioning to digital pathology solutions via incremental pilot studies and staged rollouts. Glass slides currently must still be retained on top of digitized images, adding to physical and IT infrastructural burdens. Furthermore, digitization of tissue slides does not make them broadly accessible due to siloed pathology systems.

Emergence of Computational Pathology

By converting tissue morphology, typically observed with hematoxylin and eosin (H&E) staining, into computable data, digitization has created an entry point for AI (Song et al. 2023). AI, in turn, is strengthening the case for further digitization. Early efforts in computational pathology relied on the digitization and analysis of selected regions

of interest or tissue microarrays, in which small cores (typically ~1 to 2 mm in diameter) from several patients were assembled on a single slide. These compact formats were ideal for the limited storage, computing power, and software tools of that era. The downside was that there was limited representation of broader tissue architectures and intratumoral heterogeneity that could only be captured in larger-area WSIs.

Progress in computational pathology accelerated as four trends started to converge: 1) computing and storage became capable of handling WSIs and training AI models; 2) rapid advances in computer vision provided innovative architectures and powerful learning methods that were extended to pathology image data; 3) public and institutional archives provided larger training cohorts (e.g. The Cancer Genome Atlas); and 4) pathways for the regulatory evaluation of software as a medical device became clearer.

Recent Paradigm Shifts in Computational Pathology

Rapid developments have ushered in several shifts in computational pathology. The first transition has been from handcrafted measurements to AI-generated region representations. Earlier computational pathology frameworks typically relied on handcrafted measurements such as nuclear size, glandular shape, and cell distributions, since these interpretable features could be correlated with region- or patient-level labels and could provide or be supported by intuitive biological insights. By contrast, recent AI systems often divide a WSI into thousands of image patches (regions), each of which serves as a native processing unit for modern AI architectures, including convolutional neural networks and vision transformers. These models learn to provide a compact numerical representation of individual patches, which are aggregated to predict slide- or patient-level labels (e.g., diagnostic classes and patient outcomes).

Numerous studies have since shown that AI-learned representations can include valuable sub-visual features that handcrafted approaches fail to capture, resulting in superior performance for many applications. However, their limited interpretability may pose challenges for clinical adoption (at least for certain clinicians and use cases). Researchers are therefore developing post-hoc interpretability methods to link the factors driving model predictions to potentially meaningful underlying biomarkers. Explicit biological measurements based on handcrafted features also remain valuable and can have a synergistic effect when used in tandem with the latest

AI approaches, potentially providing an optimal balance between performance and interpretability.

A second transition has been from narrowly trained task-specific models to general-purpose pathology foundation models. Early models typically employed supervised learning to predict a specific clinical outcome or diagnostic label for a single disease type. Although they could perform well on the intended task, they often generalized poorly to new applications. In contrast, pathology foundation models aim to learn task-agnostic or general-purpose morphological representations that can be reused or adapted for various tasks with minimal fine tuning (Chen et al. 2024; Ding et al. 2025; Lu et al. 2024). The emergence of pathology foundation models in recent years has benefited from several synergistic technological trends. First, the advent of self-supervised learning algorithms, in which signals are derived from the data itself rather than through data labels, has paved the way for training AI models with abundant and easily accessed unlabeled datasets (Krishnan et al. 2022). Second, the rapid increase in digitized collections of WSIs across organs and disease types has provided the large and diverse training datasets that self-supervised learning requires (Vorontsov et al. 2026). Finally, higher-performance GPUs and associated compute infrastructures (e.g., storage) have allowed for the development of larger and more capable foundation models with hundreds of millions of parameters.

As pathology AI models are rapidly being developed, rigorous evaluation protocols are increasingly necessary between development cycles and for eventual clinical deployment. For example, there is now an expectation for independent validation studies to be performed on external datasets. More recently, publicly available standardized benchmarks have also emerged (Mahmood 2025), allowing model developers to compare their models against others under fair and consistent conditions. These benchmarks help to identify models that perform well, where they fail, and which design choices generalize well.

Clinical Deployment of Computational Pathology

Clinical deployment of pathology AI is best understood as an expansion across the clinical workflow continuum: 1) primary diagnosis and screening; 2) ancillary-test triage or molecular prescreening; 3) prognostic risk stratification; 4) treatment selection; and 5) treatment-response assessment.

Detection and screening remain the most mature applications of computational pathology. In CONFIDENT-B

(Dooijeweert et al. 2024), AI-supported review of breast sentinel lymph nodes helped pathologists detect metastases while reducing reliance on ancillary immunohistochemistry. For prostate cancer screening, the recently completed Articulate Pro (Browning et al. 2026) prospective trial demonstrated reduced turnaround times and ancillary testing by up to 30 hours and 50%, respectively. These examples demonstrate a viable pathway for near-

As pathology AI models are rapidly being developed, rigorous evaluation protocols are increasingly necessary between development cycles and for eventual clinical deployment.

term clinical deployment in which AI models act as assistive triaging tools to improve diagnoses and to minimize clinical workloads while preserving the role of the pathologist for providing final diagnostic determinations (i.e. clinical sign outs).

Another application is ancillary-test triage or molecular prescreening. Here, the AI system directly predicts the likelihood of a molecular alteration from routine H&E slides, which optimizes downstream testing workflows while preserving valuable tissue specimens for other uses. Examples include EGFR AI genomic lung evaluation (EAGLE) predicting the absence of an EGFR mutation in lung adenocarcinoma or MSIntuit CRC ruling out microsatellite instability in colorectal cancer (Campanella et al. 2025; Saillard et al. 2023)

Risk stratification (i.e., prognostication) is another goal with major implications for patients. With accurate risk estimation, oncologists can assign patients to different management strategies, from surveillance or treatment de-escalation to definitive therapy and more stringent follow-up. For example, ArteraAI Prostate, authorized by the FDA in 2025 through the De Novo pathway, analyzes prostate core-biopsy images and provides estimates of 10-year risks for distant metastasis and prostate cancer-specific mortality (Artera 2025). Similarly, ArteraAI

Breast performs prognostic prediction for early-stage hormone receptor (HR)-positive breast cancer patients (Artera 2026).

Companion diagnostics may be the next major frontier for computational pathology. These specialized tests identify patients who are most likely to benefit from, or may face increased risk from, a specific therapy. A compelling example is the investigational VENTANA TROP2 Rx Dx Device, which received FDA Breakthrough Device Designation (Roche 2025), that combines TROP2 immunohistochemistry with AI-based analysis of membrane and cytoplasmic staining to identify patients with nonsquamous non-small cell lung cancer who are most likely to benefit from an antibody-drug conjugate, datopotamab deruxtecan. Successful clinical and regulatory validation could provide an early blueprint for companion diagnostics based on computational pathology.

Finally, the monitoring of treatment response is starting to be pursued through computational pathology. For example, AIM-NASH is an FDA-qualified AI-assisted liver biopsy scoring tool for patients enrolled in clinical trials for the treatment of metabolic dysfunction-associated steatohepatitis (MASH). The tool analyzes liver-biopsy images and proposes standardized histologic scores, allowing for more reproducible assessment of histologic response at predefined clinical-trial time points, which could accelerate and improve the drug-development process.

The Next Frontier of Digital and Computational Pathology

The next step for computational pathology augments the current paradigm of morphology-oriented AI analysis of two-dimensional (2D) tissue sections. Future systems will increasingly be multimodal, integrating histomorphology with molecular measurements such as next-generation sequencing, spatially resolved biomarker profiles, as well as clinical reports and longitudinal outcomes (Figure 1). Future systems will also benefit from imaging approaches capable of capturing high-resolution three-dimensional (3D) tissue architecture and molecular organization that are incompletely represented in individual 2D sections. We highlight three major directions: 3D pathology, the vision-language paradigm, and spatial omics.

3D Pathology

A particularly promising vision is 3D pathology, which extends tissue interrogation from individual, discontinuous 2D sections to comprehensive 3D volumes (Liu et al. 2021; Liu et al. 2026). 3D pathology can reveal tissue

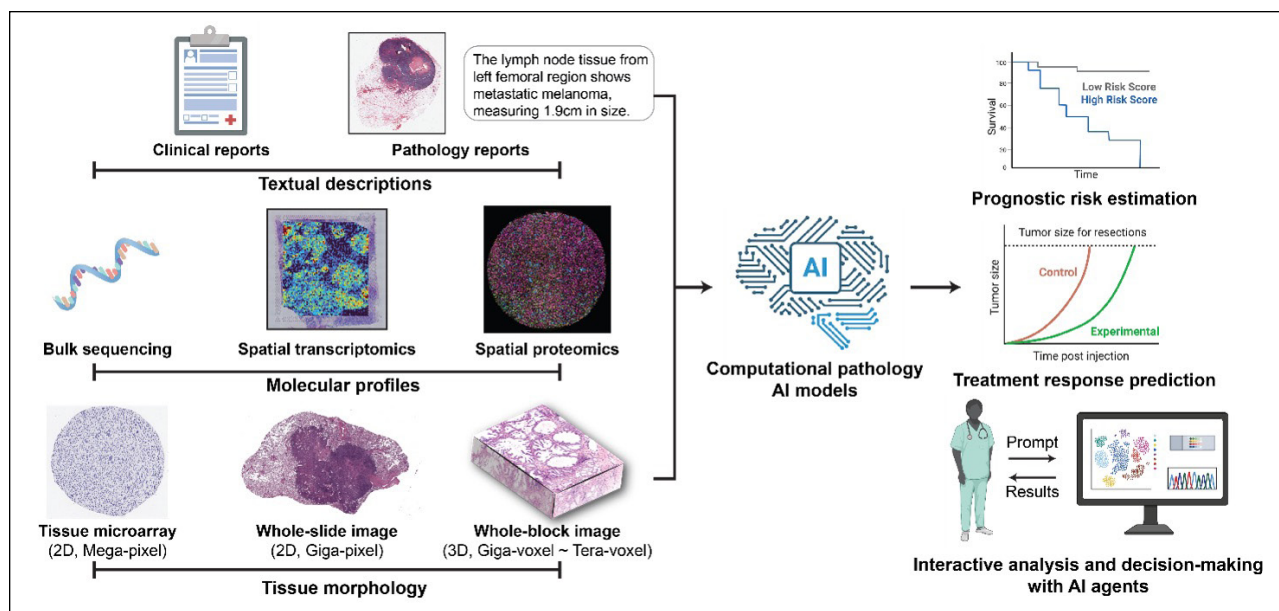


FIGURE 1 An overview of the next frontier for digital and computational pathology. Large-scale and diverse multi-dimensional and multimodal pathology data will be integrated with pathology AI models for diverse downstream tasks such as prognostic risk estimation, treatment response prediction, and interactive analysis and decision-making between clinicians and AI agents. Some illustrations generated with www.BioRender.com

architecture or spatial patterns that are misrepresented or missed in 2D sections. For example, glandular morphology, which is used for the diagnosis/grading of certain cancers, varies substantially depending upon the depth of the tissue section (Xie et al. 2022; Song et al. 2024). Similarly, sparse events, such as cancer invading the vasculature, can be missed in isolated 2D sections. Recent advances in hardware for capturing high-resolution 3D morphological characteristics such as open-top light-sheet microscopy (Glaser et al. 2017), phase-contrast X-ray tomography, and holotomography (Kim et al. 2024) allow for the “digitization” of volumetric tissue specimens. These “non-destructive 3D pathology” approaches offer the advantage of leaving specimens intact, thereby preserving valuable clinical tissues for ancillary tests (often molecular) that are increasingly required to guide clinical decision-making (Baraznenok et al. 2026).

Clinical translation of 3D pathology has been constrained by several challenges: a shortage of algorithms that scale to volumetric data, long acquisition times, and limited integration into clinical workflows. Progress on each, assisted by AI, is now defining the field’s trajectory. First, novel AI models purpose-built for volumetric data are beginning to demonstrate the superior prognostic performance of 3D pathology models over traditional 2D pathology models (Xie et al. 2022; Song et al. 2024).

Second, to improve speed, hardware-software integration in the form of adaptive “smart microscopy” is emerging to modulate what is acquired and at what level of detail. An example of this is automated, slide-free analysis of freshly excised large tissue specimens in an operating room to guide tumor-resection procedures, where stringent surgical time constraints preclude the evaluation of all tissues at the highest levels of resolution. Finally, AI-based triaging of 3D tissue specimens, where an AI model is used to identify the optimal 2D cross-sectional images for pathologists to diagnose, presents a potential rapid pathway for the clinical deployment of 3D pathology with reduced regulatory barriers (Gao et al. 2026).

Vision-Language Paradigm

The emergence of vision-language models (VLMs) has allowed natural language to be used as a practical interface between complex representations and clinical reasoning. By learning joint representations of histopathology images and language, VLMs connect visual morphologic patterns with diagnostic terms and clinical concepts. A prime example is PathChat (Lu et al. 2024; Modella AI 2025), a VLM that enables interactive and open-ended dialogue for WSIs by aligning a pathology foundation model and a large-language model (LLM). Rather than simply returning the likelihood of a diagnosis, the model

can respond to detailed questions about the tissue characteristics, discuss possible diagnoses, and explain which observations support a particular interpretation. All of this can facilitate trust and provide new insights for users, especially trainees and junior clinicians.

The language interface further provides a foundation for pathology AI agents, which can plan and execute high-level, multi-step analytical workflows (Ferber et al. 2025; Trost et al. 2026). A typical user prompt could include quantification of immune infiltration, comparison of patterns across patient groups, and retrieval of morphologically similar cases. The agent would then decompose the request into individual tasks and coordinate a collection of agentic components to address the request: for example, an LLM as the reasoning and orchestration layer; pathology foundation models capable of ingesting and representing pathology images; specialized algorithms for cell detection, biomarker scoring, or spatial analysis; and retrieval tools that access clinical records or scientific literature. The orchestrating LLM is a key component of such an agentic workflow, responsible for selecting appropriate tools, gathering the required inputs, evaluating intermediate outputs, and synthesizing the results in collaboration (ideally) with one or more human users (Figure 1).

Spatial Omics

Spatial omics, such as spatial transcriptomics and spatial proteomics, represents another frontier in computational pathology. Unlike bulk molecular assays, in which molecular characteristics are derived from large collections of digested cells, spatial omics technologies provide molecular-expression information within the context of intact tissue, often at the cellular or even sub-cellular level. This allows for the elucidation of interactions between specific cell types and microenvironmental niches that are critical to various normal and disease processes. Because spatial measurements are generated from tissue sections, they can be naturally co-registered with digitized histopathology (i.e., H&E histology) to create multimodal tissue representations. Currently, spatial omics is primarily a research tool because of its cost and technical complexity, with rapidly expanding commercial sequencing platforms yet to produce solutions for clinical downstream tasks. Nevertheless, continued technological maturation and declining costs could expand its role for diagnostic tasks.

AI is anticipated to provide the path toward clinical scalability by learning relationships between morphological and molecular attributes from paired spatial-omics

and H&E histology data. For instance, Path2Space (Shulman et al. 2026) infers spatial gene-expression landscapes from breast cancer histology, while CANVAS (Li et al. 2026) predicts spatially organized cellular neighborhoods from H&E histology images. By showing that virtual spatial profiles can be associated with patient prognosis and treatment response across large retrospective cohorts, these results demonstrate the potential for clinically scalable models to be deployed on routine digital slides (H&E histology) and potentially 3D pathology datasets.

Conclusion

Today, pathology is moving quickly toward digitization, propelled by new slide-scanner technologies in conjunction with rapidly growing capabilities in AI. These efforts promise to reinforce pathology's longstanding position as a cornerstone of diagnostic medicine and clinical decision-making. In the near term, institutions should (and are) prioritizing the development of robust digital infrastructures to enable the deployment of rigorously validated AI applications that can improve clinical accuracy and efficiency while maintaining direct pathologist oversight. Over the next decade, in order to realize the greater potential of digital pathology, including increasingly autonomous diagnostic tasks, major investments and advancements are needed from institutions and government agencies to facilitate regulatory approvals, adequate reimbursements, and clinician oversight. In the meantime, we are witnessing rapid technological advances, such as slide-free, multi-dimensional, and/or multi-model tissue-interrogation platforms, which have the potential to provide transformative value for clinicians and patients in the decades to come. In summary, we are entering an inflection point within the field of pathology driven by a convergence of new technologies.

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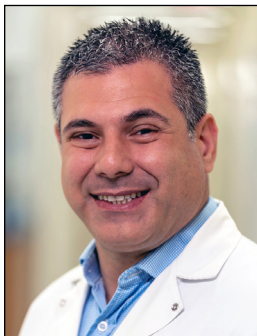
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Systems design, process control, automation, computation, regulation, and healthcare delivery will all determine whether an effective cellular product can become a practical medicine.

Engineering Cell Therapies as Living Medicines



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Cell therapies are not simply drugs made from cells. They are living systems. Their behavior is determined by the source of the cells, the genetic program introduced into them, how they are manufactured, and the environment they encounter after administration. Progress in this field therefore depends as much on engineering as on biology. Systems design, process control, automation, computation, regulation, and healthcare delivery will all determine whether an effective cellular product can become a practical medicine.

A Therapeutic Platform Defined by Living Behavior

Estimates suggest that on the order of 18,000 human diseases have been characterized, whereas fewer than 2,000 drugs have been approved (Rappaport et al. 2017). These approximate counts depend on how diseases and distinct drugs are defined, but they illustrate the scale of unmet need. Small molecules and biologics remain preferable when a stable agent can modulate a well-defined target safely, reproducibly, and at acceptable cost. Cells become

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attractive when treatment requires capabilities a fixed agent cannot readily provide, including active trafficking, integration of local signals, proliferation, coordinated effector functions, adaptation, or replacement of a lost cell population.

Living cells possess many of these capabilities intrinsically. They sense their surroundings, process multiple inputs, migrate, secrete factors, proliferate, and persist (Bashor et al. 2022). Engineering can redirect these functions by combining recognition, signal processing, effector activity, persistence, and safety in one platform (Figure 1). A cell can be designed to recognize a defined signal, act in a particular tissue context, sustain its function, and shut down when required. Such approaches are

being explored in cancer, chronic viral infection, autoimmune disease, cardiovascular injury, and endocrine disorders (Bluestone et al. 2015; Anthony-Gonda et al. 2019; Mackensen et al. 2022; Rurik et al. 2022; Reichman et al. 2025). The attraction is not simply that cells are powerful. It is that they can be programmed.

The design space has three principal elements. The first is the cellular chassis. More than 200 human cell types have been recognized (Panina et al. 2020) but only a subset can tolerate genetic modification, remain stable during expansion, reach the relevant tissue, and be manufactured at scale. The second is the engineering toolkit. Viral and nonviral systems can introduce genes, disrupt endogenous genes, and install synthetic receptors. The

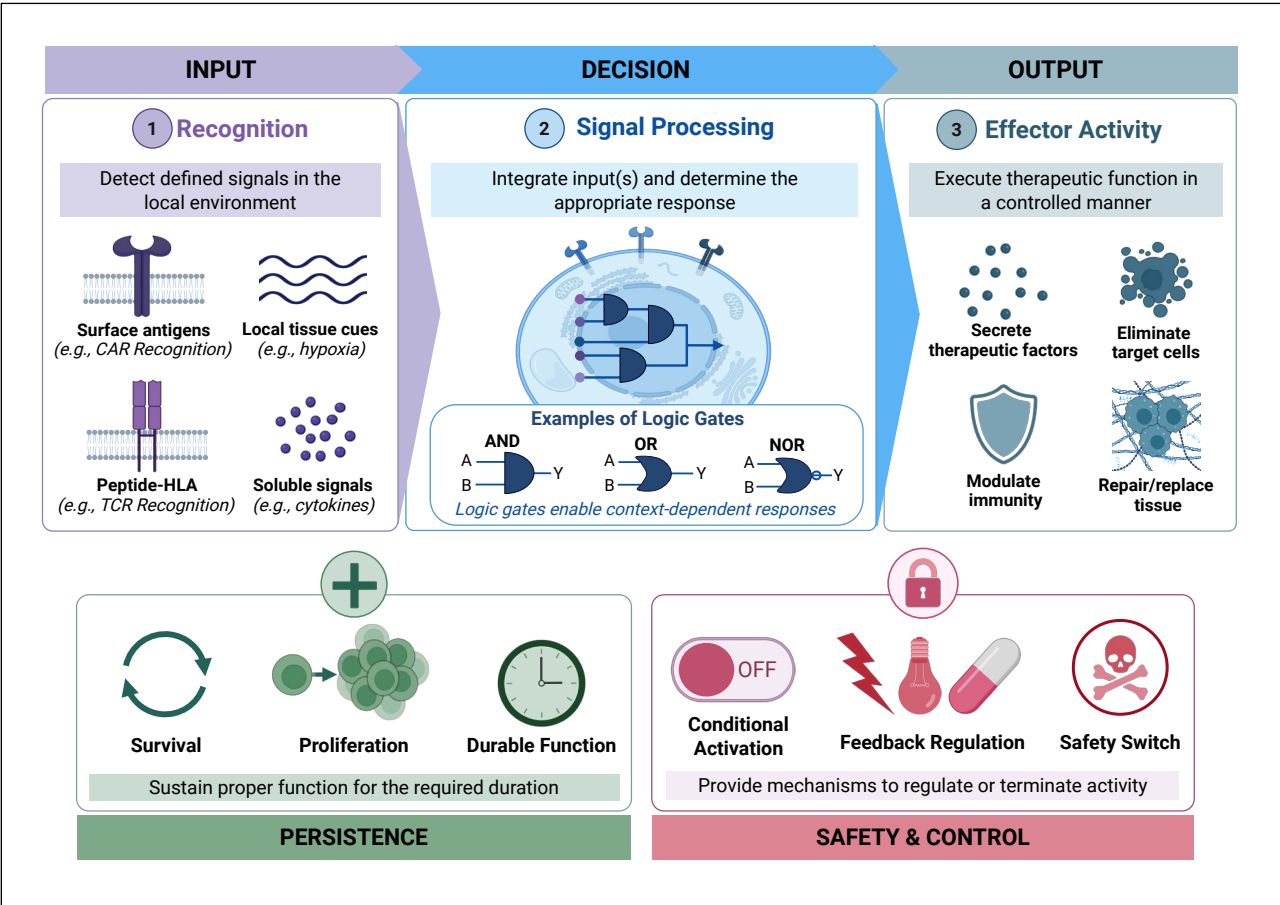


FIGURE 1 Functional architecture of programmable cell therapies. Living cells can be engineered to integrate environmental sensing with programmable therapeutic outputs. **Recognition** enables cells to detect defined inputs in the local environment, such as surface antigens, local tissue cues, peptide-HLA complexes, and soluble signals. **Signal processing** couples one or more of these inputs to determine an appropriate response using logic-gated functions (e.g., AND, OR, NOR) to enable context-dependent activity. **Effector activity** translates these decisions into therapeutic functions, including secretion of therapeutic factors, elimination of target cells, immunomodulation, and tissue repair. These input-decision-output processes are supported by **persistence** (survival, proliferation, and durable function) and regulated by **safety and control** mechanisms (conditional activation, feedback regulation, and safety switches). The schematic was created using www.BioRender.com with assistance from Elizabeth Kelly.

best-known example is the chimeric antigen receptor, or CAR, which links an extracellular target-recognition domain to intracellular signaling machinery. The third is control. Engineered functions may be constitutive, conditional, feedback-regulated, transient, or pharmacologically inducible. Together, these choices determine

Cell therapies are attractive not simply because cells are powerful, but because they can be programmed.

potency, specificity, persistence, reversibility, and metabolic demand. The product cannot be defined by genetic sequence alone. Its behavior also reflects manufacturing history, phenotype at release, and the patient in whom it is administered.

The field has advanced through progressively greater control of cellular behavior. Tumor-infiltrating lymphocyte (TIL) therapy showed that immune cells could be removed from a patient, expanded outside the body, and returned while retaining antitumor activity (Rosenberg et al. 2008). Durable responses were observed in some patients with metastatic melanoma (Rosenberg et al. 2011), and a TIL product received approval from the US Food and Drug Administration (FDA) in 2024 (FDA 2024b).

CAR T-cell therapy moved the field from naturally occurring to synthetic recognition. Since the first US approval in 2017 (FDA 2017), CAR T-cells have produced deep and durable responses in several hematologic malignancies (Maude et al 2018; Schuster et al. 2019; Munshi et al. 2021). They have also exposed the constraints of the current model, including patient-specific manufacturing, variable starting material, production times measured in weeks, high cost, relapse through antigen loss, and toxicities such as cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (Neelapu et al. 2018; Lee et al. 2019).

Engineered T-cell receptors (TCR) extend recognition to intracellular proteins by detecting peptide fragments displayed by human leukocyte antigen molecules. This expands the available target space, particularly in solid tumors where suitable surface antigens are limited. An

engineered TCR therapy received US approval for synovial sarcoma in 2024 (FDA 2024a). Severe toxicities caused by unintended recognition of related peptides have also demonstrated the need for rigorous specificity testing (Linette et al. 2013; Morgan et al. 2013).

Natural killer (NK) cells are cytotoxic lymphocytes of the innate immune system. Unlike T cells, they do not require prior antigen sensitization to recognize and kill abnormal cells. Instead, they respond to combinations of activating and inhibitory signals, including signals associated with cellular stress or the loss of normal HLA class I expression. This allows NK cells to respond rapidly to infected or malignant cells. NK cells also offer a different chassis for engineering. They can be obtained from healthy allogeneic donors, including umbilical cord blood, making them compatible with manufacturing in advance and banking. Like T cells, NK cells can be equipped with a CAR to direct the cells toward a selected surface antigen. CAR-NK cells can therefore combine CAR-directed recognition with their natural, CAR-independent mechanisms of detecting abnormal cells.

Cord blood-derived NK cells have been engineered with a CD19-directed CAR, interleukin-15 to support expansion and persistence, and an inducible caspase-9 safety switch that can be activated to eliminate the engineered cells if needed (Liu et al. 2018, 2020). Clinical studies in patients with CD19-positive B-cell malignancies have shown responses without severe cytokine release syndrome, neurotoxicity, or graft-versus-host disease (Liu et al. 2020; Marin et al. 2024). This example shows how natural cell functions can be combined with engineered target recognition, persistence, and safety control in a single cell.

The same engineering logic is moving beyond conventional cytotoxic lymphocytes. Macrophages are being developed to enter and remodel solid-tumor microenvironments (Klichinsky et al. 2020), and regulatory T cells to suppress dysregulated immunity (Bluestone et al. 2015). CD19-directed CAR T cells have induced drug-free remissions in small studies of severe autoimmune disease (Mackensen et al. 2022; Müller et al. 2024). Stem cell-derived islet products have restored endogenous insulin production in some patients with type 1 diabetes (Reichman et al. 2025), and gene editing has been used to reduce immune recognition of allogeneic islet cells in an initial clinical report (Carlsson et al. 2025).

Induced pluripotent stem cells (iPSC) may provide a particularly scalable starting material because engineering can be performed at the clonal stage, followed by char-

acterization, expansion, differentiation, and banking. A first-in-human study of iPSC-derived CD19-directed CAR NK cells has tested this model clinically (Ghobadi et al. 2025). This approach could support the production of many doses from a single, well-characterized clone but requires rigorous demonstration of genomic stability, consistent differentiation, and the absence of residual undifferentiated cells.

Designing and Controlling a Living Product

Whether the objective is to eliminate resistant cancer, reset a dysregulated immune response, restore tolerance, replace a lost cell type, or repair damaged tissue, development should begin with the clinical problem rather than with an available technology. It should determine the target, cellular chassis, route of administration, intended duration of activity, and tolerance for toxicity.

Target selection is usually the most consequential decision. A useful target should be present on diseased cells, absent on essential healthy tissues, and sufficiently important to the disease that it cannot be readily lost. The last requirement is especially important in cancer, where antigen loss or downregulation is a common mechanism of relapse. Expression must also be considered across diseased cells, normal tissues, developmental states, and stages of disease evolution. Low-level expression in an essential organ may matter clinically even when tumor expression is much higher. Multi-target and logic-gated approaches may reduce escape and improve specificity, but they also increase the complexity of design, testing, and manufacturing.

Chassis selection requires trade-offs among potency, persistence, trafficking, inflammatory potential, donor availability, immune compatibility, and manufacturability. Autologous cells may avoid immune rejection but require a dedicated process for each patient. Allogeneic cells can support centralized production, immediate availability, and batch release but they may be rejected by the recipient or, depending on the cell type, cause graft-versus-host disease. For example, a complex patient-specific process may be acceptable for a small population with refractory leukemia but is unlikely to support treatment of common autoimmune, metabolic, or degenerative disorders. Manufacturing economics must therefore be part of the initial product specification.

Genetic design converts the therapeutic concept into an operating architecture. In a CAR, this includes the recognition domain, hinge, transmembrane region, and signaling elements. Additional modules may support

expansion, improve trafficking, resist inhibitory signals, or reduce immune recognition. Cytokines such as interleukin-15 may support survival. Endogenous receptors or human leukocyte antigen genes may be disrupted. An inducible caspase-9 switch can permit rapid elimination of the infused cells if severe toxicity occurs (Liu et al. 2018; Di Stasi et al. 2011).

Each component adds capability as well as biological, manufacturing, and regulatory complexity. Multiplexed engineering can affect growth, metabolic fitness, genomic integrity, and product consistency. The most sophisticated construct is not necessarily the best product; the design must remain manufacturable, measurable, and controllable.

Safety should be layered. Target and chassis selection are the first two layers, followed by receptor and circuit design, because cross-reactivity with related proteins or peptides can injure healthy tissues (Linette et al. 2013; Morgan et al. 2013). Logic-gated receptors, inhibitory receptors, transient expression, and environmentally controlled activation may improve specificity. Additional safeguards include safety switches, dose escalation, staggered enrollment, regional delivery, retrievable devices, and careful patient selection. These measures must be

***The most sophisticated
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designed together. A safety switch cannot compensate for a poorly selected target, and cautious dosing cannot fully correct an unpredictable product. The objective is a controllable relationship between input, response, persistence, and shutdown.

Manufacturing belongs within product design because it directly changes the biological state of the cells. Culture duration, cytokine exposure, feeder systems, vector choice, cell density, cryopreservation, thawing, and transport can all alter phenotype and function. Products carrying the same genetic construct may therefore behave differently if manufactured differently.

The administered dose is the initial condition of a dynamic system rather than a fixed drug exposure. Cellular pharmacokinetics reflects vascular distribution, tissue entry, migration, local expansion, differentiation, persistence, and clearance. Cells may also encounter suppressive signals, become exhausted, engage their target, or disappear. Quantitative models linking these processes to pharmacodynamic effects could guide route, dose, and repeat dosing. Monitoring persistence, phenotype, trafficking, cytokine production, disease response, toxicity, antigen escape, and host immune responses should therefore be built into development. These measurements identify which design or manufacturing variables should change in the next product generation.

Production, Scale, and Access

Most autologous cell products remain labor-intensive. They require collection of patient material, transportation, genetic modification, expansion, quality testing, cryopreservation, shipment, and administration. Many steps remain manual or only partly closed, which increases cost, variability, scheduling complexity, and contamination risk. This model may be workable for rare hematologic cancers. It is not adequate for diseases affecting hundreds of thousands or millions of people.

Allogeneic products could allow multiple doses to be produced from a single donor or engineered master cell source. Early clinical studies using donor-derived and iPSC-derived products support the feasibility of this direction (Marin et al. 2024; Ghobadi et al. 2025). However, an economic advantage cannot be assumed solely from centralized, multidose manufacturing. It will depend on manufacturing yield, batch success and consistency, release-testing requirements, shelf-life, cryopreservation and distribution, and the proportion of manufactured doses ultimately administered. The relevant costs also extend beyond production to conditioning, supportive care, hospitalization, toxicity management, repeat dosing, and long-term follow-up (Maziarz et al. 2023). The value of an allogeneic platform should therefore be assessed in terms of the total cost of care relative to the magnitude and durability of clinical benefit achieved, as well as its performance compared with alternative therapeutic modalities.

A mature manufacturing platform would integrate cell selection, activation, gene transfer, expansion, washing, formulation, and fill-finish within a closed system. Materials and device engineering could reduce cost and variability through scalable culture, selective cell handling,

real-time sensing, and improved preservation. The platform would measure cell number, viability, phenotype, nutrient use, metabolites, and contamination risk in real or near real time. This is a process-control problem familiar to chemical and manufacturing engineers. However, cells are heterogeneous: their state cannot be fully observed, and the desired phenotype may not correspond to a single measurable variable. Adaptive systems could eventually adjust feeding, gas exchange, cytokine concentrations, or harvest timing but they will require validated sensors, interpretable algorithms, and clear regulatory rules.

Cryopreservation and distribution are equally important. Freezing and thawing can reduce viability or function, and ultracold transport limits where therapies can be delivered. Better preservation methods would reduce cost, simplify logistics, and expand treatment beyond major academic centers.

An alternative is to engineer cells directly within the patient. Targeted lipid nanoparticles or viral vectors can deliver genetic instructions to selected cell populations in vivo. Preclinical studies have demonstrated in vivo generation of therapeutic CAR T cells for cardiac injury and

Future cell therapies are likely to combine genome-scale delivery with increasingly precise engineering.

immune-mediated disease (Rurik et al. 2022; Hunter et al. 2025), and early clinical reports suggest feasibility in cancer (Xu et al. 2025; Zhang et al. 2026). Clinical experience remains limited, however, and safety, reproducibility, durability, and comparative performance relative to ex vivo products are not yet established.

In vivo engineering could replace a multistep cellular manufacturing process with a delivery product manufactured more like a conventional biologic. It does not remove the quality-control problem; it relocates it. The number and condition of target cells vary among patients, and the engineered cells cannot be tested before administration. Quality assurance must therefore focus on the delivery vehicle, targeting specificity, biodistribution, transduction efficiency, off-target delivery, duration of expression, and post-treatment monitoring.

Future Directions

The next phase of cell therapy will be driven by a deeper ability to discover, design, and control cellular function. Current products typically modify one or a small number of genes. Future therapies are likely to combine genome-scale discovery with increasingly precise engineering to create cells that can sense their environment, adapt to changing disease, and retain function under conditions that would normally limit their activity.

CRISPR (clustered regularly interspaced short palindromic repeats)-Cas systems provide a programmable way to alter gene function. A guide RNA directs a Cas protein to a selected DNA sequence, allowing a gene to be disrupted, activated, or repressed. In a genome-wide CRISPR screen, large populations of cells receive different guide RNAs so that thousands of genes can be tested in parallel. Cells with a desired property can then be selected, and the guide RNAs they contain reveal which genetic changes produced that property.

Genome-wide CRISPR screens are already identifying genes that regulate cytotoxicity, persistence, metabolism, trafficking, and resistance to immune suppression. Their greater value will come from moving beyond screens performed under simplified laboratory conditions. Screens conducted in three-dimensional models, patient-derived tissues, and eventually in vivo should identify the genetic programs that determine whether engineered cells reach diseased tissue, remain functional, and survive within hostile microenvironments. Combinatorial screens will be especially important because many therapeutic properties are controlled by networks of genes rather than a single dominant pathway.

Single-cell and spatial technologies will provide the corresponding map of cellular state. Transcriptomic, epigenetic, proteomic, and metabolic measurements can now describe how individual cells differ within a manufactured product and how those states change after infusion. Integrating these measurements should make it possible to identify which cell states are therapeutically effective, which are prone to dysfunction, and which emerge only after exposure to the patient's disease. The objective is to move from describing cellular heterogeneity to deliberately engineering it.

The engineering toolkit will also expand. More precise gene editing, targeted gene insertion, epigenome editing, RNA-based programming, and transient gene regulation should allow cellular behavior to be altered without relying exclusively on permanent transgene expression. Synthetic circuits may enable cells to integrate several dis-

ease-associated signals; distinguish diseased from healthy tissue; adjust response strength; and select among cytotoxicity, cytokine secretion, immune recruitment, tissue repair, or self-limitation according to local context.

Artificial intelligence (AI) could accelerate this process. Models trained on receptor sequences, protein structure, perturbation screens, single cell profiles, and clinical data may help identify targets, design binding domains, select signaling architectures, and predict combinations of genetic modifications. AI may also reveal relationships between cell state and clinical outcome that are difficult to identify through conventional analysis. Its value will depend on well-annotated, interoperable datasets and

The objective for single-cell and spatial technologies is to move from describing cellular heterogeneity to deliberately engineering it.

prospective validation; predictions generated from small or inconsistent datasets will not necessarily be generally applicable.

These technologies could ultimately support a more systematic design cycle. Genome-scale screens would identify candidate control points, single-cell and spatial analyses would define the desired cellular state, and AI-assisted models would prioritize engineering strategies. The resulting cells could then be tested clinically with observations from persistence, response, toxicity, and relapse informing the next generation.

The central question is no longer simply whether a cell can be engineered to recognize a target. It is whether cellular behavior can be designed at the level of genetic networks, predicted across changing biological environments, and refined through continuous learning from every product and every patient.

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*Engineering paradigms can overcome challenges
and drive the evolution and clinical translation of
therapeutic cancer vaccines.*

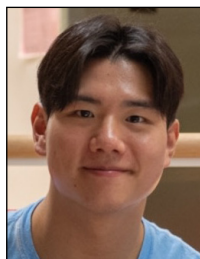
Engineering Therapeutic Cancer Vaccines

Teaching the Immune System to Fight Cancer

Giovanni Bovone, Shawn Kang, and David J. Mooney



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Introduction

Vaccines are among the greatest developments in modern medicine. The effect of vaccines on global health is perhaps most evident through the eradication of smallpox. Before vaccination, smallpox was a highly contagious and deadly disease, killing around 30% of patients and leaving many survivors with life-

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long scars or vision issues (Belongia and Naleway 2003). Through widespread vaccination, smallpox was eradicated in 1980, making it, to date, the only human disease eradicated worldwide. Similar successes have been achieved through vaccines against many other diseases such as polio, measles, and more recently, COVID-19 (May 2021).

Vaccines function by educating the immune system to recognize and eliminate harmful pathogens or diseased cells. They achieve this by delivering a harmless piece of the target, termed an antigen, often with an immune-stimulating component known as an adjuvant (Figure 1a). The antigen serves as a molecular blueprint that enables the immune system to generate a repertoire of immune cells capable of recognizing and responding to the target, including antigen-specific T cells that can clear the malignant cells, long-lived memory cells that can rapidly respond at a later time of need, and B cells that can produce antibodies against the target.

The principles underlying vaccination have also been successfully applied to cancer prevention. Vaccines against hepatitis B virus (HBV) and human papillomavirus (HPV) prevent the viral infections responsible for hepatocellular carcinoma and cervical cancer, respectively, and are the most successful cancer vaccines used in the clinic (Stanley 2017). Rather than targeting malignant cells directly, they prevent the viral infections responsible for driving hepatocellular and cervical carcinogenesis. They are preventive or prophylactic vaccines. Prophylactic cancer vaccines have also been proposed for individuals with a strong genetic tendency to develop a specific cancer type.

Extending this paradigm for the treatment of tumors, however, is far more challenging. Therapeutic cancer vaccines function with the same principles underlying prophylactic vaccines, using tumor antigen and adjuvant to expand tumor-specific immune cells, though they are used to treat an established and growing tumor, or in

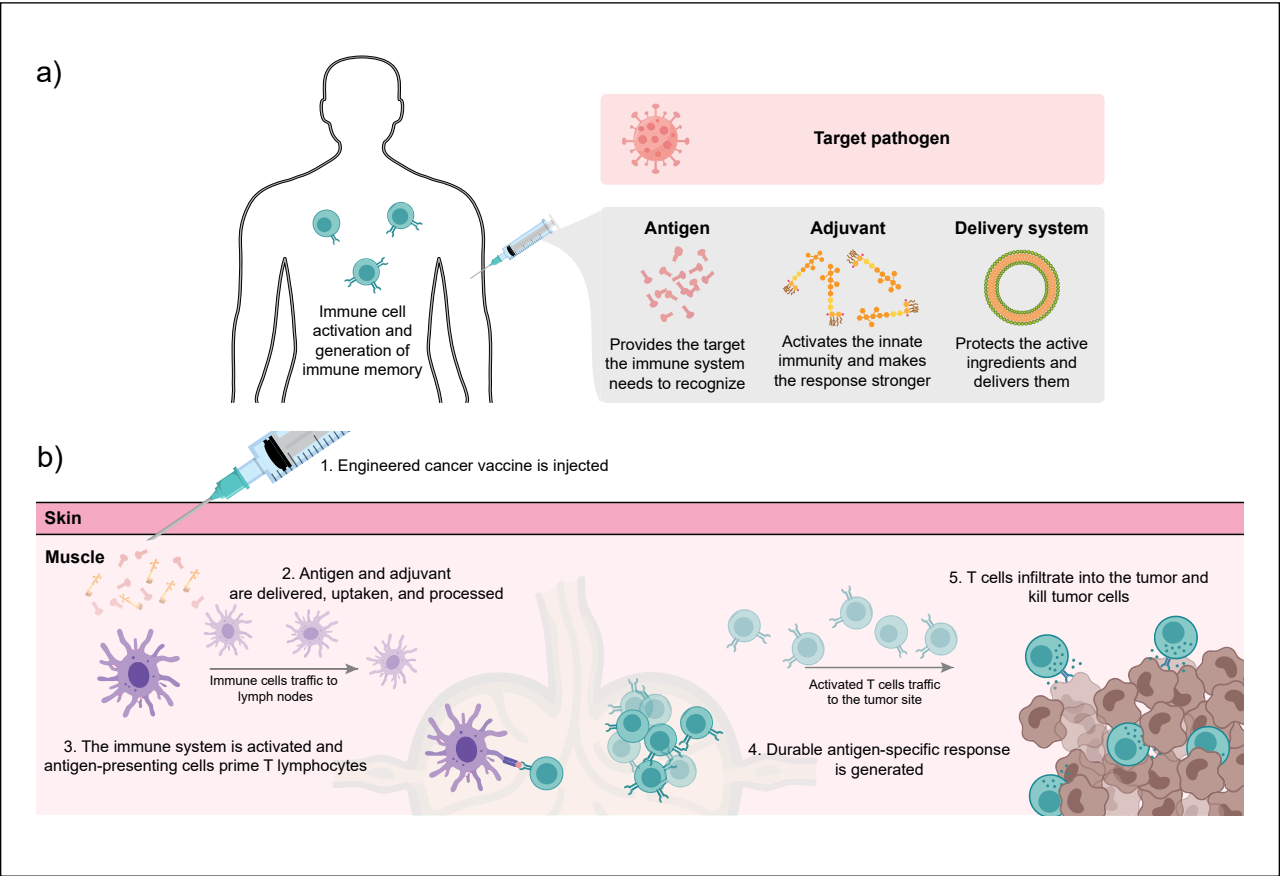


FIGURE 1 a) Example of a vaccine: antigen, adjuvant, and a delivery system activate immune cells and generate memory against a target pathogen; b) Key steps typically required for a therapeutic cancer vaccine to generate an effective anti-tumor immune response. Elements of the figure were designed using licensed images from Adobe Stock.

patients who have minimal residual disease or whose malignancy has a high chance of recurrence (Zaidi, Jaffee, and Yarchoan 2025). Thus, they face many unique challenges as many cancers progress undetected until they start to interfere with homeostasis and are already in a difficult state to eradicate. These challenges make the development of cancer vaccines an engineering problem that requires optimization across several key areas: (1) identifying the most effective antigen sequence; (2) delivering it effectively; (3) activating robust immune responses; (4) generating durable antigen-specific T cells; and (5) ensuring that these cells traffic to, infiltrate, and function

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within tumors (Figure 1b). Developing an efficient and scalable current good manufacturing practice (cGMP) manufacturing pipeline including robust quality control testing and batch release methods for both vaccine and carrier is also required.

In this perspective, we focus on therapeutic cancer vaccines and the engineering advances that can improve clinical translation. Although preliminary evidence of the clinical feasibility of cancer vaccination has been observed, we suggest that future efforts for the next generation of therapeutic cancer vaccines must focus on making these therapies scalable and broadly applicable while advancing our capability to identify targets and produce durable responses. We highlight that robust tumor control may not be achieved by single immunotherapies but rather will require coordinated combinations of complementary approaches that engage distinct but synergistic mechanisms of immunity. Therapeutic cancer vaccines are best viewed not as a silver bullet, but as a critical component of a carefully engineered silver arsenal.

From Coley's Toxins to Personalized Cancer Vaccines

The history of therapeutic cancer vaccines began in the late 19th century with William Coley, who observed

tumor regressions after injecting live or heat-killed *Streptococcus* and *Serratia* bacteria into sarcomas (Hoption Cann, van Netten, and van Netten 2003). These interventions provided the first evidence that immune activation and inflammation could promote tumor regression. However, this approach suffered from safety and inconsistent manufacturing concerns, hindering widespread adoption. In the 1990s, the field shifted toward using whole-cell and tumor-lysate vaccines to expose the immune system to a broad repertoire of tumor antigen (Moingeon 2001). Although these approaches resulted in strong immune responses in some patients, clinical efficacy was limited. For example, Phase III clinical trials of GVAX, one such whole-cell cancer vaccine, were halted in 2008 due to insufficient efficacy (Soiffer, Kooshesh, and Ho 2021).

In 2010, the first therapeutic cancer vaccine, Sipuleucel-T (Provenge), became FDA approved in the United States for the treatment of metastatic castration-resistant prostate cancer (Kantoff et al. 2010). Sipuleucel-T is an autologous dendritic cell vaccine in which antigen-presenting cells are isolated from patients, cultured ex vivo with antigen linked to the immune-stimulating cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), and reinfused. To date, Sipuleucel-T remains the only therapeutic cancer vaccine approved in the United States. However, clinical adoption has been limited due to its modest efficacy, with objective response rates rarely exceeding 15%, and the expensive individualized cell manufacturing process (Heras-Murillo et al. 2024). These first-generation cancer vaccines largely targeted tumor-associated antigens (TAAs), which are shared antigens across patients that are overexpressed in malignant tissues but are also present in normal tissues. However, because immune tolerance limits responses against self-antigens, TAAs may be suboptimal vaccine targets and this likely underlies the weak cellular responses of these vaccines.

Advances in tumor sequencing enabled a shift toward mutation-derived neoantigens, a class of tumor-specific antigens that allow precise discrimination between malignant and healthy cells. In this approach, patient-specific neoantigens are identified through sequencing and computational analysis, manufactured into personalized mRNA or peptide vaccines, and delivered to induce tumor-specific T cell responses. This strategy has resulted in promising data in clinical trials for challenging targets such as melanoma and pancreatic cancers (Sahin et al. 2017; Ott et al. 2017; Rojas et al. 2023). In

Moderna and Merck's Phase IIb KEYNOTE-942 trial, personalized mRNA neoantigen vaccines combined with the checkpoint inhibitor pembrolizumab reduced the risk of recurrence or death by 44% compared to pembrolizumab alone in patients with high-risk melanoma (Weber et al. 2024). Recently, interim data of Phase III trials demonstrated significant improvements in recurrence-free survival and distant metastasis-free survival in patients receiving the combination (Moderna and Merck 2026). These findings highlighted the importance of precise antigen selection and further suggested that therapeutic cancer vaccination may achieve their greatest clinical efficacy when integrated with complementary immunotherapies.

Therapeutic Cancer Vaccines: Challenges and Engineering Opportunities

These recent successes have renewed optimism about the clinical potential of therapeutic cancer vaccines (Haanen et al. 2026). However, several engineering challenges continue to limit their widespread clinical adoption as personalized cancer treatments. For example, identifying target antigens for each patient is a time-consuming process involving costly sequencing and long analyses, limiting the throughput and accessibility of these treatments. Cancer cells can also mutate, lose antigens, and evolve new neoantigens, further complicating the identification of vaccine targets. Activated T cells can become exhausted, particularly due to the immunosuppressive effects of the solid tumor microenvironment, limiting their persistence and affecting tumor infiltration and cytotoxic capability.

Thus, we highlight four interconnected areas that are expected to shape the next generation of therapeutic cancer vaccines (Figure 2):

1. Development of tools for efficient target identification and vaccine manufacturing;
2. Engineering immunological niches that promote robust and long-term immune activation;
3. Strategic integration of vaccines with complementary immunotherapies; and
4. Fostering diverse and robust T cell repertoires to enhance antitumor immunity.

By examining recent advances and remaining challenges in each area, we provide a framework for how engineering can overcome these challenges and drive the evolution and clinical translation of therapeutic cancer vaccines.

Engineering Tools for Efficient Target Identification and Vaccine Manufacturing

Developing individualized products for each patient requires unique rounds of sequencing, bioinformatics, antigen selection, manufacturing, and release testing, resulting in high manufacturing costs and long production timelines, significantly impacting clinical adoption. Engineering strategies could improve the scalability, affordability, and accessibility of therapeutic cancer vaccines to make them widely useful in clinical settings.

Combining next-generation sequencing outputs with computational and predictive algorithms can greatly improve our capacity to predict and screen therapeutic targets. For example, machine learning models trained on large datasets of experimentally determined binding affinities of peptide-major histocompatibility complexes (pMHCs) may enable one to predict whether a therapeutic peptide sequence is likely to be presented by a patient MHC (Xie et al. 2023). New computational tools are continuing to be deployed that can assist through the entire

Engineering strategies could improve the scalability, affordability, and accessibility of therapeutic cancer vaccines to make them widely useful in clinical settings.

pipeline of (1) identifying the patient's expressed somatic mutations (candidate neoantigens); (2) determining the patient's human leukocyte antigen (HLA) genotype; (3) generating candidate peptide sequences; and (4) predicting which peptides are likely to be presented by patient HLA molecules and induce a T cell response (Xie et al. 2023). While these tools may not fully replace experimental validation, they may greatly increase success rates and decrease costs by filtering out candidates. Thus, efforts to reduce sequencing costs and accessibility while improving the accuracy of these computational predictive models may make personalized target screening more rapid and less expensive.

Another challenge associated with personalized cancer vaccines is that their manufacturing requires expen-

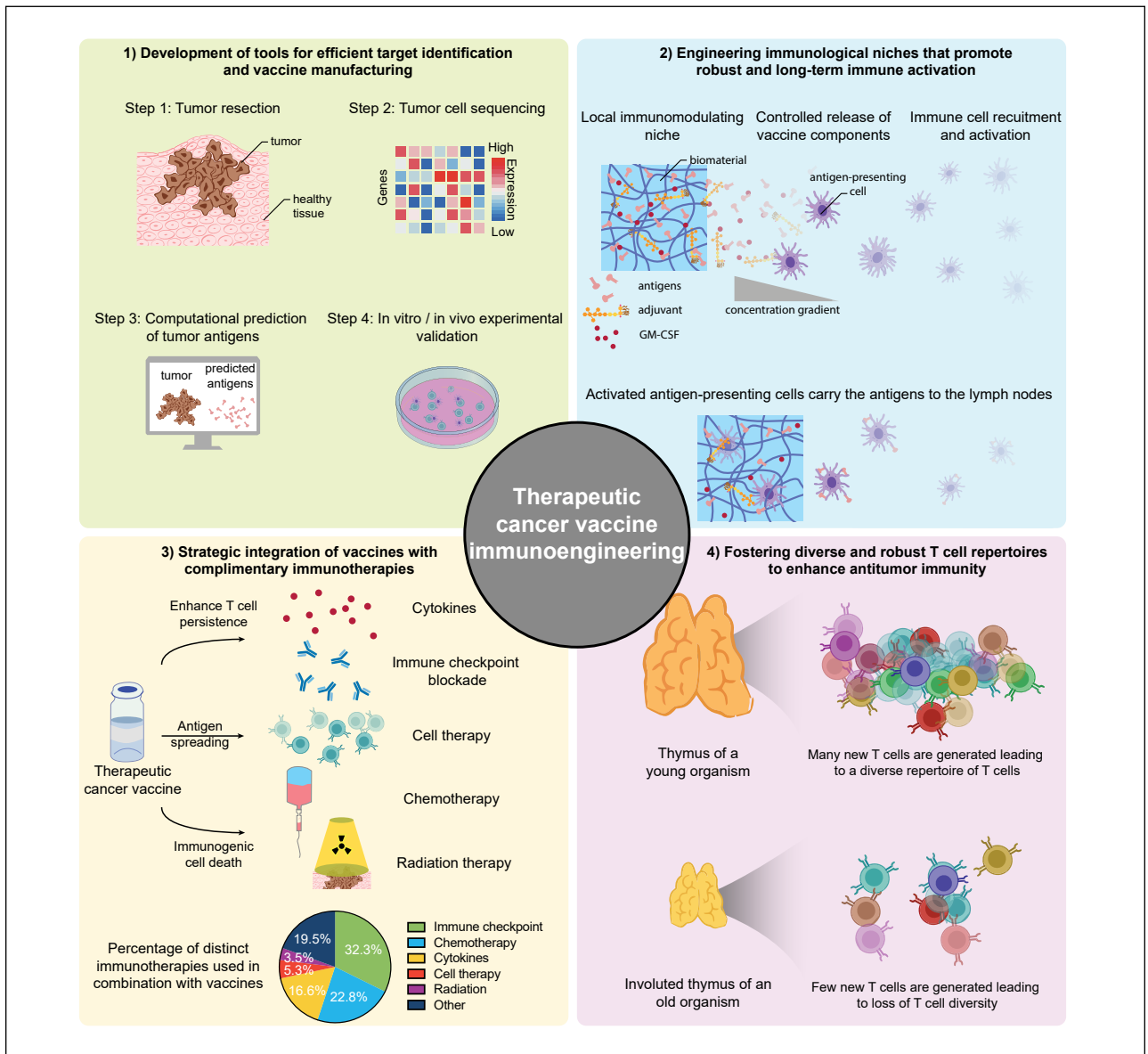


FIGURE 2 Strategies to enhance the efficacy of therapeutic cancer vaccination. 1) The process of vaccine design involves harvesting tumor samples for sequencing, computational antigen prediction, and experimental validation. 2) Immunological niches can be engineered such as injectable biomaterials that release vaccine components in situ including chemoattractive GM-CSF that attracts antigen-presenting cells and antigen which is processed by the cells to mount a systemic immune response. 3) Top: Combinations of cancer vaccines with other therapies can be coordinated to induce specific synergies such as reduced T cell exhaustion or immunogenic cell death. Bottom: Data representing the percentage of clinical trials in combination with different treatment modalities. 4) Aged thymi produce fewer naive T cells, presenting an area of interest for boosting cancer vaccine efficacy. Elements of the figure were designed using licensed images from Adobe Stock.

sive, centralized, and highly specialized facilities, as well as ultracold storage and shipping, and rigorous quality control systems. It may be possible to mitigate these challenges with technologies that distribute manufacturing capabilities directly at the sites of administration, such as hospitals and clinics, making these treatments more accessible. Initiatives such as ARPA-H GIVE are provid-

ing funding to accelerate the development of such technologies (ARPA-H 2025).

Engineering Immunological Niches that Promote Robust and Long-Term Immune Activation

Bioengineering strategies have been developed to prolong immune stimulation and enhance the durability

of cancer vaccine responses by delivering vaccines from biomaterial depots that slowly release the immunostimulatory cargo over extended periods. These materials can be injected or implanted into the body, allowing immune cell infiltration and trafficking (Yousefpour, Ni, and Irvine 2023). One of the earliest biomaterial-based cancer vaccines involved surgical implantation of porous poly-lactide-co-glycolide (PLG) discs containing encapsulated tumor lysate, an adjuvant, and GM-CSF to promote dendritic cell differentiation and activation in situ (Ali, Huebsch, et al. 2009). Sustained local release of the vaccine cargo enabled the implant to act as a local niche that recruits and activates immune cells before they produce a systemic antitumor response (Ali, Emerich, et al. 2009). By presenting these immunomodulatory cues for a prolonged duration, these materials promote durable T cell priming and memory responses. The clinical feasibility of this strategy has recently been demonstrated in a first-in-human clinical trial (Hodi et al. 2025).

Subsequent efforts have advanced this technology into an injectable format using inorganic materials such as mesoporous silica rods and macroporous polymer cryogels. In these cases, the vaccine-loaded material forms a depot in situ following injection, removing the need for surgical implantation (Kim et al. 2015). Another strategy is to tether the cancer vaccine components to lymph node-homing molecules such as albumin to form a sustained vaccine hub directly at the lymph nodes. In preclinical studies, these cancer vaccines were used to boost chimeric antigen receptor (CAR) T cell therapy. CAR ligands were conjugated to a biopolymer that, following injection, was presented on the surface of antigen-presenting cells in lymph nodes, increasing CAR T cell expansion, persistence, and functional activity (Ma et al. 2023).

Challenges hindering clinical translation of these approaches include difficulties in reproducibly manufacturing complex biomaterials at scale, as variations in starting polymer composition and processed material structure can introduce batch-to-batch variations. Transitioning from small animals to larger models and ultimately clinical trials presents challenges, particularly due to immunological differences, and variations in biodistribution, persistence, degradation, and clearance. Therefore, developing standardized manufacturing processes and predictive preclinical models are likely essential for the broader adoption of these technologies.

Strategic Integration of Vaccines with Complementary Immunotherapies

Approximately 75% of clinical cancer vaccine studies involve a combination of vaccines with other immunotherapies, such as immune checkpoint blockade, chemotherapy, cytokine therapy, cell targeting antibody, and radiation therapies (Janes et al. 2024). This reflects a shift in the field toward combination immunotherapies, whereby vaccines promote new T cell clones and the combination with other immunotherapies keeps these clones functional and active. About one third of clinically evaluated combination therapies exploit synergies with immune checkpoint blockade, including the aforementioned mRNA vaccine trials of Moderna and Merck. In this context, immune checkpoint blockade prevents vaccine-induced T cells from becoming inhibited by the solid tumor microenvironment, allowing the T cells to remain active and sustain anti-tumor responses.

Acquiring tumor antigen for therapeutic cancer vaccines is a complicated process that often involves tumor biopsies or surgical resections. One strategy to circumvent this process is to use vaccines in combination with other therapies to leverage the antigen and immunogenic cues inherently present in the tumor. When cancer cells die, they release antigen and immunogenic factors such as damage-associated molecular patterns (DAMPs) that trigger immune responses through a process called immunogenic cell death (ICD) (Galluzzi et al. 2024). Thus, rather than manufacturing a personalized vaccine ex vivo, where the antigen must be identified or extracted from the patient manually, ICD can be induced to generate antigen in situ, reducing the need for individualized manufacturing and potentially increasing accessibility of this treatment (Wang et al. 2020).

For example, preclinical studies have demonstrated that antigen-free vaccines can be loaded with chemotherapeutics to induce initial tumor killing and release antigen, while the vaccine components simultaneously activate dendritic cells to increase the processing and presentations of the released antigen to enhance the immune response. In such an approach, the tumor is essentially engineered into a vaccine. ARPA-H is currently funding a similar concept, using radiation therapy to turn solid tumors into vaccine sites (ARPA-H 2026).

Fostering Diverse and Robust T Cell Repertoires to Enhance Antitumor Immunity

Therapeutic cancer vaccines should engage a diverse repertoire of T cells to mount robust immune responses

and to retain the capacity to recognize further mutated tumor cells. One clinical strategy to expand the range of tumor-specific T cells is to identify and treat against a large cocktail of tumor antigens. Modern neoantigen mRNA and peptide vaccines often predict the top 10–20 neoantigens through sequencing and computation, and vaccinate for them all simultaneously (Sahin et al. 2017; Ott et al. 2017; Rojas et al. 2023). Recent studies have also explored how vaccines (in the context of both cancer and infectious diseases) targeting a specific antigen can activate and expand other pathogenic antigens that were not targeted, a process known as antigen spread. In one example, a therapeutic cancer vaccine in combination with adoptive cell transfer was capable of reducing growth in tumors predominantly constituted of non-targeted antigen (Ma et al. 2023). These findings suggest that antigen spreading may become an important benchmark for how next-generation vaccines induce broad antitumor immunity.

Lastly, with age, the organ responsible for generating a diverse pool of new naive T cells, the thymus, involutes into non-functional fatty tissue (Bernatz et al. 2026). As a result, both the number and diversity of newly generated T cells declines over time, limiting the immune system's ability to attack pathogenic cells. Restoring thymic function has therefore become a growing area of interest for improving immunotherapy efficacy as it can increase the population of tumor-reactive T cells that treatments can act on, particularly in older patients (Santamaria and Irla 2026). This concept has sparked considerable interest in therapies aimed at regenerating the thymus. A variety of companies are developing stem cell, antibody, and growth factor-based approaches to restore thymic output and effectively restore an aging immune system (Chen 2026). For example, mRNA encoding for thymocyte-supporting factors has been shown to enhance naive T cell production and boost immunotherapy efficacy in aged mice by creating a thymic niche in the liver, though this strategy is yet to be explored with cancer vaccines (Friedrich et al. 2026).

Although these strategies remain in early development, they represent a promising engineering frontier that could enhance the effectiveness of cancer vaccines. Future work should identify new and specific therapeutic targets and treatment modalities for thymic rejuvenation, as systemic strategies can result in off-target effects. New methods for targeted drug delivery to the thymus are also likely to be impactful.

Conclusion and Outlook

While initial clinical efficacy of therapeutic cancer vaccines fell short of expectations, recent successes in clinical trials have renewed optimism around their potential as a potent cancer treatment modality. To sustain this recent momentum, future efforts likely should focus on a number of salient barriers limiting efficacy, including suboptimal target selection, transient immune responses, manufacturing constraints, and inefficient delivery. The necessary engineering strategies should be employed to address these challenges. Furthermore, successful clinical translation and commercialization may depend on recognizing that therapeutic cancer vaccines are unlikely to be a universal solution, but rather that their greatest potential may be in combination with complementary therapies that synergize to enhance antitumor efficacy.

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Three engineering principles show how uncertainty can be identified, translated into clinical decisions, and managed through continuous real-world learning.

A Unifying Engineering Framework for Trustworthy AI Clinical Decision Systems

Lessons from Cervical Cancer Imaging in Global Healthcare Settings



Nimmi Ramanujam



Jessica de Souza

Nimmi Ramanujam and Jessica de Souza

One of the most consequential promises of engineering in healthcare is bringing medical expertise to patients, rather than requiring patients to travel to reach it. Portable imaging, digital health technologies, and artificial intelligence (AI) can increasingly bring sophisticated diagnostic and decision-making capabilities closer to patients—whether they live in an under-resourced community in Kenya, an isolated rural county in the United States, or anywhere else that specialists, infrastructure, and opportunities for follow-up are limited. Systems engineering offers the larger opportunity to help democratize healthcare: to make high-quality clinical capabilities available to more people, in more places.

This is not unique to medicine. Across other sectors, engineering has expanded access by reducing dependence on centralized infrastructure. Wireless

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communications can reach places where extensive fixed networks are impractical; distributed energy systems can provide power where connection to a large, centralized grid is difficult or unreliable. In each case, increasing and democratizing access requires more than transporting and implementing an existing system in a new location. Access expanded not simply because technology became more portable, but because the underlying system was redesigned for the conditions in which it had to operate.

The challenge in engineering healthcare for everyone is similar. If a clinical decision system can be designed to work reliably in under-resourced areas where specialists are scarce, infrastructure is limited, and follow-up is difficult, the lessons learned can extend well beyond the setting for which it was initially developed. Solutions created for resource-constrained communities in Kenya, for example, may reveal approaches equally valuable in remote areas of the United States. The environments are not the same, but many of the engineering questions are: What information can be trusted? How much uncertainty can be tolerated? What action is appropriate given the resources available? And how should the system respond when real-world conditions differ from those anticipated during development? Resource-constrained environments can therefore serve not only as settings in which engineering solutions are needed, but as settings from which more broadly applicable engineering principles can emerge.

Using cervical cancer imaging as a test case, this article presents an end-to-end engineering framework for answering those questions that shifts the focus from developing individual technologies to engineering the clinical capabilities they are intended to deliver. It connects trustworthy information generation, context-appropriate clinical decision-making, and continuous learning after deployment. The goal is not to prescribe one algorithm, threshold, or workflow for every healthcare environment. It is to develop a methodology that allows clinical decision systems to be engineered for the environments where people receive care in real life and real time.

That shift, from designing technology in ideal settings to designing systems that can function reliably across diverse conditions, is essential to the forward-looking vision articulated by the National Academy of Medicine of “health for everyone, everywhere.” Democratizing healthcare will depend not simply on distributing more technology, but on engineering clinical capabilities that can travel.

The Current Baseline

Advances in portable imaging devices, digital health technologies, and AI are reshaping where and how clinical expertise is delivered (Rossman et al. 2021; Eller et al. 2026; de Souza et al. 2024; Lekadir et al. 2025). These point-of-care technologies have the potential to expand access to care across community clinics, rural health facilities, and underserved communities by bringing specialized capabilities closer to patients (Wadie et al. 2026). As diagnostic capabilities become increasingly decentralized, the engineering challenge extends beyond generating and interpreting images to ensure that the resulting information reliably supports clinical decisions across diverse care settings (Wadie et al. 2026).

Meeting this broader challenge requires three interconnected processes: generating trustworthy clinical information, translating it into context-appropriate clinical decisions, and improving the system performance through continuous learning (Raji et al. 2020; Lekadir et al. 2025). Although each of these processes has been examined individually, they have not, to our knowledge, been integrated into an end-to-end engineering framework that traces uncertainty across the development-to-deployment continuum, determines when it matters, and identifies where to intervene.

Global cervical cancer prevention through imaging serves as a useful test case in which the reliability of AI-generated evidence and subsequent clinical decisions are dependent on real-world conditions that may not be apparent during development. First, the transition from conventional to portable cervical imaging technologies can introduce variability in device geometry and acquisition conditions (Figure 1, a-b). As more accessible versions of established technologies move from specialized centers into community healthcare settings, these sources of error may be further compounded by operator handling and clinical workflows (Figure 1, c-d).

The engineering question is therefore: How should clinical decision models be designed when both data entering the system and the AI output generated from them vary across healthcare environments? Drawing on our imaging experience in cervical cancer prevention, we connect point-of-capture quality assessment, model development, prediction stability, context-specific operating-point selection, and post-deployment engineering feedback into a single decision architecture. This framework establishes relationships that are transferable to other clinical imaging domains.



FIGURE 1 Portfolio of cervical cancer imaging technologies. The redesign of (a) a standard-of-care clinical colposcope into a portable device such as (b) the Pocket Colposcope (Calla Health Foundation, Durham, NC, USA) has expanded access to cervical cancer imaging to healthcare providers in community settings. As these technologies move from (c) specialized centers into (d) community settings, differences in device design and acquisition, operator expertise, and clinical workflows create uncertainties that must be accounted for before the computational process. Photos: Courtesy of authors.

A simple comparison demonstrates why this is important: Consider two women undergoing cervical cancer imaging, one in Kenya and one in the United States. Even if both women receive the same AI-derived estimate of disease risk, the appropriate clinical action differs. In Kenya, limited opportunities for follow-up will favor same day treatment. In the United States, the same findings may guide referral for specialist evaluation in some cases, while helping avoid unnecessary procedures for others. From an engineering perspective, these healthcare environments impose different boundary conditions—clinical, operational, and resource-related—on the same AI output. Therefore, operationalizing AI models requires balancing prediction accuracy and consistency according to the resource constraints, clinical workflows, and follow-up capacity.

A separate concern is whether model performance itself generalizes when the conditions under which the model is used differ from those represented during development. A pneumonia detection model achieved strong

in-hospital performance yet failed to generalize across institutions because it had learned acquisition- and workflow-specific patterns rather than the underlying pathology (Zech et al. 2018). Similarly, COVID-19 classifiers were significantly impacted by positioning cues (DeGrave et al. 2021). Across imaging applications, acquisition- and workflow-specific signals can contribute to poor generalization even when internal performance appears strong (Zech et al. 2018; DeGrave et al. 2021). In each case, failures occur despite relatively controlled conditions, implying that this problem will be even greater as imaging expands into broader clinical environments. These challenges reinforce a fundamental engineering principle: an algorithm can perform well and still fail in the clinical system in which it is intended to operate.

To guide clinical decisions, AI outputs must be trustworthy, an assumption that warrants rigorous scrutiny. Trustworthiness cannot be established by a single property. AI-generated evidence must be based on reliable reference ground truths and acquisition conditions, meaningful discrimination between clinical conditions, calibration between predicted and observed disease risk, consistency across repeated observations, and evidence that resulting decisions benefit patients in the intended population and care setting (Van Calster et al. 2019). Within this framework, reliability refers more specifically to whether AI-generated evidence is dependable despite variability in how and where it is generated. Equally important, transparency and explainability provide clinicians with information about how the evidence was generated, its limitations, and the factors contributing to the output, allowing AI-derived evidence to inform rather than replace human clinical judgment (Lekadir et al. 2025). For engineers, this means that trustworthiness cannot be verified at the end of development; sources of uncertainty must be traced from the point of data collection through clinical action to determine when these effects become consequential to the patient (Finlayson et al. 2021). Recent consensus initiatives such as FUTURE-AI have established broader requirements for trustworthy and deployable healthcare AI across the system life cycle (Lekadir et al. 2025). Our framework builds on this foundation by examining how uncertainty can be systematically measured and managed across the clinical AI system.

The need to establish and maintain these properties is increasingly reflected in regulatory guidelines. FDA's final guidance on predetermined change control plans for AI-enabled device software recognizes that model performance must be considered beyond initial develop-

ment and authorization. Specifically, anticipated changes to AI-enabled devices and the methods used to implement, validate, and assess their effects should be specified in advance and reviewed as part of regulatory oversight throughout the system life cycle (FDA 2025).

Figure 2 provides a visual roadmap of three interconnected engineering principles that follow the progression of a clinical decision system. The first establishes whether AI-derived evidence is sufficiently reliable for its intended use; the second determines how that evidence

should be translated into a clinical recommendation; and the third uses real-world performance to identify when and where the system requires refinement, feeding what is learned back into the preceding stages. Together, these principles ask not simply whether an AI model performs well, but whether the clinical capability it enables can remain trustworthy, actionable, and adaptable across the environments in which people receive care. This progression therefore begins by establishing the reliability of AI-derived evidence.

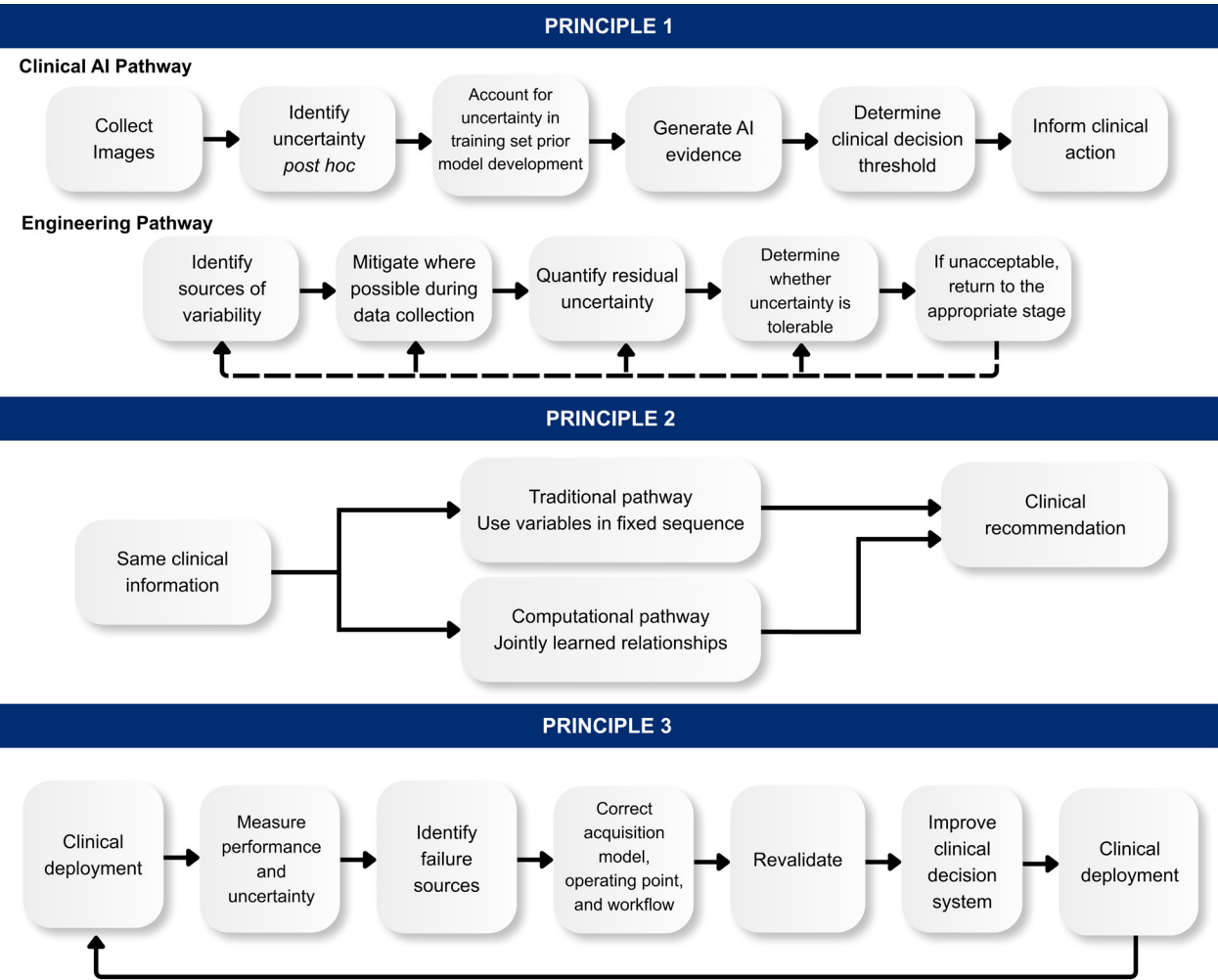


FIGURE 2. Three engineering principles for trustworthy AI clinical decision systems. Principle 1 links the clinical AI pathway with an engineering pathway that identifies and mitigates sources of variability, quantifies what remains, and determines whether it is tolerable. Principle 2 illustrates how the same clinical information can be translated into a recommendation through either a traditional pathway using predefined criteria or a computational pathway that learns relationships among inputs. Principle 3 closes the loop through real-world deployment, where performance and uncertainty are monitored, failure sources guide corrective action, and the system is revalidated before continued clinical use. Together, the principles connect information generation, clinical decision-making, and continuous learning within an end-to-end engineering framework.

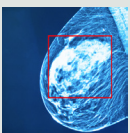
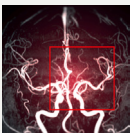
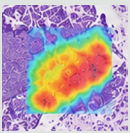
1. Clinical application		2. AI-generated evidence	3. Clinical integration	4. Clinical action
Breast cancer screening (mammography)		• Lesion localization • Malignancy probability	• Imaging • History • Prior imaging • BI-RADS	• Imaging • Biopsy • Surveillance • Routine screening
Acute stroke (CT/CTA)		• Occlusion localization • Occlusion probability	• Examination • NIHSS • Symptom onset • Imaging	• Stroke pathway • Thrombectomy • Thrombolysis • Medical therapy
Abnormality detection (digital pathology)		• Tumor localization • Biomarker quantification	• Tissue morphology • Clinical history	• Tumor grading • Biomarker testing • Treatment planning
Dermatology (lesion evaluation)		• Lesion characterization • Malignancy probability	• Dermoscopy • Patient history • Risk factors	• Biopsy • Referral • Surveillance • Reassurance
Cervical cancer screening (colposcopy)		• Risk assessment (low grade/high grade)	• HPV status • Patient age • Cytology • Colposcopy impression	• Biopsy • Treatment • Surveillance • Referral

TABLE 1 Representative AI applications illustrate how image-derived evidence contributes to clinical decision-making across diverse imaging domains. AI-generated evidence is integrated with patient-specific information, clinical risk factors, and established management pathways to inform clinical action. Across these applications, a common architecture emerges in which AI-generated evidence contributes to, rather than independently determines, clinical decisions.

How Do We Know whether AI-Generated Clinical Evidence Is Trustworthy?

Across radiology, stroke, pathology, dermatology, and cervical cancer, AI-derived evidence is increasingly being evaluated and integrated into clinical decision-making (Lekadir et al. 2025; Wadie et al. 2026). Although the technologies, computational outputs, and clinical applications differ across these domains, they all provide outputs that can be integrated with clinical risk factors such as prior treatment history and screening results to inform patient management. The cross-domain examples shown in Table 1 demonstrate the broader relevance of how AI can support context-specific clinical action. Across these applications, the first engineering principle therefore asks whether that evidence is sufficiently reliable for its intended use.

Evaluating reliability requires complementary measures of diagnostic performance and prediction consistency.

Diagnostic performance can be characterized by measures such as sensitivity, specificity, and positive and negative predictive values. Prediction stability is characterized by score range or variance, agreement statistics such as the intraclass correlation coefficient, and the frequency with which repeated scores cross a clinical decision threshold (“score flipping”) (Lemay et al. 2022). Since patients with disease probabilities near decision thresholds are particularly susceptible to score flipping, this metric can identify a grey zone of decision uncertainty where AI-derived evidence should be interpreted more cautiously.

The importance of this grey zone lies not in the magnitude of predictive variability alone, but in whether that variability changes the clinical decision. For example, if a referral threshold is 0.50, repeated scores of 0.46, 0.52, and 0.48 would repeatedly change the recommended action even though their numerical spread is modest. Failure to account for this risks translating small fluctuations

in model scores into unstable clinical decisions. This grey zone should therefore prompt efforts to identify and mitigate this ambiguity. When residual uncertainty persists, it must be quantified and evaluated to determine whether it is sufficiently small to support a reliable clinical decision.

***First Engineering Principle:
Trustworthy clinical decisions
require an understanding of
how variability propagates
through the information
generation process.***

The amount that can be tolerated will depend on the consequences of a missed referral, an unnecessary procedure, and the feasibility of repeat testing in the intended setting precluding a universal threshold.

Prediction stability provides one means of quantifying uncertainty after model development but the variability it reveals may originate earlier in the pipeline, including from image quality and the reference standards used for model development. Identifying these upstream sources allows them to be mitigated when possible or characterized so that their effects on prediction stability can be accounted for. For example, objective quality assessment at the point of capture can enable corrective action before compromised information enters the computational pipeline (Ekem et al. 2025a). When correction is not possible, these criteria can guide dataset curation by excluding inadequate observations or flagging them rather than treating all images equally reliable (Ekem et al. 2025a).

Reference standards used to define disease and assign class labels for AI model development can themselves vary. An important example is cervical histopathology, where disease classification determines whether clinical intervention is warranted. Low-grade abnormalities generally do not require treatment, whereas high-grade precancer warrants intervention; however, borderline cases may be interpreted differently among pathologists (Tao et al. 2024). Rather than forcing these cases into a definitive disease category, they may benefit from being classified separately to explicitly represent uncertainty in the reference standard.

Generalizability can be evaluated across different conditions of use. Prospective or cross-site validation tests whether model performance is maintained in independent patient populations, whereas cross-device validation tests whether it is maintained across imaging technologies or acquisition conditions. Approaches to improving generalizability include expanding or diversifying training datasets and adapting computational models to new domains. However, variability introduced during data collection and model development can propagate downstream and affect diagnostic performance, calibration, and prediction stability. Generalizability therefore cannot be addressed solely through evaluation after model development; the sources of variability that enter during data collection and model development must also be considered.

As summarized in Principle 1 of Figure 2, these processes can be organized into interconnected clinical-AI and engineering pathways. The clinical-AI pathway traces how images are translated into evidence and ultimately inform patient care, while the engineering pathway identifies sources of variability; mitigates them, when possible; quantifies what remains; and determines whether it is tolerable for the intended use. The two pathways are therefore interdependent: the engineering pathway evaluates and modifies the information-generation process represented by the clinical-AI pathway to improve the reliability of the resulting evidence.

How Should Trustworthy Evidence Be Translated into Clinical Decisions?

Translating reliable AI-derived evidence into clinical action requires determining how that evidence should be interpreted and integrated with other patient-specific information. The operating point provides one critical link by defining when an AI prediction becomes consequential to patient management. Its selection therefore depends not only on algorithm performance, but on prediction stability, the consequences of error, and the intended clinical setting. This differs from the generalizability question addressed earlier: the issue is no longer whether model properties are maintained across settings, but how reliable evidence should be used within a particular setting. Because the operating point influences who is treated, referred, reassured, or asked to return, the acceptable trade-offs among sensitivity, specificity, and prediction stability should reflect local clinical priorities and resource constraints. Table 2 illustrates how differences in clinical context influence the selection of these

Scenario	Clinical example	Consequence of missed disease	Operating point	Prediction stability
Diagnostic triage	AI-assisted chest radiography for tuberculosis screening. Patients above the AI threshold proceed to confirmatory diagnostic testing.	A false negative may prevent a patient with active disease from advancing to confirmatory testing, delaying diagnosis and treatment and potentially allowing continued transmission. False positives are less consequential because they undergo confirmatory testing rather than treatment.	Favor high sensitivity, accepting lower specificity, to minimize patients with disease who are excluded from further evaluation.	Important, particularly near the referral threshold, because instability could determine whether a patient proceeds to confirmatory testing.
Longitudinal screening	Cervical cancer screening within a reliable periodic screening program. Patients continue routine surveillance and have subsequent opportunities for screening and referral.	A false negative at one encounter may be recoverable at a subsequent screen before progression to invasive disease. False positives can lead to unnecessary referrals, colposcopy, biopsies, or treatment.	Greater emphasis can be placed on specificity while maintaining sufficient sensitivity for clinically significant disease, because unnecessary intervention has consequences and missed disease has another opportunity for detection.	Modest instability may be more tolerable because borderline findings can be reassessed at subsequent screening encounters rather than determining an irreversible action at a single encounter.
Emergency triage	Acute intracranial hematoma. AI-supported imaging informs urgent transfer, specialist evaluation, or treatment.	A false negative can delay time-sensitive intervention, potentially allowing deterioration or irreversible harm before another opportunity for detection.	Favor high sensitivity because missed disease can have immediate and severe consequences.	High stability is required because small variations near the threshold should not cause the same patient to alternate between urgent intervention and no intervention.

TABLE 2 Clinical context shapes operating-point and prediction-stability requirements. The consequences of missed disease, opportunities for subsequent detection, and costs of unnecessary intervention determine the relative importance of sensitivity, specificity, and prediction stability.

tradeoffs. These scenarios reveal a broader engineering principle: an algorithm-generated diagnosis does not prescribe one universal clinical action. What should transfer across settings is not a fixed algorithmic threshold, but a methodology for determining what level of performance and stability the clinical context requires.

The operating point connects AI-generated evidence to clinical decision-making by defining when that evidence becomes consequential to patient management. Its significance, however, depends on how it is integrated with other clinical and patient-specific information within the broader decision pathway. For example, in the cervical cancer prevention pathway, the American Society for Colposcopy and Cervical Pathology (ASCCP) risk-based management guidelines integrate current human papillomavirus (HPV) and cytology results with prior screening history and, where applicable, colposcopic and

histopathologic findings to determine recommendations such as surveillance, colposcopy, or treatment (Perkins et al. 2019). Similar structured decision pathways exist throughout medicine, including BI-RADS for breast imaging (Lee et al. 2018), Lung-RADS for lung cancer screening (Christensen et al. 2024), and AHA/ASA guideline (Prabhakaran et al. 2026) as shown in Table 1.

While clinical guidelines determine patient management through a sequence of predefined criteria, computational models such as decision trees can jointly evaluate multiple sources of patient-specific information and learn how their combined relationships contribute to individualized recommendations (Fernandes et al. 2018; Skerrett et al. 2022). Feature-attribution methods can further identify which factors contributed to the resulting recommendation, providing greater transparency and explainability to clinicians (Arun et al. 2021). As illustrated in

Second Engineering Principle: Generating reliable diagnostic evidence is necessary but by itself not sufficient to guide clinical decisions.

Principle 2 of Figure 2, guideline-based and computational approaches therefore represent two distinct decision architectures for translating the same clinical information into a recommendation.

Regardless of the decision architecture, the appropriate recommendation depends on clinical priorities and the consequences of error in the intended setting. Participatory engagement creates a critical link between clinical practice and engineering design: patients, providers, and health systems define acceptable consequences of error, operational constraints, and clinical priorities that developers translate into system requirements, operating points, and decision architectures. Through appropriately governed partnerships, these stakeholders also provide the clinical and contextual knowledge needed to translate lessons across settings while adapting operating points and decision criteria to local priorities, constraints, and practices. Participatory engagement therefore connects the clinical and engineering dimensions of the second principle by grounding the translation of AI-derived evidence in the context in which it will be used (Figure 2). The third principle extends this process into deployment, where real-world performance determines whether the choices established in Principle 2 remain appropriate in practice.

How Should Engineers Rethink Clinical Decision Systems?

Continuous learning is often viewed narrowly as periodically updating AI models with additional data. From a systems engineering perspective, however, variability encountered during implementation reveals where failures can arise in the clinical decision system and provides feedback for corrective action (Finlayson et al. 2021). Rather than treating this uncertainty as model failure, it can be measured as an engineering variable during the information-generation process, to determine if system refinement is needed and where in the devel-

opment pathway it should be introduced. Importantly, the conditions that influence system performance will continue to evolve after deployment as patient populations, disease prevalence, imaging devices, acquisition protocols, operators, preprocessing pipelines, and clinical workflows change (Finlayson et al. 2021). Therefore, prospective monitoring is needed to continually track the effects of these changes during deployment, including shifts in image quality, prediction-score distributions, calibration, sensitivity, and specificity at the selected operating point; and prediction stability. As summarized in Principle 3 of Figure 2, this monitoring initiates an engineering feedback process in which emerging problems are traced to their source, addressed at the appropriate point in the pathway, and revalidated before continued deployment.

Acquisition-related problems may require changes to the imaging protocol, or operator workflow, whereas computational problems may require model recalibration, adjustment of the operating point, or retraining and revalidation. Distinguishing the source of error is therefore critical to selecting the appropriate intervention. For example, when acquisition conditions influence the representation of disease, modifying the model alone may not resolve the problem because the resulting data may reflect how they were acquired rather than the patient's underlying disease (Finlayson et al. 2021; DeGrave et al. 2021). Although not all sources of variability can be eliminated, engineering interventions can reduce their occurrence or prevent their effects from propagating downstream.

Third Engineering Principle: A clinical decision architecture must be engineered for deployment, not just development.

One important source of variability during image acquisition is blur, which can reduce the diagnostic quality of the captured image. Figure 3 illustrates one example in which objective blur assessment can provide feedback during the examination, allowing the provider to address poor image quality before acquisition is completed (Ekem

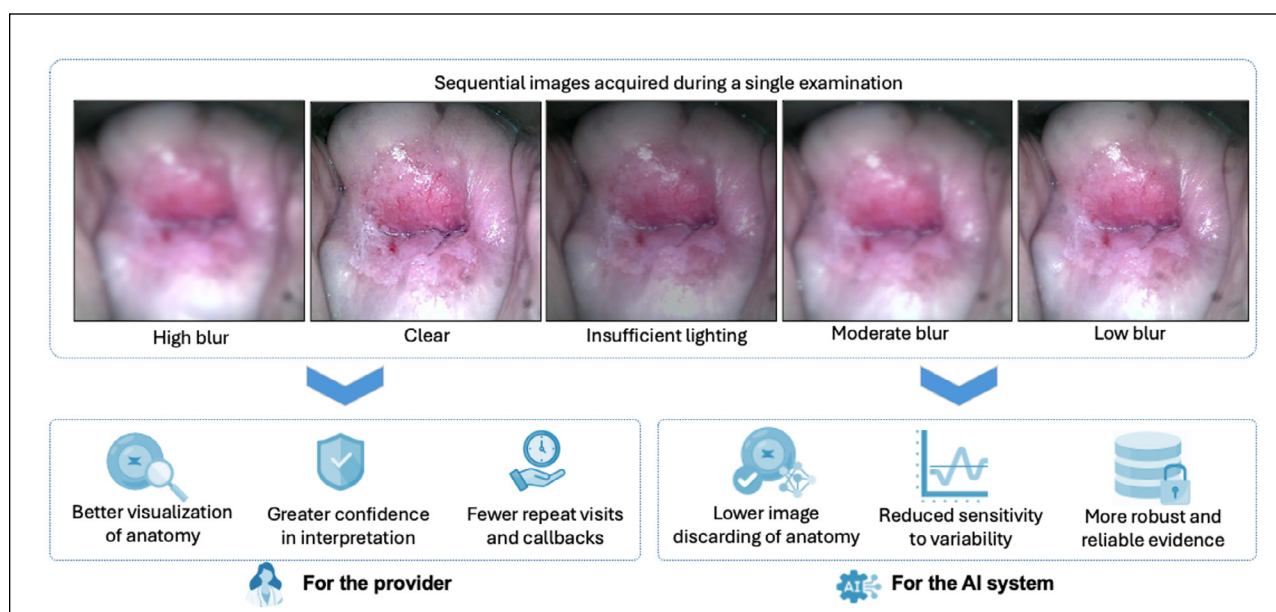


FIGURE 3 Engineering the information-generation process through vetted image-sequence acquisition. Multiple images acquired during a single examination are evaluated to assess whether they provide adequate diagnostic information before computational analysis. By accounting for variation in image quality, including blur and illumination, vetted image-sequence acquisition can improve both clinical interpretation and AI performance. For clinicians, it can enhance visualization and confidence while reducing repeat visits; for AI systems, it can reduce sensitivity to acquisition variability and improve the reliability of downstream evidence. Photos: Courtesy of authors.

et al. 2025a). On the provider side, one simple and practical strategy is to capture multiple images during a single examination to increase the yield of high-quality data without disrupting the workflow (Dotson et al. 2024). When acquisition-related problems cannot be corrected during the examination, the same image-quality assessment model can identify unsatisfactory images for exclusion from downstream computational analysis (Ekem et al. 2025b). Repeated measurements can also reveal the relationship between diagnostic performance and prediction stability, allowing both the accuracy and consistency of AI-generated evidence to be evaluated simultaneously particularly near the selected operating point or clinical decision threshold.

Clinical deployment therefore serves two purposes: delivering care today and generating the evidence needed to improve the system for tomorrow. Longitudinal monitoring can identify changes in image quality, clinical performance, prediction stability, and patient outcomes, while computational and engineering refinement use this feedback to determine whether the technology, model, operating point, or clinical workflow should be modified (Finlayson et al. 2021). Taken together, these processes form a closed engineering feedback loop in which real-world performance guides

targeted intervention, and subsequent deployment determines whether those changes improve the clinical decision pathway (Raji et al. 2020). In this way, deployment continually tests whether the reliability requirements established during model development and the decision criteria selected for clinical use remain appropriate under real-world conditions. The knowledge generated through this process can, in turn, inform improvements in other healthcare systems through the participatory processes that adopt these lessons to local clinical and operational conditions.

What Will Define the Next Generation of Clinical Decision Systems?

The next generation of clinical AI should ultimately be judged not by the sophistication of the technology, but by how widely its benefits can be shared. A highly accurate algorithm available only where specialists, advanced equipment, and extensive infrastructure already exist may indeed improve care. A clinical decision system capable of delivering trustworthy information and guiding appropriate action across widely different environments has the potential to extend the benefits of high-quality care far beyond the settings in which those capabilities are traditionally concentrated.

Viewed together, these principles provide an end-to-end engineering framework for cervical cancer imaging that connects sources of variability to their consequences on clinical decisions, while using real-world performance to determine when and where intervention is needed (Figure 2). Across healthcare settings, what should transfer is not a universal threshold or implementation but an engineering methodology for determining what information can be trusted, how it should guide care, and how the system should adapt to the conditions in which it is used.

Resource constraints are not simply obstacles to deployment. They can expose the assumptions built into our technologies and serve as a forcing function for improved system design—one that requires less specialized infrastructure, accounts for limitations, adapts to local circumstances, and remains reliable outside of ideal environments. Designing for these conditions can therefore produce not only more accessible systems, but more resilient ones—allowing lessons learned in underserved settings to inform better healthcare systems everywhere.

The next generation of clinical AI requires a shift in the engineering objective: from optimizing individual algorithms to engineering clinical decision systems. Success should therefore be measured not only by how well an algorithm performs, but by whether the clinical capability it enables remains reliable, clinically appropriate, and responsive to the conditions in which care is delivered. Achieving this broader impact requires multidisciplinary and participatory collaboration throughout this life cycle (Kim et al. 2023, 2024). Clinicians and patients help define clinical priorities and acceptable trade-offs; engineers translate these requirements into technologies and computational systems; implementation scientists support their integration into local practice; and regulators provide oversight for safety, accountability, and transparency.

That is the larger promise of medicine everywhere, for everyone: not just developing and distributing more technologies, but engineering healthcare systems capable of extending the benefits that technological innovation has brought to modern medicine far beyond the places where they are available today.

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*As prediction of health trajectories becomes
ever more robust, healthcare can move increasingly
from a reactive to a proactive paradigm.*

Predictive AI, Personalized Prevention, and the Future of Health

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Daniel Rueckert



Marzyeh Ghassemi

A critical aspect of modern medicine is predicting the future. Physicians routinely employ finely honed instincts, augmented to varying degrees by medical data, to predict the future development of disease and recommend protective measures. In other cases, they predict the response of already-diagnosed disease to putative therapy in order to guide treatment decisions. One of the

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great successes of engineering in the arena of health-care has been to provide ever more advanced tools to aid not merely in the diagnosis of current disease but in the detection of early signs of disease before it arrives in force. Blood tests, medical imaging devices, and sensors capable of augmenting natural human senses are now used regularly to inform medical predictions. Recently, humans have developed new tools to do the predicting for them. Artificial intelligence (AI)-based algorithms for medical prediction have burgeoned both in academia and in industry, and such algorithms have increasingly been employed in clinical practice. Meanwhile, a new sector of proactive health companies has arisen, with the ambitious thesis that regular biological monitoring combined with AI will catch disease so early that the full onset can be prevented, ultimately extending the human health-span. The aim of this article is to lay out some of the recent history of predictive AI in health, assessing the current state of the art and, to the extent possible, separating rigorous scientific underpinnings from the hype that inevitably accompanies new technologies like AI. The intent is also to look forward to where things might stand in several years' time; in other words, to predict the future of predictive health in the modern era of AI.

The History of Medical Prediction

Long before the advent of computers, physicians were already in the business of prediction. Prognosis—the forecasting of a disease's likely course—has been a pillar of the healing arts since antiquity, resting on pattern recognition honed through years of clinical experience. Similarly central to medical care is the prediction of response to therapy, which involves recognizing, from experience, which interventions will cause particular manifestations of disease to resolve. In the 20th century, experts began to formalize the practice of pattern recognition. Statistical methods, including linear regression, allowed clinicians to relate measurable risk factors to future outcomes. From such efforts emerged the risk index: a compact tool for estimating an individual's probability of developing disease. Cardiovascular risk, for example, has been especially well studied, with the Framingham Heart Study yielding scores still in use today. Even the taxonomies clinicians use to describe disease are, at heart, predictive. Tumor grading and staging systems as well as the reporting and data systems (RADS) frameworks radiologists use to report imaging findings are designed in part to forecast a disease's future course, and thereby to guide the timing of follow-up and the choice of therapy.

The Advent of Predictive AI

As modern deep learning picked up steam in the 2010s, its rapidly evolving tools were quickly turned not only to medical diagnostics but also to problems of medical prediction. One essential advance was representation learning: rather than relying on features handcrafted by experts, deep neural networks learned to distill diverse data (e.g., blood test values, images, and electronic health record entries) into internal representations from which patterns predictive of disease could be read out. Early exemplars proliferated across specialties: algorithms anticipated septic shock at the bedside (Henry et al. 2015), predicted cardiovascular risk factors from retinal fundus photographs (Poplin et al. 2018), and forecast clinical events from the electronic health record (Rajkomar et al. 2018). The COVID-19 pandemic then became an unplanned proving ground. Hundreds of models were rushed out to predict COVID progression and prognosis (e.g., Yan et al. 2020; Liang et al. 2020). However, systematic appraisals soon found nearly all of them at high risk of bias and of little clinical use (Wynants et al. 2020; Roberts et al. 2021; Seyyed-Kalantari et al. 2021). These developments constitute a cautionary tale about the perils of prediction under pressure.

The State of the Art Today

Dedicated Predictive Models

Dedicated prediction models—algorithms trained for a single, well-defined task—have matured rapidly, and their targets read like a map of where modern medicine most needs help (Figure 1).

It is instructive to organize a few examples around the so-called “four horsemen:” cancer, cardiovascular disease, neurologic disease, and metabolic disease, which represent leading causes of death across much of the world (at least, where they are not outpaced by infectious diseases). What follows is far from a complete catalogue; it is instead a suggestive illustration of recent progress.

Breast cancer risk prediction has become a proving ground for the field. Deep-learning models now read directly from screening mammograms to estimate a woman's future risk, outperforming traditional questionnaire-based scores. The Mirai model, developed at MIT and commercialized by the company Clairity, is a widely validated example, forecasting risk up to five years out across diverse populations (Yala et al. 2021, 2022), and various other algorithms have been developed and evaluated (Rothwell et al. 2026).

(Gadd et al. 2024), from routine medical data (Jin et al. 2025), and from continuously sensed physiology (Narayanawamy et al. 2026).

These promising developments come with caveats the field is only beginning to reckon with: erroneous model outputs, clinically unjustified performance differences across distinct patient populations (Seyyed-Kalantari et al. 2021), privacy risks (Gichoya et al. 2022; Knolle et al. 2026), and performance degradation when deployment conditions deviate from expectations (Wong et al. 2021), to name a few. It should be noted that even traditional risk scores are subject to some of these limitations (such as lack of generalization to understudied

Many promising developments come with caveats the field is only beginning to reckon with, meriting continuous monitoring and careful governance.

populations). While AI can address some limitations, it can also obscure others and even create new ones. Technical solutions, moreover, may not always suffice to address these challenges, and continuous monitoring and careful governance are merited.

A few themes recur across these examples. The signs of incipient disease are often subtle, and are easily confused with benign variation. Here AI can excel, detecting faint presentations and fusing multiple modalities in ways that outstrip human perception. Yet the same models remain brittle when confronted with an unexpected feature outside their training distribution—precisely the territory in which human judgment, sometimes, still shines (Xu X et al. 2026).

Large Language Models, Frontier Models, Health Agents, and Medical Chatbots

If dedicated models have been the quiet workhorses of medical prediction, large language models (LLMs) have been its loud disruptors. Frontier models—and, increasingly, the agentic reasoning systems built upon them—now dominate the conversation. Where do they stand on medical prediction? The promise is real. On the one hand, general-purpose models have shown that they

encode a startling breadth of clinical knowledge (Singhal et al. 2023, 2025), and multimodal successors extend that reach across images and text (Saab et al. 2024). LLM architectures have been explicitly retrained to predict the progression of disease (Shmatko et al. 2025), and generative models that integrate genetic data with longitudinal electronic health record data have been able to predict individual health trajectories over time (Urbut et al. 2026). Conversational agents such as Google's AMIE (articulate medical intelligence explorer) have begun to rival primary-care physicians in simulated diagnostic dialogue (Tu et al. 2025), and to manage disease longitudinally rather than in a single exchange. Notably, a recent evaluation from NYU found that general-purpose frontier models outperformed specialized, commercially marketed clinical AI tools on medical benchmarks (Vishwanath et al. 2026).

On the other hand, fluency is not the same as reliability. These systems still hallucinate, generating confident falsehoods that are especially dangerous in medicine. At least as recently as 2024, careful empirical study confirmed that frontier models, left to act autonomously, still made clinically consequential errors (Hager et al. 2024). They can also inherit the biases of their training data, at times propagating race-based medical misconceptions (Omiye et al. 2023). Their headline benchmark scores can be a mirage (Asadi et al. 2026; Zhang et al. 2026). Models that answer standard questions correctly often collapse under dynamic probing of the same knowledge from unfamiliar angles (Pan et al. 2026), a sign of memorization rather than understanding. Indeed, the very mechanisms by which models are evaluated may systemically inflate expectations of their performance (Raji, Daneshjou, and Alsentzer 2025; Zhang et al. 2026). Fluency itself, meanwhile, carries its own nontrivial dangers, including sycophancy in models and dependence in their users (Cheng et al. 2026). Understandably, regulatory and ethical frameworks are still catching up. Figure 2 summarizes the current pros and cons of frontier models when applied to medical prediction.

Google's recent cardiometabolic prediction efforts (Metwally et al. 2026) may hint at a synergistic combination of dedicated predictors with frontier models. They pair a bottom-up world model, which distills raw wearable sensor data into succinct representations, with a supervised multimodal predictor of insulin resistance and a special-purpose language interface for questions and interpretation. Dedicated precision below, controlled

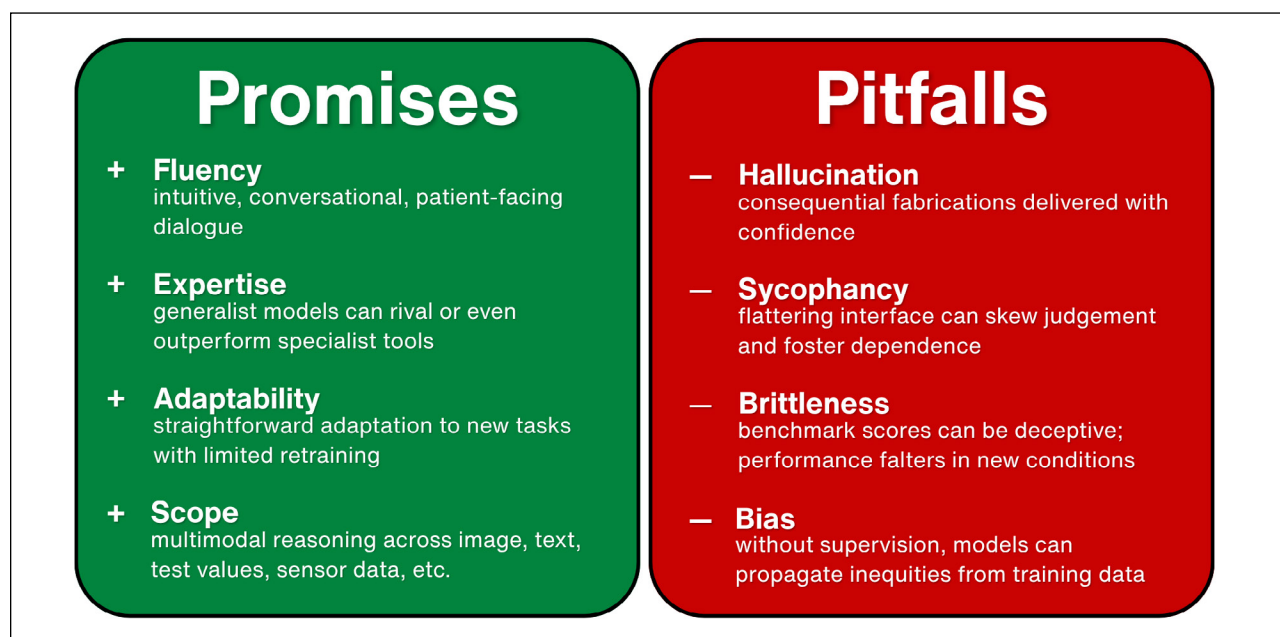


FIGURE 2 Promises and pitfalls of frontier models used for medical prediction.

conversational fluency above; this pairing may represent the best of both worlds.

An Emerging Proactive Health Industry

While advances in AI continue to drive clinicians and patients alike into private conversation with chatbots, the increasing power of predictive models is also beginning to drive changes in the practice of medicine. The benefits of early diagnosis are many: saved lives, improved quality of life, and reduced costs for late-stage sick care. In pursuit of these benefits, there has been a quiet growth of opportunistic screening and longitudinal monitoring protocols in medicine. Tests designed for breast cancer are being pored over by algorithms that also evaluate cardiovascular health, detecting breast arterial calcifications on routine mammograms as a marker of cardiovascular risk (Watanabe et al. 2025). Routine abdominal and chest CT scans, likewise, are increasingly mined by algorithms for opportunistic markers of osteoporosis, body composition, and coronary artery calcium (Pickhardt et al. 2023). Rather than waiting for symptoms to develop, all too often too late, people with known risk factors for lung, liver, prostate, or breast cancer are increasingly being followed with repeated imaging studies to monitor for concerning changes over time (Wolf et al. 2024; Ahn et al. 2022; Fazekas et al. 2024; Monticciolo et al. 2023).

Somewhat less quiet has been the advent of direct-to-consumer health monitoring. Some high-profile com-

panies now operating in this space have their origins in wearables and other wellness sensors: Oura, Whoop, Apple Health, and Google's Fitbit division, for example. Others, like Function Health, gather broad panels of blood tests and imaging studies over time. This emerging approach to medical monitoring has engendered vigorous debate, in medical and scientific circles as well as in the popular press, around questions of accuracy, access, and impact. After a 30-year career in academia building imaging technologies and algorithms to improve diagnosis and guide treatment, one of us (Daniel Sodickson) recently joined Function Health with the explicit aim of extending the safety net of early detection to broad, pre-symptomatic populations.

The Future of Predictive AI

Coming Soon: Context-Aware AI for Individualized Prediction

Far and away the most common objection to broad-based health screening focuses on the risk of overdiagnosis. If the rate of false positive findings significantly exceeds disease prevalence, the argument goes, then many people will receive unnecessary, expensive tests and potentially risky interventions. Meanwhile, testing for conditions that are at present difficult to treat may increase the apparent incidence of disease without leading to improved health outcomes. This reasoning has driven understandable cau-

tion in the medical community about proactive testing. Many articles have been published evaluating the sensitivity and specificity of screening protocols, and various economic analyses have attempted to balance up-front costs of screening against downstream savings from avoiding late-stage care. But one thing not often addressed in the literature is the question of whether false positive rates can be changed.

In fact, there is evidence that appropriate use of context may bypass some traditional trade-offs of screening studies, enabling significant increases in specificity without sacrificing sensitivity.

Context is everything in medicine. For example, a lesion that may appear highly concerning in a single imaging study generally becomes far less concerning if it presents the same appearance in prior imaging studies. Meanwhile, the recent successes of LLMs and frontier models attest to the growing power of context in an era of abundant digital data.

Context is also powerful for dedicated prediction models. Figure 3 provides one straightforward illustration. A representation learning model, trained on longitudinal imaging and clinical data from nearly 30,000 men followed for prostate cancer over a decade, was designed to predict the risk of clinically significant prostate cancer in five years' time (Umapathy et al. 2025). When the model was provided with data from a single visit only, its performance for this admittedly quite difficult prediction task was poor: 73% false positive rate for clinical data only (prostate specific antigen level, age, and prostate volume), and 64% for imaging data only (biparametric MRI). As data from prior visits were fed into the model, its predic-

tions improved dramatically and progressively, reaching a false positive rate of 9% at a constant sensitivity of 88% with data from three prior visits. In this case, incorporation of multimodal context over time enabled the algorithm to learn individual norms, rather than applying population norms across the board.

Results like these suggest that, when it comes to predictive AI, the statistics of longitudinal monitoring are not necessarily the same as those of single-snapshot screening. If increasingly rich context can be leveraged to achieve

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sufficiently low false positive rates, the subjective experience of health monitoring may also begin to change. Testing may begin to be perceived not as an uncommon and anxiety-producing procedure likely to tell you that you are sick, but rather as a familiar routine that assures you that you are still healthy, flagging risks, when it finds them, in time for you to course correct.

This example using a single model, of course, remains anecdotal. While other recent models are also beginning to show improvements using longitudinal context (e.g., Xu Y et al. 2026), it will be essential to gather broad efficacy data—including actual prospective outcomes data in addition to performance in retrospective test sets—in order to establish the true power and practical limitations of individualized context-aware predictive algorithms. Fortunately, the datasets required for such evaluations are becoming more common. Growing academic and consumer interest in proactive monitoring is in itself engendering a rapid growth in diverse, longitudinal datasets (e.g., Reicher et al. 2025), which were once exceedingly challenging to collect, at a scale that may soon rival or exceed traditional resources like the UK Biobank. As the performance of algorithms trained on these datas-

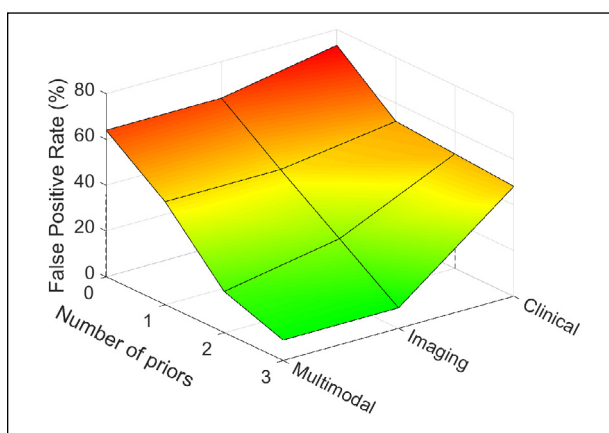


FIGURE 3 Context is everything: Incorporation of longitudinal and multimodal context decreases false positive rates (at constant high sensitivity) for five-year prediction of clinically significant prostate cancer (adapted from Umapathy et al. 2025).

ets improves, we can also look forward to technological advances of a different kind.

On the Horizon: A New Sensor Ecosystem Driven by Context-Aware Predictive AI

Even if concerns of overdiagnosis are addressed, and even if downstream cost savings are shown to outweigh the costs of upstream testing, broad-based deployment of predictive health monitoring still confronts key challenges of accessibility. Repeated testing that relies on high-performance technology would remain unavailable to large swaths of the human population who live in resource-limited regions. Predictive AI offers a potential answer here as well.

The key, once again, relates to uses of context. Just as incorporating prior data can improve risk prediction, the availability of robust priors can also allow one to gather less, and less expensive, current data if all one needs to do is to assess change from an established individual baseline. This is an example of what might be called “upstream AI”—a reliance upon learning algorithms not merely to change the interpretation of existing data, but also to change what data are gathered, along with the machines used to gather them.

Imagine you have established your baseline state of health with a state-of-the-art MRI examination and a full panel of blood tests. Your next examination may not require the same high-performance technology. Perhaps, instead, your interval scan can be performed with an accessible scanner built into a seat, and your next biochemical tests can be a targeted panel derived from capillary blood draw or home sampling of other body fluids. Signals from inexpensive wearable sensors can be pulled into predictive algorithms, not to do the heavy lifting of *de novo* diagnosis on their own, but simply to assess change from the individual health state established by prior testing. In other words, instead of independent tests evaluated in isolation, one might envision multiple tiers of interconnected monitoring technology, linked over time by context-aware AI. Sufficient experience with such technology might even eliminate the need for the high-performance starting step, enabling characterization of baseline health with the right combination of accessible signals. In short, instead of the current dichotomy of sparsely distributed and expensive testing technology on the one hand, and cheap sensors with limited predictive power on the other, future generations may have access to a connected network of what might be called “Everywhere Scanners” (Sodickson 2025).

Such a network would begin to resemble a Global Positioning System for health. A GPS knows where you have been. It has used interconnected sensors to map out the landscape around you. And it can predict where you will end up if you continue onward in your current direction. This combination of continuous monitoring with context-aware prediction is what allows a GPS to show you where, exactly, you need to turn in order to get where you want to go. Likewise, a combination of diverse monitor-

A combination of diverse monitoring technology with context-aware predictive AI would constitute a GPS that steers people toward the destination of healthy longevity.

ing technology with context-aware predictive AI would constitute a GPS that steers people toward the destination of healthy longevity. Figure 4 provides a schematic illustration of such a system.

One additional analogy may be apt here. The paradigm of AI-driven predictive medicine we have been discussing is also analogous to the operation of biological senses. Senses allow humans and other creatures to navigate a perilous world, providing early warning of danger (a saber-toothed tiger, say; or, these days, an errant automobile) as it approaches—while there is still time to react. The human sensory system is composed of multiple sensory modalities connected by a central nervous system that is known to operate as an integrative prediction engine. Against this biological backdrop established long ago by evolution, is it really that futuristic to imagine a network of artificial senses designed to kick in before natural senses do?

The Future of Health

The theme of this issue of *The Bridge* is “Engineering a New Era of Human Health.” So, what will health look like in a decade or two, if humans (and, increasingly, their AI agents) do the job of engineering well? As prediction of health trajectories becomes ever more robust, healthcare can move increasingly from a reactive to a proactive para-



FIGURE 4 A GPS for health, grounded in context-aware predictive AI.

digm. Episodic health interventions can move to a more continuous model, and tools for preventative health, which are currently sparsely distributed at best, can become increasingly omnipresent, reducing the worldwide burden of chronic disease. Along the way, there will be numerous hurdles to overcome (devising appropriate regulatory oversight, for example), and numerous pitfalls to avoid (such as over-reliance on models that remain subject to sporadic hallucination). As both predictive models and longitudinal datasets proliferate, it will be ever more essential to gather robust data on outcomes, and to analyze that data rigorously. That said, engineers and physicians today have a historic opportunity before them: an opportunity to reengineer people's relationship with their health, providing a new predictive and personalized safety net for everyone, everywhere.

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An Interview with . . .

Dava J. Newman, aerospace biomedical engineer, explorer, and educator



Photo: Douglas Sanders

Dava J. Newman

RONALD LATANISION

I'd like to welcome everyone back to *The Bridge* series of interviews. We're speaking today with Dava Newman, Apollo Program Professor of Astronautics and Director of the Human Systems Lab at the Massachusetts Institute of Technology, who is a long-term colleague of mine. Dava, it's great to see you again and good to have you here. We're also joined by David Butler, J. Herbert Holomon Scholar at the NAE.

DAVA J. NEWMAN

Thank you so much—it's really an honor and I'm so glad to join you, Ron and David. Let's talk about the future!

DR. LATANISION

Let me start at the beginning. I identified your affiliation as the Apollo Program Professor at MIT. Could you give us a little bit more of a background? Where did you grow

up and go to school? How did you choose aerospace engineering as your profession? We'll start there to give our readers some context.

DR. NEWMAN

Absolutely. I'm going to start with a couple things that I'm super excited to talk with you about and I'll cover some background as well. I really want to start with what I think is the most exciting quest right now—the search for life in the universe. When are we going to find life elsewhere? And that wonder, that awe—those questions that, maybe, people think can't be answered have always been a spark for me, since I was a young girl growing up in Montana and with the Apollo program in the 1960s.

Human spaceflight taught me to dream. It taught me to look beyond. Looking up at the stars, of course, and the Moon was very prevalent in the Big Sky of Montana growing up. Apollo's important idea for me was that anything's possible, with vision, hard work, breakthrough technology, and so on. And, if we do it together—focusing on that vision that we have a mission and we work together—anything's possible. Today, that translates to my excitement about the search for life in the universe, and looking at other planetary bodies, the solar system, and now looking at exoplanets.

I didn't know I was going to be an aerospace engineer. There are no engineers in my family, except for one wonderful uncle. I really didn't know what engineering was. So that took a while, until I got into college, when I started asking: What is engineering all about? Thinking, I'd love to solve problems. I'd love to think about teams working together to solve those "impossible" problems. And when I figured out that's what engineers do, I said that'd be fantastic and switched my major. But you know, electrical engineering, I didn't know if I could do that. Mechanical engineering—I could never really fix my car very well.

But space was a different story. Space was always exciting to me, both flight, the aeronautics aspect of it, and also astronautics. During my graduate work and doctoral work, I got to combine aerospace with biomedical engineering. And that really was the home run for me—this

cross-disciplinary work where I can study astronauts and astronaut performance and apply engineering principles.

I had the great privilege of starting my faculty career at the University of Houston. They didn't have aerospace, so I got to bring in some aerospace classes. Then I returned to MIT as a faculty member and had previously earned three degrees at MIT. My work focuses on human spaceflight, the breakthrough technology developments for both astronauts in space as well as on Earth—the dual use of our technologies.

I also got to dabble in policy, earning a second master's degree in technology and policy and serving as director for a decade, which I know you're both also interested in. It really is about how are we going to think about the future vision? I've always been an educator and it's always about the next generation and my students. I had the great privilege to go to Washington, DC, and serve as NASA Deputy Administrator (the number two for the entire agency) with NASA Administrator Charlie Bolden during the Obama administration. My career kind of came full circle after that. I was very glad to come back to academia and MIT to get back to research and teaching.

DR. LATANISION

When you were in high school, did you have a teacher, a mentor, or someone who gave you some advice or some counsel on the direction you were heading? Or were your parents involved in any way in aerospace activities? How did you even think of it? When I think back, my decision to become a materials scientist was because I didn't want to become a coal miner. I grew up in northeast Pennsylvania and mines were very tough on my family. I had a mentor in high school who gave me some really good advice and help. I'm curious about whether you had any similar experiences.

DR. NEWMAN

I grew up in a mining family as well in Montana. My grandpa Dave, who I'm named after, was a miner and state senator, but my folks and aunties were K-12 public school teachers, and so I think that kindled that love of education and learning in me. Early on, I still didn't know what engineering was, but I was very good in the STEM fields. I had propensity and loved those fields, I just didn't know where it was going to lead.

Today, I call it "STEAMD." I always bring in the art, I always bring in design, because I want to make sure that the message is that STEM (STEAMD) needs to be open to everyone. I have the best job in the world, being the

Apollo Professor, and I get to build things and design things and train astronauts and fly experiments into space. But we need everyone. So, I work with philosophers and poets, and artists, always the visionaries.

What I love about engineering (and how I kind of literally stumbled into it) is thinking about the teamwork needed and putting teams together to solve big, audacious problems. And very important, too, for our engineering ethic is that as we are designing and building. Whatever we do in engineering, it should be in service of humanity. Are we helping the human condition? I think that's important to keep at the forefront.

DR. LATANISION

What is the mission of the Apollo program at MIT? Is it a large program? What are some of the specifics?

DR. NEWMAN

Well, so that's my chair, the Apollo Program Chair, in honor of NASA's Apollo Program. There's a really great story here. You might know the name Robert Seamans from MIT and his NAE work.¹ He was also NASA Deputy Administrator. He was a wonderful mentor of

***Whatever we do in
engineering, it should be in
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mine. How lucky was I that I got to meet Bob? He was the first engineer as deputy of NASA. Hans Mark was also a NASA Deputy Administrator. Those two were huge mentors to me.

Both academics, Bob Seamans was with us at MIT at the AeroAstro Department (where my home is), and Hans Mark became the Chancellor of the University of Texas. The fact that they were both aerospace engineering Deputy Administrators of NASA was a really important message for me—the thinking that leadership and technical engineering skills could all go hand-in-hand. With our technical leadership, all of us in the STEM fields, there should be a place for us in terms of leadership, policymak-

¹ Ed. note: Dr. Robert C. Seamans Jr. served as the NAE's president during 1973–1974.

ing, and decision-making, especially within our government agencies and especially in Washington, DC.

So that's where the named chair comes from, the Apollo Program Chair at MIT, from the historic, wonderful accomplishments of NASA and the United States back in the 1960s and 1970s. And now play it forward, I just couldn't be more honored. Because now human spaceflight is so exciting; the most exciting thing I can think of. And that includes the health challenges we have with our astronauts, the human health challenges. That's my specialty, aerospace and biomedical engineering combined.

Aside from human health, I also work on planetary health. Now I'm splitting my time, probably about 50/50, on human spaceflight and on climate and planetary health. We're looking at how all our technologies and all our data from space (from Earth-observing satellites, looking down to Earth) can help us with really important, complex challenges that we have with climate change. I call them "vital signs of Earth from space." More than 50% of all climate data now is measured and monitored from low-Earth orbit. So, you know, space to Earth and Earth back to space—full circle. These are the areas I'm so passionate about.

DR. LATANISION

I understand that you participated in the Sea Space Symposium in 2025. What was the nature of the symposium? What was the character of the event?

DR. NEWMAN

Oh, thanks for asking. It's a few ocean explorers and space explorers. It was founded by Buzz Aldrin and Jacques Cousteau. Sylvia Earle, her deepness, is a member, as well as Kathy Sullivan, the first female astronaut to perform a spacewalk, lead NOAA, and go to the depths of the oceans. It's really a small community. We get together to listen to lectures and work, and we also go to some fabulous places to get some diving in. People might not realize this: All of our space technologies that we're designing for very extreme environments—isolated, confined, very, very harsh environments—are not just for human space flight, but also for space science missions, for example, going to Jupiter and looking for exoplanets. Those are really tough design challenges in extreme environments.

And those technologies have similar applications for ocean research, especially when you're a human diver; all the physiology, all the extremeness of the deep. Going underwater, viscosity changes (the fluid dynamics) and pressure increases, but it's very similar to space exploration.

All of us are explorers at heart and have that exploration spirit. So, the convenings are to learn from one another at the symposium. But then also to kind of push the boundaries, push the frontiers, and to connect across oceans to space.

DR. LATANISION

I think it's so important, frankly. I mean, when you think about the Earth, we're covered by about 70% water and we're in this massive, unknown planetary system (well, not totally unknown) but we should be concerned about preserving the quality of both. I did not know there was such a symposium and I think it's exactly what we should be doing, trying to understand where we fit in this whole perspective, the planet Earth. I'm curious: How often do you folks meet?

DR. NEWMAN

There are two meetings a year to give everyone the opportunity to attend hopefully once because there's usually travel involved. It's a small, curated group so that we can really focus on the current issues and bring in guests and listen to experts. This time we did some diving safety lessons. We talked about national security, and satellites; especially satellites, and not just in low-Earth orbit, but getting further out into geosynchronous orbit. When I first became a member, I went and talked about some of the technologies we were developing for advanced space suits, my BioSuit™, to keep astronauts alive and medical applications for here on Earth.

Back to your point, it is really amazing. Most people know of the "overview effect." When astronauts go into space and they look back on Earth—ah, it's so beautiful. It really is the most magical view, I think, you could ever have, looking back on Earth with that overview effect and that picture in your mind's eye. Let's go back to Apollo. Those first images, the Earthrise, when humanity saw that famous photo from Apollo 8, that might have started an environmental movement. It showed us maybe a little bit more of our place in the universe. But it also showed us our home planet, and how precious and magical it was and emphasized that responsibility to take care.

I tell everyone that we're all astronauts. All my students want to be astronauts and they're training and getting their doctoral degrees and one is flying in space right now on the International Space Station! But I say, humanity, we're all astronauts. We're on Spaceship Earth, and guess what? We're going really fast around our Sun. So, for this planet, if we would act like crew, if we would act



Launch of the Apollo 8 lunar orbit mission; December 21, 1968.
Photo: NASA.

like astronauts and really have the respect and care for all biodiversity on this planet, I think we'd be better off.

In talking about subsystems of Earth (i.e., oceans, land, air, and near space), the oceans are the largest. They're the most important in terms of biodiversity. We like to say, "Without any blue, there's no green." So, the message is let's take care of our oceans and our biodiversity. And, to me, that's completely related and connected to a lot of how we're pushing boundaries in spaceflight and with human spaceflight. But really, it should teach us about how to do things better for planet Earth. This is my favorite planet.

DR. LATANISION

I remember the first time I saw that image of the Earth from space. And frankly, it just made me feel incredibly small. It's just amazing. It was such an unusual photograph. It's hard to imagine that you're on that little planet and there are people looking at it from space. I was just blown away by that. However, that leads me to another

question. I know you're interested in exploration and humanity on Mars. What are your thoughts there?

DR. NEWMAN

Oh, I'm so glad you asked. That's my passion. That's the long goal, getting humans to Mars. I've had the great pleasure to co-chair the National Academies' committee on A Science Strategy for Human Explorers of Mars. This will be for the first human exploration of Mars missions. It's a decade or two out and we're really trying to have a blueprint because exploration really should be science driven. Let's get those science priorities right. The focus is the search for life. Can you imagine when we find life elsewhere, on another planet? And we're getting close. The evidence is mounting. Mars is a good place to look. There are also other moons in our solar system that are good places to look; we call them "ocean worlds." We know they have water, so they might have life.

But humans are going to go back to the Moon next. We have to improve our technologies. We have to get ready. We can't go to Mars tomorrow, but we can do it if we invest in the technologies. We'll get back to the Moon first and learn from that. Hopefully that will be a very international, global mission. We have a great model for international cooperation in space through the International Space Station. We've had people from all over the world living in space together for the last 26 years, 24/7. It's remarkable. I think anyone out there reading who's 26 or younger, they are the true space generation. Their entire lives, every day of their lives, there have been astronauts from all over the world, multicultural, multinational folks living and working on our International Space Station.

But that's just step one: next, back to the Moon, a three-day trip. We still need to invest in technologies. We need the heavy-lift launch to get us there. We need life-support systems; pressurized habitats, advanced spacesuits, and radiation protection for people to live there. And that helps us get to Mars—those technologies are also very applicable to getting to Mars. And Mars is hard, and it's far away. But it's not "Option B." What will be successful, from my perspective, is to push those boundaries, to do the most excellent work we can, and again to keep thinking about life here on Earth in these future explorations.

DR. LATANISION

Do you find that we have the political will to do this in the United States or on the planet Earth at this point? Do we have the political will in the nations that are capable

of astronautics to follow that lead? What is your sense of that at this point?

DR. NEWMAN

I think we definitely have humanity interested across nations. We have to focus and muster the political will, the coalition of the willing. I'm very focused on the breakthrough science and the priorities in science for humanity and what that will mean. I only see it working with global peaceful cooperation—cooperation based on a science-based strategy for that audacious goal. This is a generational opportunity. Here we are now with the capabilities and investments, to send people back to the Moon and to Mars.

So, for me, what an incredible time to live. I've dreamt of this for my entire academic career, for the last three decades. And we're there. It's happening. The public-private partnerships put in place are critically important. The government is investing, and not just the US government. Governments around the world are investing. I think that's what it really takes. This time, if we leverage national investments along with the private sector—if we get that right, then it's on us because we have the opportunity to realize some of these future Mars and other breakthrough space missions.

And we'll keep doing our robotic missions as well. It's never humans versus robots. It's humans and our machines. That's what we work with every day, our machines, our AI. In our recent report, we talk about human, machine, and AI teaming. Our teams now are people. But guess what? We have a lot of agents and machine teaming as well. They can help us search for and find evidence of life, past or present, on Mars.

We think initially it might be past life, like a fossil, because Mars and Earth are “sister” planets, both about 4.5 billion years old each. Life worked out pretty well here for us on Earth, thank goodness for us. On Mars, we think it was very likely to have been a habitable planet, but something maybe went awry 3.5 billion years ago. It went from a warm, wet, wonderful world to now, where we know that the Sun has ionized the atmosphere. Today, Mars has an atmosphere made almost entirely of carbon dioxide that is only about 1% as dense as the Earth's atmosphere.

But maybe it had life before. Does it still have life today? We do know it has running water. That's a recent finding. We knew it had ice on the North and South poles, but now we know there's water running on Mars—it has the chemistry. We always look at the chemistry. What can support life? Do you have hydrogen, oxygen, sulfur?

DR. LATANISION

That's a good beginning.

DR. NEWMAN

Yeah, it's like a chemistry candy shop for life to exist. I think life wants to exist. We just have to prove it.

DR. LATANISION

I know that when you were Deputy Administrator at NASA that public-private partnerships were a major part of your agenda. Are they still functional and operating since you left?

DR. NEWMAN

Absolutely. I think it's a key. There are a lot of lessons learned, of course, but the rest of the government agencies are really trying to look at NASA and adopt that model. And you want to get it right; it needs the public investment but then you get the private folks who can move faster or quicker. It's really kind of magical when it works out. But it's 50/50 sharing; it can't be all dependent on the government or private folks to come in. They have to learn hard lessons, especially in human space flight and space flight in general. It's hard, so you're not going to get it right every time. The physics still rules. We have the rocket equation, for example, and it's really tough. So you have to keep learning. We're talking about a culture of safety and that's, again, systems engineering and a culture of safety. You can't skip steps. That's why it's a give-and-take with the government helping the private folks, the private folks coming along and trying to help the government be more innovative, be quicker. I think it's a really good model that can help us do more and move with a little bit more agility into the future. It allows for disruptive innovation.

DR. LATANISION

Well, I think that public-private partnerships are absolutely required to do this. Frankly, the costs are such that I don't think it can be done by governments alone, but I think it can be done by a partnership. I think that's a major contribution that you've made during your years at NASA, and I applaud that.

DR. NEWMAN

Oh, thank you. It's 10 years of work and everyone over the last decade or decades at NASA has been involved in it. I'm really glad that it is starting to pay off and it's taken as a model going forward for other agencies as well.

DR. LATANISION

On a similar subject, and this is on the exploration of space, how did you come to develop the BioSuit™? What inspired you to look at developing an alternative to suits that astronauts had been using for decades and create the BioSuit™? How did you do that?

DR. NEWMAN

I was just asking a simple question. Can we do better? We have these amazing spacesuits that are gas pressurized and they're your life-support system. They're providing everything that we take for granted here in our life-support system on Earth but are taking a spacecraft and shrinking it around a person. That space suit is the ultimate engineering challenge to me, because it means considering all the same systems to keep a person alive. Especially because I've been always thinking about the Moon and Mars in terms of planetary environments (i.e., not just thinking about low-Earth orbit where you're floating) and considering gravity on the Moon or Mars—I wanted astronauts to be like an Olympic athlete. I was an athlete growing up, and that just made sense to me. So I asked, do we have to be in this pressurized balloon that I can't move in? I'm wasting up to 75% of my energy in a conventional spacesuit. No, I want to find life; I want to search these planets!

So there had to be a way to flip the design paradigm. And rather than taking all the systems from a spacecraft and shrinking it around a person, I said, what if we start with a human body and design a suit—a life-support system and a suit—a very mobile suit from the skin out? And so, literally, it's this kind of crazy idea: a second skin. Space suits don't look like that, but is it possible to develop a second skin? The technology that can put the pressure (we call that mechanical counter pressure) directly on the skin? To keep someone alive, we have to provide 1/3 of an atmosphere, not a whole atmosphere. Just 30 kilopascals, a third of an atmosphere. And so we said, do we have the technology to do that? We use 3D scans of people—a digital astronaut. Because if we could produce a pressure layer, this mechanical counter pressure, then that changes the paradigm. Now it's very lightweight, now you have a lot of mobility, so it's just a win-win-win.

But again, it was one of those crazy ideas. And I have to compliment NASA, as the first funding for this was from NIAC [at the time, NASA Institute for Advanced Concepts]. So, for innovative advanced concepts, they said, don't send us a proposal if you can get this done in 10 years. We're looking for the far-reaching projects. And I said, okay, I think I have a crazy idea that might just fit that.

And that's where it started. Plus, another great story about that is that we wrote most of that proposal for the BioSuit™ on our boat. Gui, my life partner, and I were sailing around the world alone, circumnavigating, while on sabbatical and teaching kids about exploration by sea and space. And it was such a fun proposal to write because I thought ... "I'm going to tell them, 'I want to study giraffes; I have to figure out giraffe musculature (they have a built in g-suit). And I want to study snakes (that are kind of anti-gravity), and geckos who can run on the wall!'" I was just fascinated with how we can learn from nature and thinking, maybe I could take some of those learnings into the design of a spacesuit.

Almost two decades later, we're still working on the technologies. We've made a lot of improvements. We have prototypes and concepts. We don't have a flight system, but we've proven out a lot of the technologies that actually seem feasible to have a very mobile, lightweight, order-of-magnitude lighter suit—very, very flexible for Moon or Mars locomotion and exploration. And at the end of the day, again, I just want you to be a very high-performing astronaut akin to an Olympic athlete, so that all your energy and all your work is not wasted on fighting the spacesuit. Rather, it's getting you farther and farther, many more kilometers, so that you get to spend much more of your time on science.

DR. LATANISION

What is the astronaut reaction to these things? You can build it, but will they come?

DR. NEWMAN

Oh, the astronauts love it. They want to look good and they want a lightweight system. It's a very light system and you can work in it very well, so the astronauts are my biggest supporters. I even had one NASA administrator note the benefits of customizing it for different genders. You need an individual suit.

It's super simple. We do a 3D laser scan and add a lot of technology, and you get your personalized suit. Currently, NASA doesn't have small-sized suits for small people (mostly women). We can do better. To get back to your original question (what got me excited about this), to me, it was just this marvelous engineering challenge. There's only two ways to keep an astronaut alive; you have to put them in a gas pressurized shell, or you can apply the pressure directly to the skin. But the BioSuit™ just has so many advantages—for safety and weight and mobility and performance—that's why we thought, we have to give this a go.



Apollo 8 Mission image, Earth over the horizon of the Moon; December 24, 1968. Photo: NASA.

DR. LATANISION

That's fantastic. Has it become useful on Earth for various medical purposes?

DR. NEWMAN

We're always designing for space applications, but at the end of the day there's going to be a small number of astronauts wearing the suits or using the technology. However, all of the medical applications for pressure and compression here on Earth are very important. And those are easier design goals by comparison. For an astronaut, I have to apply one-third of an atmosphere, but it's 10% or less for any medical application here on Earth. For space, we have to invent active materials and some really advanced new materials for radiation protection. For here on Earth, we've already hit the pressures and the compression that we need. So, there are medical applications on Earth, and then there are some athletic applications as well; in warming up or warming down and for muscle performance.

This technology is applicable on Earth for both medicine and athletics. And I hope that we can continue this work into the future, so that the same technology can benefit millions of people, not just a few people traveling to space. That challenge to design for space with such an extreme environment, the great thing really is then thinking about the Earth applications. It's dual use, dual thinking. As a matter of fact, usually the teams are a biomedical student and an aerospace student working together, and a design student coming in, too, with everyone saying: How can we work together? Typically, our papers and thesis work then go in different directions—it might be the space applications, it might be more for medical, or it might be more for athletic performance.

DR. LATANISION

There's always been an incredible originality in the things you've done, and this speaks to that precisely. You've always had a knack for finding things that really make a difference, not only to astronauts; here you have it in

terms of biomedical engineering for people on Earth. I think that's a wonderful conclusion to that part of this story. So, I congratulate you on that.

DR. NEWMAN

Oh, thank you. You're very kind. There's more work to do.

DR. LATANISION

Yes, of course. There's always work to do, right? How does the MIT Media Lab fit into your history here? I'm curious about that.

DR. NEWMAN

Oh, great. Yes, so when I came back from serving as NASA Deputy Administrator, I was, you know, going to be a "normal professor" and just go back to AeroAstro at MIT. I was really excited to have students again and get back into my research. So, I did that when I first came back in 2017–2018 and I was minding my own business. Then the opportunity arose and I was asked by some colleagues and friends as the MIT Media Lab was looking for a new director. And they said "Hey, Dava, would you be interested in this?" And I love the Media Lab because it goes with my ethos of putting art, design, engineering, and science all together.

I always thought of the Media Lab as a nice microcosm of MIT—we can put people together, and we enjoy working together, and we can learn so much. I don't need to sit around the table with just a whole bunch of rocket scientists, because I know how they think. But boy oh boy, do I learn a lot when I'm sitting around the table with everyone. I can still be focused on my search for life and human exploration, but when I'm sitting around the table with a composer and a designer, oh my goodness, they're going to teach me a lot. So that was my interest in going to the Media Lab, and it was good timing for some new visioning.

At that point, the Media Lab was 40 years old, so we started asking, what do the next 40 years look like? What are we going to do in the future? And for me, it was really important that it is always going to be with our students, with the young folks. We began very intentionally hiring new faculty, bringing on the new faculty of the future. We also focused on getting faculty positions that were from the Media Lab as well as cross-institute. So, for example, the Media Lab program called Media Arts and Sciences (MAS), but also with AI; or hiring an architect to come into a design and MAS position. These folks really have dual appointments. It's taking the best of the Media Lab

and then really connecting it to MIT (which, is pretty awesome) and to MIT's priorities and initiatives. So that was some of the work that I did over four years of leadership; I served as the director and focused on enhancing culture, hiring faculty and bringing in new students.

I also focused on the strategy of asking and answering, "What are the big challenges in the next 10 to 20 years that we could best contribute to?" We put together that strategy, and collective areas came out of that. There's, of course, AI, but the Media Lab's specialty is human design. Do we have responsible AI? Are we designing human-centered design? This is really important. Not just the algorithms (we do plenty of algorithms)—but is it working for humanity or not? And we have to be willing to say if it is or not. That's a big area and the Media Lab stretches across about 500 people, so we have a lot of expertise and human-centered AI (or "life with AI"). Now again, this is four years ago, but we could see that this was coming. The first paper for agentic AI was written 30 years ago. It's come full circle.

We're also thinking about the health-related aspects because the Media Lab also has great expertise in health. And we call that "connected mind and body"—so health for the body, but also mental health and wellness. We specialize in the "Internet of things," but now we have the Internet of things for sensing and wearables for health and wellness, and that's going to be pervasive and much, much more of the future. The Media Lab has really been foundational for the "Internet of *all* things," as I call it. We're really putting a focus on human health, the connected mind and body, and then superhumans. Superhumans are out there, enhanced with robotics.

The Media Lab is also looking at and considering planetary stewardship, one of my passions. So, thinking about future worlds—future worlds are, of course, about life out there in the future but, as we've talked about, we have to take care of Spaceship Earth. What's the bold vision for the design and action for the world we want to live in? I think that's the simple question for planetary health.

DR. LATANISION

That that leads me to another question. I think technology at best shows a social purpose. You led MIT's technology and policy program for many years, and I wonder, with the rapid advance of technology over the last decade or two, are we in danger of diminishing the public trust in technology? For example, let me be more concrete: I think the Internet and the Web have been wonderful additions

to our technology. They provide us with information all over the planet, but they've also provided a capacity for people who wish to do harm, to abuse the system and create havoc. I wonder, now, with the evolution of AI, whether we're extending this information-age dilemma to an even greater extent. Are we putting the public trust and technology at risk, or how should we not do so? How should we manage this? What's your thought on that?

DR. NEWMAN

Well, I think we have to be transparent about this. The public trust has been eroded, I think, but I think erroneously so. As educators, as scientists, as engineers—we have to be speaking to the public more about our technologies. Technologies aren't going to save the day; I don't believe that, as a technologist. We need to be speaking about the ethics and the right way to use technology. Because technology has always been here and people have always been worried about technology. Now, AI is just the latest technology, and it's very powerful. I think it's a human choice how we use it and how we're called to use it and our responsibility to use it.

Can we use it for education, where we equalize the playing field? And every kid has access to some great agents, if you will? What are they interested in? What are they passionate about? What do kids want? At MIT, we have a "Day of AI" for K-12 students and teachers. And we are very frank with the students. You can use it for good. You can use it for bad. What are your interests?

I think you have to be very transparent, right up front. Let's have this discussion and listen. I don't think it's going to take over the world. I think it's a really useful, powerful tool. And as engineers but also as designers, it's our responsibility: How are we designing these algorithms? That's step one. We have to get back to being responsible, taking accountability, and having really transparent discussions about this.

You mentioned the Internet, and that was the dream—it was going to democratize and give access to everyone. And it did in a way. But we didn't foresee the companies and that profit model and how that would take off. So, what's coming next with AI? Especially with generative AI? I think genbio is coming next. I see this technological "supercycle," with generative AI kind of morphing into genbio. And this idea of the "Internet of all things"—we're measuring and monitoring and sensing almost everything, or we have the capability to do that. I think that's where the technology is going.

Humans are designing and inventing this, so I think it's definitely within our power to ask the hard questions. And humanity's been faced with this for all time, especially when thinking about peaceful or war times. You get to ask those questions about how you are going to use your technologies. Are you going to use them for good? Or not?

I think it's really a responsibility for all of us, now, at the front end. How are we going to use these technologies? What are they made for? Because they offer amazing potential for education and learning. And then even for work, not so much that they're taking jobs—I want to create the work of the future. What are those high paying jobs in the future using these beautiful technologies and tools? So, we have to reinvent it; we have to be forward thinking. Change is hard, but it's important to not get entrenched because technological progress is moving very rapidly. The exponential is actually hard to keep up with because our other systems don't move quite at exponential speed.

At the end of the day, let's have serious, transparent conversations about it. Let's make sure to keep humanity first, and I would extend that to all living things. I think if we start from that point, then we can see some really wonderful, beautiful uses that that really help people. But if it's only going to help a few, or if it's very much just a business model, that's not going to change the world. So let's have these real discussions and debates. I'm an eternal optimist, so I think we can get it right. We know we have this chance. That's why it's such an important question right now. It's such an important debate. This is complex. These systems are complex. There are no silver bullets, no easy answers. But let's engage and see how we can best use our rapidly evolving technologies.

DR. LATANISION

I generally agree with that. I think any new technology is a double-edged sword. It all depends on how you use it. I don't want to get too far into this, but my concern is that this technology is developing with virtually no standards or regulation. And it's providing an opportunity for scammers, for example. The density or frequency of scamming has increased dramatically. And it's going to increase even more if we don't do something to control it. It can be enormously, supremely useful. But it must be done in a way that is thoughtful, and I don't think we're doing that right now. That's my concern.

DR. NEWMAN

I agree with you. Going unregulated typically doesn't work out well. In this case, I look at the European stan-

dards because they're ahead of us, and those standards are logical and well thought out. I think we need to look around and say, who's doing this really well? Who's doing this right? And some companies are as well. So, taking some of those policies, some of those regulations, maybe we can scale that. I think there's a place to start, but I agree with you. We should make those decisions; we should try to accelerate some policy and some regulation and get them implemented.

Is it working for everyone? That's the way I approach it. For example, with an AI algorithm, I say, "Is it working for everyone in this room?" And typically, the answer is no. So, if you look around a diverse room and ask if it's working for everyone—if we can answer that question and it's working for everyone, then we know it's working. And until we can answer that question, I'll just say it's not working. If it doesn't work for me, then I know it doesn't work for a whole bunch of other people as well. So that's where we have to be much more intentional. We're at the infancy of this. Let's ask those hard questions. Let's hold each other accountable as colleagues, as academics and industry folks, who are really designing the field and this technology.

DR. DAVID BUTLER

If I could ask a follow up question, circling back to something you were mentioning before about communication, I was wondering: In your capacity of working with a variety of folks in the MIT Media Lab, what you are learning from artists and designers about communicating complex technological engineering problems? And, equally, what are you learning from the students in your program about that same communication challenge?

DR. NEWMAN

David, thanks for the question. I love that question. At MIT, for our students, we have a communications requirement, and that used to be written (of course) and oral communications. But I think a lot of people weren't putting emphasis on visual communication, which gets to your point. We know a picture is worth 1,000 words. I think in terms of communication, first, it's about helping creativity. Every little person you've ever met is infinitely creative. What happened to them? We go through education and all of a sudden, there's a right answer and they try to get it right, and that's a terrible thing. We want to go back to everything I learned before kindergarten. We have to be, I think, more like that—more childlike in learning, questioning, and playing.

The artists and designers, in my experience (and I live with an architect and I've learned a lot from Gui), a lot of what they bring is the visioning, opening the door to possibilities. Creativity is not one answer; it's "let's explore the concept." I think it brings in really rich discussion. With artists, I love the visionary approach. Just think about it, for example: Michelangelo, he has a big

How do we have action and awareness on behalf of Spaceship Earth, so that we can live in balance with our resources?

hunk of marble. How did he envision David, right? How could you do that? To me, that's just amazing; all of that creativity and such great talent to vision, to know what it's going to look like. I find that when I have artists and designers on my teams join the engineers, we make each other better because they're seeing that future vision and they're communicating it, lots of times with a sketchbook or something like that. Engineers, we might jump on the computer and be in MATLAB or write some code or something like that. It's so great to learn from the other disciplines and say, what can we do together?

At MIT, design is now our second favorite minor chosen by the students. They get it. Design thinking is a real thing. And they know that they have to learn some other skills. That's something that's changed over the last decade or two decades—the triad of communication to be more sustained across written communication, oral communication, and visual communication. We know that there's learners of all types, too, so I like to look at that triad of communication a little bit more holistically. And all of us need to work on all elements of communication. I just love the visualization that our artists and our design colleagues bring to the table. They've taught me an enormous amount as an engineer.

DR. LATANISION

Let me pose a closing question to you. You've had a lot of experience in academia. You've had experience in innovative research and development activities. You've had tremendous experience in technology- and policy-related

matters. Where do you see Dava Newman going next? What's next on your agenda?

DR. NEWMAN

Oh well, it's what I've been working on kind of my whole life: it's to the stars. I don't know about physically, but my mind is there and it's this search for life. It's the exploration. I'll never stop exploring my whole life. And it's really about my students and the next generation, and seeing how I can mentor and advise for that search for life in the universe coming full circle to the health implications, planetary health for Earth.

Most specifically, I'm very focused on working on women's health right now. Some of those technologies that we'll develop for space (the textiles for soft suits), we can look at applications for here on Earth. One example is for women's breast cancer. Can you imagine embedding these amazing sensors in preventative healthcare? The monitoring, measuring—let's see if we can do that, because that would be a game changer, especially when it comes to cancers. I'm really excited to see some of these things commercialized, sooner than later. I'd feel great about that. And there's a team of wonderful colleagues I'm working with on that.

Every day, I get up and say what's the most important thing I can be working on? And that's planetary health. From space, how can we help? We have the data. We have the sensors. So, we're immersing people in what we call "Earth Mission Control," and sharing the data. 100 terabytes per day of data—what do we do with that? We have to show people. But let's play it forward because we have real simulations based on data. We know that the next flood is coming, the next wildfire is coming. Well, can we show those data to people and get people out of harm's way? I really think we can do that through supercomputing, but also through these very immersive visual environments that let people do the simulation—be the answer. If it's a flood coming, how do you get people out of harm's way? If it's a fire, how do you get that information to the first responders?

My big dream is our phones, right in our pockets. You should have the information you need right on the cell phone, not on the laptop. The world doesn't all have laptops or even the Internet, but billions of people are running around this Earth with phones. So, how can we get people the information they need, especially when it comes to natural disasters and get them out of harm's way? I call it the Climate Pocket.

And then the flip side of that, it's really hard: How do we change human behavior? How do we have action and awareness on behalf of Spaceship Earth, so that we can live in balance with our resources? And that kind of takes me full circle to culture and ancient wisdom and indigenous folks. When I sailed around the world, we went to 33 island nations. And people who live on island nations, they know how to live in balance with their resources. They're flourishing. With space travel, we have closed-loop life-support systems that we have to provide. We have to live within all of our resources. Take that down to Earth; everyone has to live within those planetary boundaries and really appreciate all the resources and still live well and flourish. To me, that kind of goes full circle—I'm inspired by looking outward, searching for life, and then bringing that back to the health implications on Earth. My specialty is astronauts and biomedical work, and then always keeping very mindful of planetary health. These are pretty amazing things that I get to work on and think about.

DR. LATANISION

Yes, they really are. We mentioned the concept of mentors a couple of times during this conversation. You've had experiences and a career path to this point that would be an inspiration to any young person. I just have the feeling that if anybody's going to pull off what you've described in terms of the interface between Earth and space and making it more livable for everybody, I think you're going to do it. And I think it's partly because of the fact that you are such an inspiration. This has been a wonderful conversation. I hope we'll have a bunch of kids reading this.

DR. NEWMAN

Thank you so much. And thank you very much for the interest. I'm honored and I really appreciate the National Academy of Engineering doing these interviews. What a thrill. And, exactly. Let's blast it out there. I'm a lifelong educator, so I always say, it's one student at a time. It's one little person at a time, because they can change the world if they're taught that lesson I was taught: Just dream big. Don't accept "no." It takes a lot of hard work and effort, but we can do it. I believe in the human spirit for adventure, for exploration, and, again, for scientific and educational benefits for all.

NAE News and Notes

NAE Newsmakers

John Alf Lennart Agren, professor emeritus of materials science, KTH-Royal Institute of Technology, was awarded the **Adolf Martens Memorial Steel Lecture Award** by the Association for Iron & Steel Technology. The award recognizes individuals who have made outstanding lifetime contributions to the fields of physical metallurgy and computational materials science. Professor Agren's work has significantly advanced the understanding of steels, superalloys, and cemented carbides, as well as powder metallurgy and heat treatment, and has had a lasting impact on both academia and industry.

Anantha P. Chandrakasan, dean, School of Engineering, Massachusetts Institute of Technology, is being awarded the **Helen Chin Schlichte Community Builder Award** by the Asian Community Fund (ACF) at the Boston Foundation. The award honors leaders who uplift solidarity with other communities and promote connection, mutual understanding, and collective progress. He will receive the award at the Third Annual "Rising Together" Gala in Boston in October.

Birol Dindoruk, director, Interaction of Phase Behavior and Flow (IPB&F) Consortium, University of Houston, earned the Society of Petroleum Engineers (SPE) **Improved Oil Recovery (IOR) Pioneer Award**, for his research and technological contributions in improved and enhanced oil recovery. Over the course of 30 years of service in the field, his work in carbon dioxide flooding, misci-

bility prediction, solvent injection processes, and reservoir fluid characterization has helped bridge the gap between fundamental research and field-scale applications.

Elazer R. Edelman, Edward J. Poitras Professor in Medical Engineering and Science, Massachusetts Institute of Technology, has been named the recipient of the 2026–2027 **James R. Killian Jr. Faculty Achievement Award**. Professor Edelman is being honored for his work at the interface of engineering, science, and medicine, and for significant contributions to tissue engineering and to deciphering the fundamental biological processes underling cardiovascular disease.

Stephen R. Forrest, Peter A. Franken Distinguished University Professor of Electrical Engineering and Paul G. Goebel Professor of Engineering, University of Michigan, has been elected a fellow of the **Royal Society**.

Dan M. Frangopol, Inaugural Fazlur R. Khan Endowed Chair of Structural Engineering and Architecture Emeritus, Lehigh University, received the **2026 Raymond C. Reese Research Prize** from the Structural Engineering Institute of the American Society of Civil Engineers (ASCE). He shares the award with Sunyong Kim and Yanzhi Yang for their paper, "Optimum Seismic Retrofit of Deteriorating RC Bridge Columns Based on Risk, Cost-Benefit, and Real Option Analyses." The award was presented at the Structures Congress in Boston on May 1.

Amit Goyal, SUNY Distinguished Professor and SUNY Empire Innovation Professor, State University of New York College at Buffalo, was recognized for his transformative contributions to superconducting technologies through the development of advanced coated conductors with the **ICSM 2026 International Career Achievement Award in Superconductivity**. The award was presented at the 11th International Conference on Superconductivity and Magnetism held in Türkiye in April.

Carol K. Hall, Worley H. Clark, Jr. Distinguished University Professor, North Carolina State University, received the **Alexander Quarles Holaday Medal for Excellence**, the highest honor bestowed by NC State and the university's Board of Trustees, on May 5. She shared the award with Francis de los Reyes III. The two received the medal for outstanding and sustained contributions to the university through achievements in research, teaching, or extension and engagement.

Geoffrey E. Hinton, emeritus professor, University of Toronto, and **Terrence J. Sejnowski**, professor and head, Computational Neurobiology Laboratory, and Francis Crick Chair, Salk Institute for Biological Studies, share the inaugural **Scientific Breakthrough Award** from the World Digital Technology Academy (WDTA) for their foundational development of the Boltzmann Machine—a precursor to modern AI tools. Their pioneering research bridged biological

intelligence and computational models. WDTA noted that their work is “the architectural bedrock for deep learning, generative AI, and the large-scale systems now driving digital civilization.”

Jen-Hsun Huang, CEO, Nvidia Corporation, received the **2026 Van Fleet Award**, presented by The Korea Society. The award recognizes Mr. Huang’s visionary leadership and his contributions to the artificial intelligence and semiconductor industries, which have become central to the evolving US-Korea economic partnership. The award ceremony took place at a gala in September in New York.

Ahsan Kareem, Robert M. Moran Professor of Engineering at the University of Notre Dame, received the **inaugural 2026 Wilfred W. Iwan Award for Mentors in Engineering Mechanics Research** from the American Society of Civil Engineers. The award recognizes excellence and leadership in mentoring in engineering mechanics research and pedagogy. Dr. Kareem was honored for educating and mentoring an impressive number of students, postdoctoral fellows, and practicing engineers who have gone on to improve the safety, sustainability, and resilience of civil infrastructure in the face of natural hazards and climate change.

Robert Samuel Langer, David H. Koch Institute Professor, Massachusetts Institute of Technology, was awarded the Cold Spring Harbor Laboratory **Double Helix Medal** for his “unyielding dedication to pushing the envelope in science, engineering, and medicine.” He was specifically honored as a prolific pioneer in biotechnology whose revolutionary discoveries have profoundly improved human health and revolutionized medicine. He received the medal at

the 20th annual Double Helix Medals gala on November 19, 2025.

Sir Cato T. Laurencin, University Professor and CEO, The Cato T. Laurencin Institute for Regenerative Engineering, University of Connecticut, was awarded the **2026 Othmer Gold Medal** by the Science History Institute. The medal, the Institute’s most prestigious award, honors individuals who have made extraordinary contributions to chemical and materials sciences. Dr. Laurencin was nominated for his groundbreaking work in the use of polymeric biomaterials chemistry and engineering to treat musculoskeletal conditions and to improve the human condition.

Asad M. Madni, independent consultant and retired president, COO, and CTO, BEI Technologies Inc., has been elected to the **National Academy of Artificial Intelligence (NAAI)**. According to NAAI, “This distinction is awarded to individuals who have demonstrated meaningful achievements and sustained contributions to the advancement of artificial intelligence. Your election reflects the recognition of your academic accomplishments, professional excellence, and growing impact within the global AI community.”

David K. Matlock, Armco Foundation Fogarty Professor Emeritus, Colorado School of Mines, was honored by the ASM Rocky Mountain Chapter with the **Charles S. Barrett Silver Medal Award Lecture** at the Colorado School of Mines. This lecture award is presented to those individuals whose contributions to the science of metallurgy most exemplify the efforts and career achievements made by Dr. Barrett, who was a pioneer in the study of the structure of metals and the application of x-ray diffraction techniques. Dr. Matlock presented the lecture, “Learning

from the Past: Perspectives on Failure Analyses with an Emphasis on Fatigue.”

Chad A. Mirkin, George B. Rathmann Professor of Chemistry and director, International Institute for Nanotechnology, Northwestern University – Evanston, will receive the **2027 Priestley Medal** from the American Chemical Society in recognition of his landmark research and distinguished service to the field of chemistry. Professor Mirkin is a global leader in supramolecular chemistry, nanoscience, and nanotechnology. His work has led to the discovery and development of new classes of nanomaterials, which has led to life-changing diagnostic tools and therapeutics based on the principles of structural nanomedicine.

Glaucio H. Paulino, Margareta E. Augustine Professor, Princeton University, was recognized for distinguished achievement in engineering mechanics by the ASCE Engineering Mechanics Institute with the **2026 Theodore von Karman Medal**. He was specifically cited for pioneering contributions to the field of mechanics, including advances in geometric mechanics associated to origami and tensegrity engineering, which led to the creation of multifunctional structures and configurational metamaterials with unprecedented properties.

Milo E. Rivero, Senior Advisor to the President & the Board, Manhattan University, received the National Academy of Construction’s (NAC’s) **Richard L. Tucker Award** on September 25 at NAC’s Annual Meeting in Nashville, Tennessee. The award was established in 1999 to honor those who have substantially impacted the engineering, design, and construction industries throughout their careers.

John A. Rogers, Louis Simpson & Kimberly Querrey Professor of Materials, Northwestern University – Evanston, has been elected into the **American Philosophical Society** in recognition of extraordinary accomplishments in his field. Professor Rogers is a world leader in flexible, wearable electronics and bioelectronic medicine. He and his team created a new class of technology called “transient electronics,” devices that harmlessly disappear in the body or the natural environment after no longer needed.

David W. Roop, principal consultant, DWR Associates, LLC, has been inducted into the **Virginia Tech Academy of Engineering Excellence**. This top honor from Virginia Tech’s College of Engineering recognizes remarkable alumni for their career achievements and meaningful impact in their fields. Mr. Roop is a nationally recognized leader in electric power transmission, grid reliability, and infrastructure resilience.

Dawn M. Tilbury, Ronald D. & Regina C. McNeil Department Chair of Robotics and professor, University of Michigan, has been elected as a **Corresponding Member of the Austrian Academy of Sciences**

(ÖAW). Election to the ÖAW, one of Europe’s most distinguished scientific institutions, is a significant honor that reflects a career of exceptional achievement. Dr. Tilbury is recognized for her sustained contributions to the fields of control systems, manufacturing systems, and robotics.

Andrew Stuart Whittaker, SUNY Distinguished Professor, University at Buffalo, is a recipient of the **2026 UB President’s Medal** in recognition of extraordinary service to the university.

The winners of the **Global Energy Prize 2026** have been chosen by the Global Energy Prize International Award Committee. For the creation of large-scale systems for monitoring, control, and situational observation of smart grids, **Yilu Liu**, Governor’s Chair Professor, University of Tennessee, was awarded the **Traditional Energy Prize**. **Yushan Yan**, Henry B. Dupont Chair, University of Delaware, received the **Non-Traditional Energy Prize** for forward-looking ideas and work facilitating clean hydrogen production technology and progress in transforming this technology into a global commercial project. The **New Ways of Energy Application Prize** was presented to

Johann W. Kolar, professor emeritus, Department of Information Technology and Electrical Engineering, ETH Zurich, for breakthrough advancement in energy conversion technology to drive energy efficiency, electric mobility, and renewable energy systems.

The California Institute of Technology in May announced its **2026 Distinguished Alumni Award** recipients, the highest honor the Institute bestows upon a graduate. They are **Leonidas J. Guibas**, Paul Pigott Professor of Engineering, Stanford University, and principal scientist, Google DeepMind; **Eddy W. Hartenstein**, retired founder and CEO, DIRECTV, Inc.; and **Shouleh Nikzad**, chief technologist, NASA’s Jet Propulsion Laboratory.

NAE members included in the newest class of **American Academy of Arts & Sciences inductees** are **Mark G. Allen**, Alfred Fittler Moore Professor, University of Pennsylvania; **Andrew G. Alleyne**, dean, University of Minnesota; **Kyriacos Athens Athanasiou**, Distinguished Professor and Henry Samueli Chair, University of California, Irvine; and **Henry T. Yang**, chancellor, University of California, Santa Barbara.

NAE Welcomes New Leadership: Election Results Announced for Chair, Vice President, and Councillors

On June 2, the NAE announced the results of the 2026 spring elections. This year’s outcomes reflect both continuity and renewal within the Academy’s leadership. The NAE reelected the Chair, Vice President, and two Councillors who will continue their service on the NAE Council, and elected two new members to the Council.

These leaders—returning and new—bring a breadth of expertise, vision, and commitment that will strengthen the Academy’s mission. Their collective experience will help guide the NAE in addressing emerging challenges and seizing opportunities across engineering, science, and technology. All terms began July 1, 2026.

James O. Ellis Jr., retired US Navy Admiral and former Councillor, was reelected to a two-year term as Chair of the NAE Council. He will continue to bring deep experience in national security, energy policy, and strategic leadership. He currently serves as the Annenberg Distinguished Visiting Fellow at the Hoover Institution, where he leads

several initiatives focused on global policy and technology strategy.

Wesley L. Harris, Charles Stark Draper Professor of Aeronautics and Astronautics has been reelected to a second four-year term as Vice President. He will continue to bring his thought-provoking wisdom and wealth of knowledge and experience to the leadership team of the NAE.

Fiona Doyle, Donald H. McLaughlin Professor Emerita and Distinguished Professor Emerita of Materials Science and Engineering at the University of California, Berkeley, and **Elsa Reichmanis**, Professor and Carl Robert Anderson Chair in Chemical Engineering in the Department of Chemical and Biomolecular Engineering at Lehigh University,

were both reelected to serve second three-year terms as NAE Councillors.

Newly elected to serve three-year terms as Councillors are **John Wall**, Vice President and Chief Technical Officer, Cummins, Inc. (retired), and **Wanda Reder**, Reder Advisors, LLC (formerly Grid-X Partners, LLC) (retired).

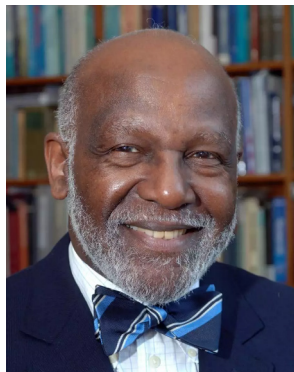
The NAE extends its sincere gratitude to outgoing Councillors **Anjan Bose** and **Cherry Murray** for their dedicated and impactful service. Their contributions have strengthened the Academy's work, advanced its mission, and helped shape the direction of the NAE. As of June 30, Anjan Bose concludes six continuous years of exemplary leadership on the NAE Council, providing thought-

ful guidance and steadfast commitment throughout his tenure. Cherry Murray concludes three years of distinguished service and departs the Council to begin her term as International Secretary for the National Academy of Sciences.

The Academy also extends its sincere appreciation to all candidates who participated in this year's election process, as well as to the NAE members whose engagement ensures the vitality of our governance. The NAE looks forward to the continued contributions of our Council members as they support the Academy's strategic priorities and uphold its values of excellence, integrity, and service.



Admiral James O. Ellis, Jr.
Chair



Wesley L. Harris
Vice President



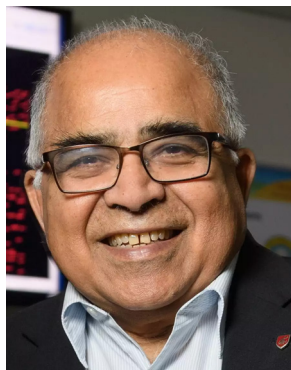
Wanda Reder
Councillor



Fiona Doyle
Councillor



John Wall
Councillor



Anjan Bose
Councillor (Outgoing)



Cherry Murray
Councillor (Outgoing)

Howard B. Rosen Named Next Executive Officer of the National Academy of Engineering



Howard B. Rosen

The NAE announced that Howard (“Howie”) B. Rosen is the organization’s next Executive Officer, effective August 24, 2026. Rosen was selected through an open search process that identified multiple well-qualified candidates for the role. He stood out for his outstanding contributions to engineering and his extensive leadership experience, including service as an NAE Councillor since July 2019 and as NAE Home Secretary since July 2024.

Rosen brings a distinguished record of executive leadership in engineering and life sciences. He previously served as President of ALZA Corporation, Vice President of Gilead Sciences, CEO of AcelRx Pharmaceuticals, and President and CEO of Pearl Therapeutics. At ALZA,

where he spent 10 years, he held roles including Vice President of Product Development, with responsibilities spanning product development, portfolio management, corporate and new product planning, mergers and acquisitions, R&D planning, and technology ventures. At Gilead Sciences, as Vice President of Commercial Strategy, he oversaw strategic marketing, global brand management, health economics, competitive intelligence, market research, and the company’s overall portfolio and business planning.

“Howie’s experience building and leading engineering organizations, combined with his deep understanding of the NAE gained through his service as Councillor and Home Secretary, make him exceptionally well prepared to oversee and manage the programs, activities, and operations of the NAE in fulfilling its mission,” said Tsu-Jae Liu, President of the National Academy of Engineering.

Rosen was elected to the NAE for the invention of bioerodible polymers and leadership in the development of drug-delivery systems. His technical interests center on managing the multidisciplinary work required to bring life-sciences products from concept through launch and market support, in both start-up and established companies—with particular focus on market analysis,

R&D portfolio management, strategic planning, and international markets. He has also worked extensively in drug delivery, including transdermal, oral, implantable, ocular, transmucosal, and pulmonary systems.

Rosen currently serves on the boards of directors of Entrega, Inc. and Hammerton, Inc. He is an Adjunct Professor in the Department of Chemical Engineering at Stanford University and a Lecturer in Management at the Stanford Graduate School of Business, where he teaches entrepreneurship. He is a past member of the Stanford University Advisory Council on Interdisciplinary Biosciences and the Stanford School of Engineering Advisory Council, and currently serves on the Biomedical Engineering Advisory Board at City College of New York and the Industry Advisory Board of the Lampe Joint Department of Biomedical Engineering at the University of North Carolina at Chapel Hill and North Carolina State University.

“I am honored to take on this role,” said Rosen. “Having worked alongside NAE’s members and staff over the past several years, I’ve seen firsthand the caliber of talent and commitment to advancing engineering for the benefit of society. I look forward to building on that foundation and supporting the NAE’s mission in this new capacity.”

2026 Bernard M. Gordon Prize for Innovation in Engineering and Technology Education



Photo: MIT ChemE.

(L-R) Lance Collins, NAE Gordon Prize Committee Chair and Vice President for the greater Washington, DC, area at Virginia Tech; Simon Pitts, Director and Head of the Gordon Institute of Engineering Leadership at Northeastern University; Professor T. Alan Hatton, Gordon Prize recipient; Tsu-Jae Liu, NAE President; Paula T. Hammond, MIT Dean of Engineering; and Anantha Chandrakasan, MIT Provost.

T. Alan Hatton, Ralph Landau Professor and director of the David H. Koch School of Chemical Engineering Practice, Massachusetts Institute of Technology (MIT), was awarded the 2026 Bernard M. Gordon Prize for Innovation in Engineering and Technology Education on April 30. The award was presented at a cel-

ebratory dinner held at the Samberg Conference Center, MIT, Morris and Sophie Chang Building.

The prize was awarded “for advancing an immersive, industry-integrated educational model that has produced thousands of engineering leaders, strengthening US technological competitiveness and workforce readi-

ness.” NAE President **Tsu-Jae Liu**, and Simon Pitts, director and head of the Gordon Institute of Engineering Leadership at Northeastern University, presented the award on behalf of the National Academy of Engineering. The public lecture will take place on October 4 during the 2026 NAE Annual Meeting.

2026 Bernard M. Gordon Prize Acceptance Remarks by T. Alan Hatton

Thank you for your warm words of congratulations and support. It is truly an honor to accept this incredible award on the behalf of the School of Chemical Engineering Practice and on behalf of all who have contributed to its successful evolution over the decades. This is a truly unique program that has led to the

education and professional growth of almost 4,000 students over the past century, and launched many of the titans of industry, academia, and government. Thank you, Bernard Gordon, for your generous support of this award, recognizing the importance of engineering education for the future strength of our society.

Arthur D. Little conceived the program when, in his first job upon graduation, he was given the daunting task of overcoming production issues at a paper company following the abrupt departure, with all his papers and plans, of the engineer in charge. Little quickly recognized that while he'd had an excellent educa-



Photo: MIT ChemE.

T. Alan Hatton

tion in the science and principles of chemical engineering, he had no idea as to how to *practice* chemical engineering. So, he and William Walker conceived of the practice school concept in which, following completion of coursework, students would work as independent teams within industrial facilities on real-world problems with joint on-site supervision by MIT faculty and company personnel, and get academic credit for their efforts. And the rest, as they say, is history. The program was founded in 1916, so it is 110 years old this year!

While the operational details have undergone changes over the decades in response to changing economic and industrial demands, the underlying principles have not been compromised at all, and the program still strives to meet the ideals espoused so long ago. Indeed, the Practice School is designed to challenge the students more than they have ever been academically, by taking them well beyond their comfort zone, driving them to learn and then practice new skills in ways that cannot be learned effectively in the university academic environment. A key to the success of the program is the incredible cadre of lecturers, the Station Directors—their

role is to work with the host companies to define projects that have a strong pedagogical focus, while still providing great value to the companies, and then to provide on-site mentoring of the students when they are at the companies, to help guide them toward these new skills.

Over the past 30 years, the program has evolved to be more flexible and expand the number of companies and industries with which we work, becoming a truly global operation with stations across the globe. We now have as Station Directors a dedicated team of retired professionals and company execs who are keen to share their expertise with the next generation of engineers to move our profession forward. New courses have been developed to prepare the students for their real-world experiences, to keep them abreast of new technologies, and to utilize new tools, such as AI, as they are developed. A great strength of the program structure is its versatility in being able to respond to changing industrial needs and, indeed, to changing industries. We look forward to deploying the Gordon Prize Award funds to further enhance and expand the program, and have formed a committee com-

prised of academic and industrial leaders to explore the most effective way to do so.

I was fortunate to have been associated with this truly innovative and impactful program since I originally signed on as Program Director for a three-year stint in 1989. I soon became enamored of the program, however, and carried on for another 33 years. It has been a wonderful journey, invigorating always but also challenging as we navigated the vagaries of international economies, adapted to differing cultural norms of hosting companies and countries, new communications and other technologies, and, not so occasionally, graduate student antics. But I would not have wished for anything else. I am truly pleased that, upon my retirement a year ago, Professor Fik Brushett assumed the mantle of Program Director, and hope that he derives as much pleasure and satisfaction from running the program as I have over the years.

I have cherished the long-term support and friendship of Practice School Administrative Assistants, first Carol Phillips and then Beth Tuths—they defined how the Practice School should interface with students, staff, and companies, and have had an enduring and lasting impact on the lives of over a thousand students over the past three-and-a-half decades. And thank you, Amanda Bendzel for continuing their good work.

The Station Directors are the true not-so-secret sauce in the success of the program, and I give my heartfelt thanks to them all for their contributions and dedication to the program and to the students. I treasure the long-standing personal friendships that I have developed with many of these colleagues over the years.

Without the students, of course, we would have no program. I want to recognize the thousands for their intellectual curiosity, their creativity, and their work ethic. With grit and determination, they invariably delivered results under tight timelines and beyond expectations (mostly at the expense of sleep). They are the true stars of the program, and we deeply appreciate their contributions.

Similarly, we would not have a program if it were not for the depth of engagement of the hosting companies—they open their facilities and resources to provide a crucial “home,” challenging projects, and strong mentoring for the students. Their sponsorship is invaluable and we thank them for it.

As in any academic pursuit, its success or otherwise depends on the support of the department heads, and here I have been very fortunate to have had the strong backing of **Bob Brown, Bob Armstrong, Klavs Jensen, Paula Hammond, and Kris Prather**—I take comfort in knowing that I survived working with them all!

Of course, without the strong support and understanding of my lovely wife, Marianne, and children, Ross and Kent, I would never have been able to juggle the demands of a hectic globe-trotting schedule with those of a family life. Thank you for all your loving support, Marianne—you have no idea how much I value that you

have stuck by my side for exactly 50 years and one week today.

I would like to thank **Monty Alger** for spearheading the nomination for this award, and all those who helped in this process—Bob Hanlon, Beth Tuths, Amanda Bendzel, and many others; and also those who took the time to write supporting letters—thank you!

Finally, I would especially like to thank the NAE Gordon Prize Selection Committee for according the Practice School this great honor, and for providing the incentive to further the goals of the program and expand its reach. Thank you so much!

Ninth China–America Frontiers of Engineering Bilateral Symposium Held in Hong Kong

The 2026 China–America Frontiers of Engineering (CAFOE) Symposium was held April 13–16 at The Chinese University of Hong Kong. NAE and Chinese Academy of Engineering member **Bruce Logan**, Evan Pugh University Professor and Kappe Professor of Environmental Engineering at Pennsylvania State University, and Jing Cheng, member of the Chinese Academy of Engineering and professor at Tsinghua University, co-chaired the symposium. The NAE carried out the meeting in partnership with the Chinese Academy of Engineering, featuring The Chinese University of Hong Kong as the event host.

The first fully in-person CAFOE meeting since the COVID-19 pandemic brought together 60 outstanding early career engineers from China and the United States to discuss leading developments across

four key engineering fields. Opening remarks emphasized the importance of international scientific exchange, interdisciplinary collaboration, and engineering innovation in addressing complex global challenges. The four technical session topics included Carbon Capture, Utilization, and Storage; Fusion of Engineering Science and Traditional Medicine; Critical Metals and Materials: Separation and Purification; and Co-Design of Intelligent, Interdisciplinary, and Integrated Energy Systems.

Carbon capture, utilization, and storage is moving from laboratory research and proof-of-concept projects toward large scale deployment. The first session explored technologies for capturing, transporting, converting, and safely managing carbon dioxide, with particular attention to scalability, resource recovery, and the use of artificial intelligence. The

first presentation described an integrated approach that uses carbon dioxide and industrial residues to produce commodity materials while recovering critical metals. The next speaker discussed digital and intelligent technologies for the safe operation of long-distance carbon dioxide pipelines, including digital twins, corrosion prediction, and leakage monitoring. This was followed by a presentation on designing electrocatalytic materials that can convert carbon dioxide into fuels, chemicals, and low-carbon construction materials. The final talk described an artificial intelligence–driven framework for developing carbon capture solvents and processes, from molecular screening through industrial demonstration.

The session on the Fusion of Engineering Science and Traditional Medicine examined how biomedical



engineering, artificial intelligence, nanotechnology, and advanced sensing can support the modernization and evaluation of traditional medical approaches. The first speaker presented nanoscale technologies for cancer diagnosis and treatment, including nanoparticles derived from fucoidan, a compound used in traditional Chinese medicine, that can deliver drugs across tissue barriers. The next presentation described joint-on-a-chip systems that use human cells and microfluidic technology to model arthritis and evaluate herbal nanomedicines in a more human-relevant setting. The third speaker discussed computational methods and wearable sensors for tracking mental and physical health states and evaluating responses to interventions. The final presentation focused on flexible and wireless bioelectronic systems for detecting wound infections, monitoring surgical sites, and measuring intracranial pressure.

The rapid expansion of energy storage, electronics, advanced manufacturing, and other strategic industries is increasing demand for critical metals. The Critical Metals and Materials session focused on improving the efficiency, selectivity, and environmental performance of extraction, separation, purification, and recycling processes. The first talk provided a framework for understanding critical metal enrichment, separation of chemically similar elements, and production of ultra-high purity materials. The next speaker described ion-selective electrochemical technologies that could recover lithium, nickel, and other valuable materials from mined ores and recycled feedstocks. This was followed by a presentation on a lower-emissions process for extracting vanadium and producing high-purity products for energy storage applications. The final speaker discussed electrochemical leaching of unconventional lithium

resources at room temperature, with the goal of reducing energy use, toxicity, and environmental impacts.

The final technical session considered how energy generation, storage, transportation, buildings, and industrial systems can be optimally designed together. The first presentation reviewed advanced power electronic technologies for integrated energy systems, including artificial intelligence assisted design, digital twin monitoring, and new approaches to converter cooling. The next speaker examined the relationship among urban density, building height, transportation demand, and carbon emissions. The third presentation proposed a methodology for designing multi-energy systems around the principles of safety, resilience, and environmental performance. The session concluded with a discussion of artificial intelligence in power systems, including the need to combine machine learning with

formal guarantees for grid stability, safety, and operational constraints.

Audience participation was strong throughout the technical sessions, with presentations prompting extensive discussion about commercialization, system scaling, resource circularity, and the practical challenges of deploying emerging technologies. The interdisciplinary format allowed participants to identify connections among disparate topics, including the role of artificial intelligence across many of the technologies and the need for local engineering solutions that have broader global impact.

In addition to the formal presentations, two poster sessions gave participants the opportunity to share their own technical work and network informally. The meeting also included tours of The Chinese University

of Hong Kong's Multi-Scale Medical Robotics Center, an animal research facility supporting biomedical and disease research, and InnoPort, the university's innovation and entrepreneurship hub. A cultural visit to Victoria Peak provided participants with an opportunity to experience Hong Kong and continue conversations outside the formal symposium setting. The symposium program, list of attendees, presentation information, and poster topics are available through the 2026 CAFOE page at www.naefrontiers.org.

Funding for this activity was provided by The Grainger Foundation. The next China–America Frontiers of Engineering Symposium is expected to be held in the United States in 2028.

The NAE has hosted the annual US Frontiers of Engineering Sympo-

sium since 1995 and, in addition to CAFOE, has bilateral Frontiers of Engineering programs with Germany, Japan, and the European Union. These meetings bring together highly accomplished early career engineers from industry, academia, government, and national laboratories and provide opportunities to learn about developments, techniques, and approaches at the forefront of fields other than their own. The program also supports the formation of professional relationships and future collaborations among the next generation of engineering leaders.

For more information about the activity, or to nominate an outstanding engineer to participate in a future Frontiers of Engineering meeting, visit www.naefrontiers.org or contact Stephanie Houser at shouser@nae.edu.

2026 Yvonne C. Brill Lectureship in Aerospace Engineering

The American Institute of Aeronautics and Astronautics (AIAA) and the NAE are pleased to announce that Marilyn J. Smith, David S. Lewis Professor of Aerospace Engineering in the School of Aerospace Engineering at Georgia Institute of Technology, and Director of the Georgia Tech Army/Navy/NASA Vertical Lift Research Center of Excellence, has been selected as the recipient of the 2026 Yvonne C. Brill Lectureship in Aerospace Engineering.

Professor Smith will present her lecture “Rotorcraft—The New Frontier in Extrplanetary Exploration” on Monday, October 5, in conjunction with the NAE Annual Meet-

ing. The lecture will explore both the advantages and limitations of rotorcraft for extrplanetary missions, including rotorcraft design for extreme environments, opportunities to leverage current autonomous uncrewed aerial systems development, and mitigation of unknown planetary characteristics that could negatively impact mission requirements. The lecture will also identify research areas where innovations can lower risk in these long-term missions. Registration is free and open to the public.

The Yvonne C. Brill Lectureship in Aerospace Engineering was established in 2013 to honor the

memory of the late pioneering rocket scientist, AIAA Honorary Fellow, and NAE member **Yvonne C. Brill**. Brill was best known for developing a revolutionary propulsion system that remains the industry standard for geostationary satellite station-keeping. The lectureship emphasizes research or engineering issues for space travel and exploration, aerospace education of students and the public, and other aerospace issues such as ensuring a diverse and robust engineering community.

EngineerTeen 2026 Writing Contest Winners

On June 29, the NAE announced the winners of its [2026 EngineerTeen Writing Contest](#), “The Art of Engineering.” Students in elementary through high school were invited to explore the connections between art and engineering by creating an original piece of artwork that illustrates how engineers make the world a better place, accompanied by written reflections on their creative process. Students were challenged to apply the engineering design process—from research and planning to creation, testing, and reflection—to showcase at least three engineering contributions that improve society. Prizes were awarded to students based on grade level.

“Congratulations to the students selected as winners of this year’s EngineerTeen Writing Contest,” said NAE President Tsu-Jae Liu. “While art and engineering are distinct disciplines,

both rely on observation, imagination, and the ability to bring ideas to life. It is especially inspiring to see creative expression used to communicate the impact of engineering and the many ways it shapes our world.”

NAE congratulates the following first place winners:

- Verity Truitt, a fourth-grade student at Puesta Del Sol in Medina, WA, placed first among elementary school students with [“Engineers Power Our Past and Future.”](#)
- Chaitra Hasini Appani, an eighth-grade student at Mountain View Middle School in Bonney Lake, WA, placed first among middle school students with [“Engineering: The Design Behind It All.”](#)
- Grace Xie, an eleventh-grade student at Seven Lakes High School in Katy, TX, placed first among high school students with [“Sketching Solutions.”](#)

Awards for contest winners are \$1,000 for first place, \$750 for second place, and \$500 for third place. Winning entries, along with honorable mention entries, are published on the EngineerTeen website: www.engineerteen.org/23279. Additional winners are listed below.

Elementary School Winners:

- Second Place: Sofia Alanis Lara, [“Engineering Adventure: A Journey Between Earth and the Moon”](#)
- Third Place: Connor Kimbrough, [“Ideas and Engineers”](#)
- Honorable Mention: Ira Bolli, [“My Smart Clock That Helps Me Every Day”](#)

Middle School Winners:

- Second Place: Aydyna Johnson, [“Engineering All Around”](#)
- Third Place: Aanya Yadav, [“Engineering the Future”](#)



- Honorable Mention: Marisa Tantalà, [“The Art of Engineering!”](#)
- Honorable Mention: Yeema Liu, [“Gears of Possibility”](#)

High School Winners:

- Second Place: Audrey Wang, [“Engineering: Built for the Moments That Matter”](#)

- Third Place: Bomin Kim, [“Engineering for Peace of Mind”](#)
- Honorable Mention: Suri Shirali, [“Drawn Into Reality”](#)
- Honorable Mention: Sianna Walia, [“Learning from the Surface”](#)

The National Academy of Engineering applauds all participants in

the 2026 EngineerTeen Writing Contest for engaging with this year’s topic and sharing unique ideas and insights that highlight engineering’s role in the world around them.

Powering the Future Through Engineering Education

The engineers who will solve society’s biggest challenges may be sitting in today’s middle and high school classrooms. Yet for many young people, particularly those without access to mentors, professional networks, or role models, engineering never feels like a path within reach.

For Zoom Cares, expanding opportunity has become a defining focus of its philanthropic work through the \$10 million AI For Good commitment. As artificial intelligence transforms education, the workforce, and nearly every aspect of society, the company believes that preparing the next generation of innovators requires more than access to technology. It requires helping young people see themselves as future engineers, problem-solvers, and leaders. That vision led Zoom Cares to the NAE.

As Zoom celebrates its 15th anniversary, the company is investing in young engineers who will shape our future. Through a \$500,000 gift from Zoom Cares, the NAE will expand its Pathways into Engineering initiative by growing EngineerTeen, a program that engages students at a pivotal point in their educational journey through mentorship, connections with engineers, and real-world experiences. The program helps young people see engineering as both accessible and achievable while deepening



Zoom founder and CEO Eric Yuan and student attendees at the 2026 NAE National Meeting.

their understanding of how engineers improve lives.

“For too many students, engineering is a world they view from the outside. EngineerTeen changes that by inviting them in: into conversations with real engineers, into a community of peers who share their curiosity, into the sense that this field has a place for them,” said Simil Raghavan, Director of NAE’s Pathways into Engineering initiative. “When a student stops being a spectator and starts belonging, their whole sense of what’s possible begins to shift.”

For more than six decades, philanthropy has helped the NAE advance initiatives that strengthen both the engineering profession and its future workforce. This year marks the final year of the NAE’s Campaign for Leadership in a World of Accelerating Change, which strengthens the Academy’s ability to identify and promote expertise, provide trusted independent advice to government leaders, elevate and advance appreciation for engineering, and engage and inspire future generations of engineers. Zoom’s investment in EngineerTeen directly advances that final

goal, helping more young people discover pathways into engineering.

The Academy's distinguished members not only drive innovation through their own discoveries and leadership but also extend that impact through the companies and foundations they lead. That commitment is embodied by Zoom founder and CEO **Eric Yuan**, elected to the NAE in 2025, and Chief Technology Officer **Xuedong D. (XD) Huang**, elected in 2023. Their leadership reflects a shared belief in engineering excellence, innovation, and creating opportunities for future generations.

Xuedong Huang shared: "What excites me most about EngineerTeen is not only what students learn, but



Xuedong D. Huang

the confidence they gain to see themselves as engineers and problem-solvers. Engineering is about applying creativity, collaboration, and sound

judgement to challenges that matter. At Zoom, we believe connection drives progress and this collaboration with the NAE extends that belief to the next generation. I am proud to support an initiative that broadens access to engineering and helps young people prepare to lead responsibly in an AI-enabled world."

As artificial intelligence becomes an increasingly important engineering tool, EngineerTeen will help students understand both its potential and its limitations. The program emphasizes that while AI can accelerate innovation, engineering will always depend on human creativity, ethical judgment, collaboration, and the ability to solve complex problems.

New Staff Join the NAE

We are pleased to announce that Arzoo Rasoly has joined the NAE Finance team as an accountant. Prior to joining the NAE, Arzoo served as a senior accountant with International Business & Technical Consultants, Inc. for five years, where she supported the financial management of USAID-funded projects. In this role, she managed a broad range of accounting functions, including accounts payable and receivable, project accounting, financial reporting, reconciliations, budgeting, and compliance. She worked closely with program teams to monitor project expenditures, prepare financial analysis and reports, support audits, and ensure adherence to organizational policies and federal funding requirements. Arzoo holds a Bachelor of Business Administration from Rana University and a BS from Kabul University in Afghanistan. She is currently pursuing an MBA at the University

of the People, further strengthening her expertise in accounting, finance, and organizational management. Arzoo brings an international perspective shaped by her academic and professional experiences across diverse environments.

She is passionate about lifelong learning, professional development,



Arzoo Rasoly

and leveraging financial expertise to support mission-driven organizations. On a personal note, Arzoo enjoys spending time with family and friends, exploring new cultures, reading, traveling, and pursuing educational opportunities that foster personal and professional growth. Arzoo is based in Keck W825 and can be reached at arasoly@nae.edu.

We are pleased to announce that Lauren Stiller has joined the Program Office as our senior program assistant for The Grainger Foundation Frontiers of Engineering (FOE) program. In this role, she supports the planning and coordination of FOE symposia in the United States and abroad and assists the program director in helping to grow and improve the FOE portfolio.

Prior to joining the NAE, Lauren served as the program assistant for the Legislative Affairs team at the United



Lauren Stiller

States Institute of Peace, where she helped coordinate and manage the institute's congressional engagements, provided administrative support to leadership, restructured internal data systems, and tracked federal policy developments. She also brings experience in program support from 1870 Farm in North Carolina, where she managed environmental education programs and agricultural operations, working with a veterinarian to care for livestock and helping visitors of all ages connect with animal husbandry and gardening. Lauren holds a BA in public policy and a BA in environmental studies from the University of North Carolina at Chapel Hill, where she also served as a research assistant on emerging renewable energy technologies at the UNC Institute for the Environment. Throughout her experiences she has developed a passion for engaging different audiences with scientific concepts, supporting policy research and expert collaboration, and gaining a better understanding of the world around us.

Outside of work, she enjoys swimming, museums, photography, singing in choir, and hiking the Appalachians. She is based in Keck W831 and can be reached at lstiller@nae.edu.



Lauryn Williams

We welcome Lauryn Williams to the NAE President's and Executive Office. Lauryn joins us from the National Academy of Medicine, where she served as a senior program assistant for the past two years. Before joining the NAM, she worked at the Prince George's County Memorial Library System, where she led government programs focused on advancing digital equity and literacy within the community. Lauryn is currently pursuing a BA in computer technology at Bowie State University. In her spare time, she enjoys watching films, relaxing by the ocean, and playing board games with her family. She is based between NAS 226 and Keck W824 and can be reached at lwilliams@nae.edu.

We are pleased to welcome Carolyn Wood to the Office of Outreach and Communications as a communications/media associate. In her role, she supports NAE's digital and print communications, including social media, newsletters, graphics, and promotional content that highlight the Academy's members, programs, publications, and initiatives while helping expand its digital reach.



Carolyn Wood

Before joining the NAE, Carolyn served as director of marketing and social media for Cruel Tunes, where she led the organization's digital strategy, shaped its brand and voice, and built an engaged online community around music. She also brings experience in radio production and project management from her time at WMUC Radio, where she hosted her own on-air program and managed the station's extensive record library. She holds a BA in hearing and speech sciences from the University of Maryland, College Park, where her studies deepened her interest in how people receive, understand, and respond to information. Together, these experiences shaped her passion for thoughtful storytelling, creative communication, and making information clear and accessible to a wide range of audiences. She is excited to bring that perspective to the NAE and contribute to communications that connect more people with the Academy's work.

In her free time, Carolyn enjoys traveling, exploring nature, attending live music events, photography, trying new recipes, and watching films. She is based in Keck W833 and can be reached at cwood@nae.edu.

The NAE Office of Outreach and Communications is also pleased to welcome Adrienne Young to the team as an editor. Prior to joining the NAE, Adrienne worked as a freelance editor and writer, providing substantive editing, copyediting, writing, and copywriting under both long- and short-term contracts. Prior to that, she served as senior communications lead at the EFI Foundation, led by former US Secretary of Energy Ernest J. Moniz.

Earlier in her career, Adrienne spent 12 years at Resources for the Future (RFF), a DC-based think tank focused on environmental, natural resource, and energy economics and policy, where she developed a spark

for working with technical experts to help shape complex writing into com-



Adrienne Young

elling storytelling. At RFF, she served for eight years as managing editor and oversaw the institution's suite of print and digital publications, including leading the production of its flagship quarterly magazine, *Resources*. She holds a BA in economics with a minor in environmental studies from St. Mary's College of Maryland.

Outside of work, Adrienne enjoys seeing live music, keeping up with the Premier League and Formula 1, and spending time with her family and nine-year-old puppy. She is based in Keck 869 and can be reached at ayoung@nae.edu.

Calendar of Meetings and Events

June 11	NAE Member Led Event (MLE) – Wide Area Time Synchronized Power Grid Monitoring and Its Many Applications; Virtual	September 30	NAE Business Session; Virtual
		October 3	NAE Council Meeting; Washington, DC
		October 3	Peer Committee Meeting; Washington, DC
July 9–10	Facilitating Experiential Learning for Emerging and Novel Technologies (ExLENT); Washington, DC	October 3–5	NAE Annual Meeting; Washington, DC
		October 5	AIAA-NAE 2026 Yvonne C. Brill Lecture in Aerospace Engineering; Washington, DC
July 16	NAE MLE – State of Reliability; Virtual		
July 21	Section 12 Seminar – Building Capacity: “How Engineering Shaped America’s Land, Sea, and Mind”; Virtual	October 27–28	NAE MLE – From Resilience to Advantage: Building the North American Supply Chain of the Future; Monterrey, Mexico
July 28	Section 9 Section Meeting; Virtual		
July 31	NAE MLE – Prospects for Commercial Fusion Energy; Virtual	October 29	NAE MLE – Project 2050: Exploring the Future of the Construction Industry; Washington, DC
August 5–6	NAE Council Meeting; Irvine, CA		
August 12	NAE <i>The Bridge</i> Webinar – AI-Driven Data Centers; Virtual	November 12	NAE MLE – Precipitation Enhancement and Weather Modification: Evidence, Verification, Safety, and Responsible Governance; Irvine, CA
August 12–14	NAE MLE – Design Science and AI: Engaging Stakeholders—An Evidence-based Assessment of the 5C Process	December 2–3	Committee on Membership Meeting; Irvine, CA
August 13	NAE MLE – Engineering Challenges of the Computing-Energy Nexus; Virtual	December 6	NAE MLE – Conference: Grand Challenges in Mechanics: Shaping the Future of Science and Society
September 10–11	NAE MLE – The ISEH First Annual Summit on Engineering the Elimination of Diseases; Houston, TX	December 7	NAE MLE – Beyond dBA: Understanding the Importance of Low-frequency Noise including Sonic Boom; Washington, DC
September 21–24	The Grainger Foundation Frontiers of Engineering 2026 Symposium; Austin, TX		

In Memoriam

Young-Kai Chen, 72, deputy chief technology officer, Coherent Corporation, died May 1, 2026. Dr. Chen was elected in 2004 for contributions to the development of high-speed compound semiconductor electronics and optoelectronics for telecommunications.

Erroll Brown Davis Jr., 81, retired chancellor, University System of Georgia, died April 26, 2026. Mr. Brown was elected in 2021 for leadership in research and development of renewable resources integration with the grid, and public education.

Jack B. Dennis, 94, professor of computer science and engineering emeritus, Massachusetts Institute of Technology, died March 14, 2026. Dr. Dennis was elected in 2009 for contributions to sharing and protection in computer systems and parallel architectures based on data flow principles.

Delores M. Etter, 75, professor emeritus, Southern Methodist University, died April 17, 2026. Dr. Etter was elected in 2000 for the authorship of textbooks on computer applications in engineering, contributions to digital signal processing, and service to the profession.

Daining Fang, 68, Beijing Institute of Technology, died February 27, 2026. Professor Fang was elected an international member in 2022 for contributions to the mechanics of ferroelectric/ferromagnetic materials and lightweight multifunctional structures under extreme conditions.

Paul A. Fleury, 86, Frederick William Beinecke Professor Emeritus of Engineering and Applied Physics, Yale University, died April 30, 2026. Dr. Fleury was elected in 1996 for discoveries related to ferroelectric, acoustic, and nonlinear performance of materials, and for management leadership in materials.

David H. Gustafson, 85, professor emeritus of industrial and systems engineering and director, CHESSE, University of Wisconsin-Madison, died March 3, 2026. Dr. Gustafson was elected in 2013 for industrial and systems engineering methods to improve the care of aging, lung cancer, severe asthma, and drug addiction patients.

Tony Hoare, 92, visiting researcher, Microsoft Research Lab – Cambridge, died March 5, 2026. Sir Tony was elected an international member in 2006 for fundamental contributions to computer science in the areas of algorithms, operating systems, and programming languages.

Antony Jameson, 91, Jack E. and Frances Brown Chair, Texas A&M University, died June 11, 2026. Dr. Jameson was elected an international member in 1997 for contributions to aircraft through the development of computational fluid dynamics.

Bede Liu, 91, professor emeritus, Princeton University, died May 7, 2026. Dr. Liu was elected in 2002 for contributions to the analysis and implementation of digital signal processing algorithms.

David G. Luenberger, 88, professor emeritus, Stanford University, died May 19, 2026. Dr. Luenberger was elected in 2008 for contributions to control theory, optimization algorithms, and economic dynamics.

William L. Maxwell, 91, senior scientist, Arkieva Inc., died March 31, 2026. Dr. Maxwell was elected in 1998 for the theory and practice of real-time production planning and scheduling systems.

Cleve B. Moler, 86, chairman and chief scientist, MathWorks, died May 20, 2026. Dr. Moler was elected in 1997 for conceiving and developing widely used mathematical software.

Michael Prats, 100, president, Michael Prats and Associates, died January 26, 2026. Mr. Prats was elected in 1986 for distinguished contributions to petroleum engineering technologies and to the development of oil recovery processes.

Lee R. Raymond, 87, retired chairman and CEO, Exxon Mobil Corporation, died June 6, 2026. Dr. Raymond was elected in 1999 for keeping a major oil company at the forefront of exploration and production technology.

Freeman D. Shepherd, 89, retired senior scientist for infrared arrays and sensors electromagnetics, US Department of the Air Force, died March 16, 2026. Dr. Shepherd was elected in 1999 for contributions to metal-silicide devices and infrared cameras.

Richard P. Simmons, 94, retired chairman, Allegheny Technologies Inc., died April 23, 2026. Mr. Simmons was elected in 1998 for engineering in the specialty steel industry.

Richard A. Tapia, 87, University Professor and Maxfield-Oshman Professor in Engineering, Rice University, died May 22, 2026. Dr. Tapia was elected in 1992 for contributions in

linear and nonlinear programming, and for creative leadership in minority education in computer science.

Byron D. Tapley, 93, Clare Cockrell Williams Centennial Chair Emeritus in Engineering, The University of Texas at Austin, died June 22, 2026. Dr. Tapley was elected in 1987 for exceptional contributions to orbit determination theory, significant

applications to satellite geodesy and oceanography, and leadership in engineering education.

Robert V. Thomann, 91, professor emeritus, Manhattan College, died April 19, 2026. Dr. Thomann was elected in 1999 for contributions to the prediction and management of water quality in streams, estuaries, lakes, and oceans.



LEADERSHIP IN A WORLD OF
Accelerating Change
CAMPAIGN FOR THE NATIONAL ACADEMY OF ENGINEERING

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- **Stock Donation:** By donating appreciated stock to the NAE, you may deduct the current fair market value and avoid capital gains tax on the appreciation.

Help complete the NAE's *Campaign for Leadership in a World of Accelerating Change* and invest in the engineering leadership our nation's future depends on.

Visit nae.edu/waystogive to learn more or contact Radka Nebesky, Director of Development, at RNebesky@nae.edu or 202-334-3417 to learn more.

*Land-grant universities helped build US
engineering leadership and continue to redefine
their public mission today.*

Member Perspective

The Continuing Promise of Land-Grant Principles for US Engineering Education



Leah Jamieson (NAE) is Ransburg Distinguished Professor of Electrical & Computer Engineering and Professor by Courtesy of Engineering Education at Purdue University.

Leah Jamieson

In the 19th century, the United States was expanding rapidly—but its system of higher education was not built for the settlers and workers helping to shape its new communities and economies. As new territories became states and agriculture, industry, and infrastructure grew, the country needed a different model for education: one that combined broad learning with practical knowledge and opened its doors beyond a small elite. The Morrill Acts of 1862 and 1890 established land-grant colleges and universities, greatly expanding access to higher education for the working classes while advancing “agriculture and the mechanic arts” (Morrill Act 1862) as vital to the well-being of the nation. The Hatch Act of 1887, Smith-Lever Act of 1914, and Equity in Educational Land-Grant Status Act of 1994 extended that vision, building a national system of education, research, and public service that would help propel the United States to global leadership in engineering and agriculture.¹

¹ Ed. note: This Member Perspective article is an adapted and expanded version of Leah Jamieson’s contribution to “[Building Capacity: How Engineering Shaped America’s Land, Sea, and Mind](#),” in the special Summer 2026 issue of *The Bridge*, which celebrated the 250th anniversary of the United States with articles about engineering’s impact on the nation since its founding.

Snapshots of Higher Education Prior to the Land-Grant Acts

American higher education began as a small and highly selective enterprise. Starting with the founding of Harvard College in 1636 and following into the 18th century, colleges and universities in the American colonies were largely patterned after British institutions and associated primarily with religious dominations. Arts and sciences, trigonometry, ancient history and languages, ethics, and rhetoric dominated the fields of study. Aimed at preparing political, military, and religious leaders, these schools purposefully served a very limited population, and most excluded Black and women students.

The advent of public schools in the United States marked the first systemic attempts at democratizing education. The 1780s saw the chartering of the University of Georgia and the University of North Carolina, with a modest number of others to follow. Public colleges and universities expanded access to education beyond the elite in this era, reflecting a growing belief that higher education could serve a broader civic purpose and with goals including the creation of an educated US citizenry. Progress, however, was slow: by 1859, only 29 of the nearly 300 colleges and universities in the United States were public.

Engineering education also began to distinctly take shape during this period. In 1802, driven in part by lessons from the Revolutionary War and supported by the Founding Fathers including George Washington, John Adams, and Thomas Jefferson, the United States Military Academy at West Point was established as both the nation's first military academy and its first engineering school. By the mid-1830s, the Rensselaer School (now Rensselaer Polytechnic Institute) and Norwich University had joined West Point in offering engineering degrees, laying the groundwork for the expansion of technical education that would follow.

The Morrill Land-Grant Acts

On July 2, 1862, President Abraham Lincoln signed into law the Morrill Land-Grant Act to establish educational institutions in each state "to teach such branches of learning as are related to agriculture and the mechanic arts ... to promote the liberal and practical education of the industrial classes in the several pursuits and professions in life" (Morrill Act 1862). Introduced by Vermont Senator (then Representative) Justin Morrill, the act provided each state and territory with a land scrip (certificate) worth 30,000 acres of federal land for each of

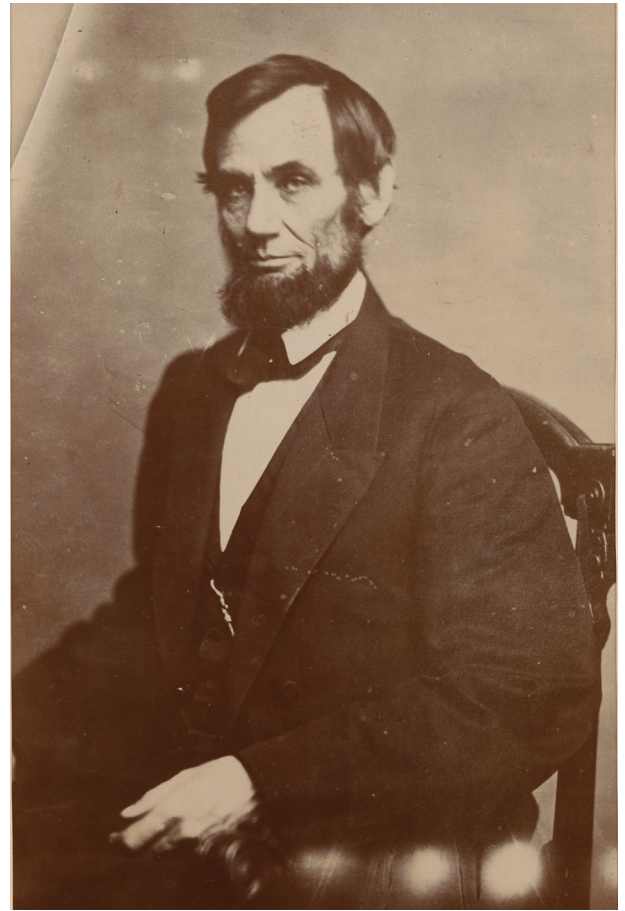


FIGURE 1 Abraham Lincoln, circa 1861. Photo: US National Archives.

its members of Congress. States were required to sell the scrip and invest the money to create a permanent endowment fund, the principal of which could not be spent. The terms also held the states responsible for physical infrastructure, so that the land-grant institutions were, from the outset, a partnership between the nation and the state. The act, which represented the first federal aid to higher education, was not passed without controversy. Morrill's first bill was introduced in Congress in 1857 and passed by a narrow margin in 1859, but was vetoed by President James Buchanan. Morrill resubmitted his bill in 1861. With the secession of Southern states and a new president, the bill became law (Figures 1 and 2).

Within the land-grant framework, the states had significant latitude in implementing the Morrill Act. The Iowa legislature became the first to accept the terms, designating the existing State Agricultural College and Model Farm, now Iowa State, as its land-grant institution. In 1863, Kansas State became the first institution

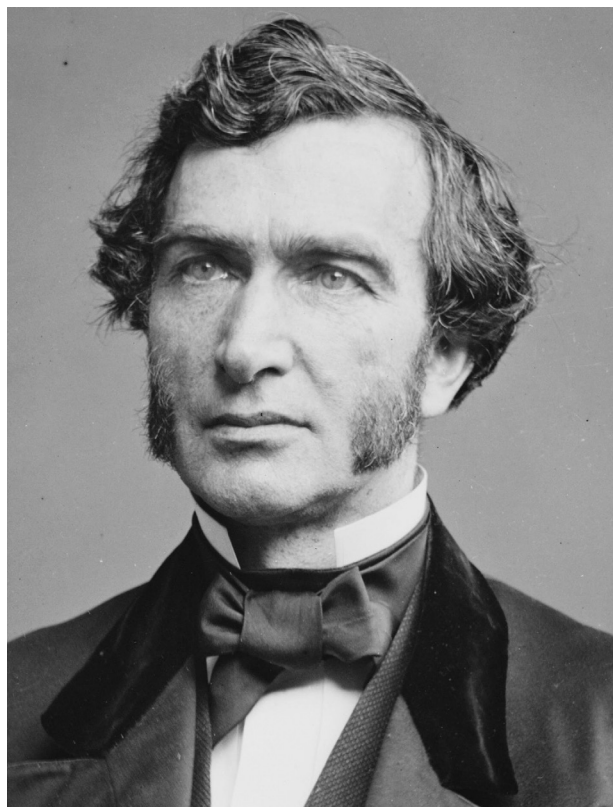


FIGURE 2 Justin Smith Morrill, circa 1862. Photo: Brady-Handy photograph collection, Library of Congress, Prints and Photographs Division.]

wholly created under the Morrill Act. By 1870, 36 states had signed on to the land-grant terms; by 1900, there were 60 land-grant institutions. Although not specified in the 1862 act or later acts—by 1890, every state included women in their land-grant charters.

Subsequent legislation expanded the populations served by land-grant institutions. Aimed primarily at the Southern states that blocked admission of Black students to their existing land-grant colleges, the Morrill Act of 1890 required states to open their land-grant institutions to Black students or establish separate land-grant colleges for them. The Southern states all chose the latter. Starting with Mississippi's Alcorn State University, 19 Black colleges and universities were founded under the 1890 act, most of which, including Florida A&M University, Prairie View A&M University, and Tuskegee, count among the Historically Black Colleges and Universities (HBCUs) of today.

More than a century later, the Equity in Educational Land-Grant Status Act of 1994 conferred land-grant status and support to 36 American Tribal Colleges and Uni-

versities (TCUs), including the United Tribes Technical College, Southwestern Indian Polytechnic Institute, and Navajo Technical University. It is worth noting that some colleges and universities that became land-grant institutions under the earlier bills have, on their own, started recognizing the history of the land and the Native people who were its original stewards by adding a land acknowledgment to their statements of identity (Bickell 2022).

Over time, congressional acts also laid out broader expectations of land-grant universities. The 1887 Hatch Act established funding of agricultural experiment stations and agricultural and veterinary research under the direction of land-grant universities, formally adding the expectation of research to the mission of the land grants. The 1914 Smith-Lever Act initiated federal funding of cooperative extensions associated with land-grant schools, to disseminate new learnings and practices throughout the state, setting the expectation for service. Taken together, the Hatch Act and Smith-Lever Act added research and service to the Morrill Acts' teaching focus, institutionalizing the three-pronged mission—the three pillars—of land-grant institutions.

Snapshots of Impact

As the number and mission of land-grant institutions grew, so did their impact. This boom in US land-grant institutions led to a striking increase in engineering graduates. In 1866, only a handful of colleges awarded engineering degrees and, by some counts, there were only 300 engineers in the United States. By 1911, the engineering workforce had grown to 38,000, and US schools were graduating 3,000 engineers per year—well above Germany's annual graduation rate of 1,800, at a time when Germany was considered one of the global engineering powerhouses. Within five decades of the 1862 Morrill Act, the United States had emerged as a global leader in engineering education (Williams 2009). On the business front, a 2018 study from the State University of New York identified the land-grant system as a significant contributor to the economic growth whereby the United States overtook the United Kingdom as an economic superpower by the 1940s (Erlich, Cook, and Yin 2018).

From 1862 through the 20th century, by transforming access to engineering education and expanding engineering education's mission to include research and service to states and communities, the Morrill Acts played a major role in making the nation a world leader in engineering.

The Morrill Acts in the 21st Century

Today there are between approximately 106 and 115 land-grant colleges and universities, with at least one in every state and in the five permanently populated US territories.² These include approximately 58 created under the Morrill Act of 1862; 19 HBCUs under the Morrill Act of 1890; and 36 TCUs under the Equity in Educational Land-Grant Status Act of 1994 (Bickell 2022). In 2020, across all majors, two million students were enrolled in land-grant institutions (Bickell 2022). In 2023–2024, of the over 193,000 total engineering degrees granted at the undergraduate, masters, and doctoral levels, 33% were awarded by land-grant schools (NCES/IPEDS 2026).

The tripartite land-grant mission continues and has become the mission of many state and public universities and colleges in the United States as well. However, the years leading up to the millennium saw many changes in higher education, including rising costs; a perceived loss of identity as advances in engineering were increasingly interdisciplinary rather than discipline-centric; declining public trust in higher education, leading to questioning both the value of a college degree and the return on investment; globalization; a climate of aversion to affirmative action; and, fueled by technological advances, rapidly expanding alternatives to the traditional on-campus education. It is no coincidence that ABET Engineering Criteria 2020 (ABET 2001; Henricksen 1997) and the NAE reports *The Engineer of 2020* (2004), *Educating the Engineer of 2020* (2005), and *Changing the Conversation* (2008) all date to the first decade of the 21st century. The world had changed but, in many ways, higher education had not.

In this context of disillusionment with colleges and universities, in 1996, the W. K. Kellogg Foundation awarded a grant to the National Association of State Universities and Land-Grant Colleges (NASULGC)³ to “create an awareness among public universities of the need for higher education reform” (APLU 1996). The resulting Kellogg Commission on the Future of State and Land-Grant Universities consisted of 24 university presidents and chancellors—21 from land-grant institutions and

three from other public universities. Highlighting the societal, economic, and technological changes that had had a profound impact on higher education over the 130-plus years since the first land-grant act, the commission explored topics at the heart of the land-grant missions and the goals of public institutions. Using the lenses of the disillusionment of the 1990s and the hopes for the upcoming century, between 1996 and 2000, the Commission released six reports assessing the state of the land-grant principles and public education more broadly—identifying critical new challenges, and developing potential roadmaps for the 21st century, to set the nation on paths whose impact might, in the future, be seen as worthy of the land-grant legacy.

Across the reports, the Commission traversed foundational topics around student access and experience, learning and society, engagement of colleges and universities beyond their own doors, and campus culture. The series culminated with a summary: *Renewing the Covenant: Learning, Discovery, and Engagement in a New Age and Different World* (Kellogg 2000).

In the process of envisioning the 21st century land-grant institutions, the Kellogg Commission redefined the language of the land-grant missions. The one-directional act of *teaching* became the interactive process of *learning*. *Research* became *discovery*, encompassing “research, scholarship, and creative activity that reveal new knowledge, integrate it into existing bodies of disciplinary work, cross-pollinate disciplines, and possibly create something entirely new” (Kellogg 2000). And *service*—the act that originated as the giving of knowledge or assistance through extension offices—became *engagement*, to emphasize deep two-way partnerships that would connect educational institutions and local, state, national, and global communities to the benefit of all. The renamings remained true to the core areas of the three original pillars, but, perhaps because of the deepening challenges of the new century, could be seen as raising expectations for each of the pillars—challenging land-grant and public institutions to do better.

The Kellogg Commission reports were circulated widely in the land-grant and public university communities. Five years after the release of the final Kellogg Commission report, NASULGC sent a survey to 40 presidents and chancellors and 31 others, asking for their perceptions of the effectiveness of the commission’s work. All 35 of the respondents credited the Kellogg reports with making the case for reform and noted concrete “transformative” (Byrne 2006) changes being made at their institutions,

² The number of land-grant institutions varies depending on factors including the source (e.g., agriculture-focused studies do not include MIT); publication date; how schools in university systems are counted (e.g., California schools counted as one system, which is how they are represented by the Association of Public and Land-Grant Universities) or individually; and changing accreditation status.)

³ Renamed the Association of Public and Land-Grant Universities (APLU) in 2009.

especially in the areas of the student experience. These included increasing opportunities for research, study abroad, and service-learning, and the creation of learning communities and bridge and jump-start programs. The responses also included reports of adding engagement to mission statements or strategic plans, the creation of engagement officers at the vice president or vice provost level, and the expansion of programs for outreach, public or civic service, or engagement. Although limited in reach, the 2006 survey suggested that the Kellogg report was influencing change.

Two subsequent surveys specifically tracked changes in the status of engagement: a 2015 survey of the 203 Association of Public and Land-Grant Universities (APLU) member institutions (Van Egeren 2015) and a repeat survey in 2024 of the same institutions. Released 25 years after the publication of the Kellogg Commission reports in *Public Purpose Renewed: Future-Leading Engagement in Higher Education* (APLU 2026), the comparison of the 2015 and 2024 surveys gives evidence of both the growing status and nature of engagement in today’s land-grant and public institutions. The quantitative comparison is summarized in Table 1.

Tracking elements of the “engagement ecosystem” document the growing infrastructure to support engagement. From 1999 to 2026, the number of journals focused on engagement increased from 13 to 39; the number of networks and organizations from 12 to 47. The number

of awards increased from 12 to 44, with the Carnegie Elective Classification for Community Engagement (first awarded in 2006) and the APLU Innovations in Economic Prosperity designation (first awarded in 2013) being the most notable.

Taken together, the 1996–2000 Kellogg reports along with the 2006, 2015, and 2024 follow-on assessments demonstrate that, more than 150 years after the initial Morrill Act, there is still resonance with the goals of the collective Morrill Acts. At the same time, they also serve as evidence of a work in continual progress, as the work is not done.

Conclusion

The 1862 Morrill Act addressed a national need: supporting the population that would expand the nation to the western edge of the continent. The subsequent acts of 1890 and 1994 expanded the reach of the original act. The Hatch Act of 1887 and the Smith-Lever Act of 1914 added missions of research and service to the initial focus on teaching, recognizing that both research and service inform teaching and that teaching enriches both research and service. Since the start, the acts have held true to Justin Morrill’s initial principles but have evolved with the needs of the growing nation. In the last years of the 20th century, the Kellogg Commission’s renaming and reframing of teaching, research, and service to learning, discovery, and engagement reflected the broadening of

Percent of Institutions Identified with Indicators of Institutional Engagement		
INDICATOR	2015*	2024
Engagement or outreach present in mission, vision, goals	46%	83%
“Outreach” or “engagement” appears on the main institutional homepage or as a button/dropdown on the main page menu	23%	20%
Received Carnegie Elective Classification for Community Engagement	47%	59%
Received APLU Innovations in Economic Prosperity designation	21%	40%
Chief engagement officer (e.g., vice, associate, or assistant vice provost or president)	10%	19%
Central office for community engagement or outreach, community partnerships, engaged scholarship	24%	37%
Central office or center for community-engaged, service, or experiential learning	61%	76%

TABLE 1 Percent of institutions identified with indicators of institutional engagement. Reproduced with permission from the Association of Public and Land-Grant Universities (APLU), *Public Purpose, Renewed: Future-Leading Engagement in Higher Education* (2026). Copyright 2026 APLU. All rights reserved.

all three missions over time and emphasized their interdependence (Kellogg 2000). As the Kellogg study shows, the land-grant principles have the potential to serve—and potentially transform—the nation well into the future, provided we continue to honor the mission of higher education and are attentive to the ever-changing global, societal, cultural, technological, and human contexts that shape education's needs and opportunities.

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Invisible Bridges

What Keeps a Nation Free



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In 1839, J.M.W. Turner painted *The Fighting Temeraire*. The old warship, once a hero of the Battle of Trafalgar in 1805, glides like a ghost across the canvas, towed by a small steam tug belching smoke on its final voyage to the ship-breakers. The image shows a clear moment of change: sail giving way to steam, and with it, a major shift in power. The ship relied on timber, rope, canvas, and Britain's seafaring towns. The tug depended on coal mines and iron foundries that supplied machine shops in the Midlands. Turner showed the tension of this time, when new technology changed who held power.

By Turner's time, the United States had already defeated Britain's navy in two wars—one for liberty on land, another for freedom of the seas. The 13 colonies used new technology in creative ways to win their freedom, and by keeping up with innovation, they managed to defend their freedom. Now, as the US celebrates its 250th anniversary, we can ask: What does it really mean for a country to be independent?

We tend to focus on how nations and individuals defend freedom but rarely turn that focus to the tools and systems that sustain freedom. Declaring independence is only the beginning: Independence must still be engineered.

Forging Freedom

Long before the first shots were fired at Lexington and Concord in 1775, Britain had drawn the lines of conflict through technology. The Wool Act of 1699 choked colonial textile exports. The Hat Act of 1732 crushed local hat-making. The Iron Act of 1750 forbade finished iron goods. Each statute tightened the knot: Colonial capabil-

ity existed only at Britain's discretion. The Boston Tea Party may have been a loud response, but resistance also took subtler, more empowering forms. At a 1769 Virginia ball, more than a hundred women arrived in homespun gowns. Every thread was defiance.

When war came, everyday tradespeople pivoted to the fight. Farmers turned plowshares into gun barrels, while clockmakers turned their precision skills to making firing mechanisms. By 1777, two weapons production models had emerged—centralized sites like the Springfield Armory that could produce high-quality guns in large quantities, and household workshops that were more agile and could meet local needs. In parallel, the new nation developed an equally important source of supplies and support: France sent gunpowder and loans and eventually opened a second naval front in 1781, which proved as decisive as any weapon.

After the war, the young republic pursued industrial strength with the same resolve it had shown in battle. In 1789, Samuel Slater arrived from England with textile-spinning technology that he'd memorized, sowing the seeds of US manufacturing, whose early growth rested on domestic cotton, slave labor, and copied techniques. By 1816, gun manufacturer Simeon North's milling machines were producing interchangeable metal parts, allowing the armed forces to cannibalize parts. In 1822, Thomas Blanchard's copying lathe automated the shaping of gunstocks. In the 1830s, the federal government imposed tariffs that shielded infant industries, fulfilling Alexander Hamilton's vision for industrial policy: Build capacity first, then compete.

At the 1851 Great Exhibition in London, American revolvers and reapers with swappable parts stunned international observers. By the 1860s, land-grant colleges were spreading technical education across the nation. Engineering moved into the mainstream, from niche to national necessity, driving broad, though uneven, prosperity. As the Industrial Revolution bloomed, the early US focus on industrial capacity via farms, factories, and formidable wealth positioned the country to compete with the most advanced industrial powers in the world.

The Right and Responsibility to Repair

For nearly two centuries, that ethos endured, with government-guided infrastructure and markets deciding the details. But around the US bicentennial, in 1976, a conviction took hold across party lines. Finance began to outrank fabrication, and Wall Street prioritized futures contracts over companies owning the factories that made up their supply chains. Domestic factories closed or moved offshore, and companies turned to just-in-time manufacturing and shipping, ostensibly as a way to save on costs. Shipbuilding felt this shift as much as any industry. Shipyards closed, and suppliers of specialized castings and components disappeared along with them, as did skilled technical workers who retired without replacement. Now the US Navy struggles to build submarines fast enough to replace its aging fleet.

Other changes took hold, among them the idea that the company that builds your tractor or medical equipment could prevent you from fixing it yourself. Invasive “terms of service” prevented customers from reaching for

a wrench, instead allowing companies to keep reaching into customers’ pockets. These changes are symptoms of both structural and infrastructural fragility. When we lose the ability to understand and sustain the systems we rely on, we lose control—bit by bit.

No nation can build everything alone, of course. From hand-forged muskets to finely printed microchips, the sovereignty etched into our tools demands a prudent calculus: what to make at home, what and with whom to trade. Engineering is how a nation keeps its independence alive. Independence requires both the courage to innovate and the stewardship to maintain what has been built. The American Revolution was itself an act of engineering—daring in vision and deliberate in pairing anvil and alliance. Generations later, can a nation that cannot see its own dependencies, build and maintain its critical tools, or repair what breaks still call itself free?

Turner’s *Snow Storm—Steam-Boat off a Harbour’s Mouth*, completed three years after *The Fighting Temeraire*, captures this part of the story. Sea and sky dissolve into a churning vortex around the ship. Turner claimed he had himself lashed to the ship’s mast for four hours so that he could paint the sensation of standing inside a system too vast and tangled to comprehend. A nation that loses sight of what it depends on stands there too: lashed to nothing except the churn.

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