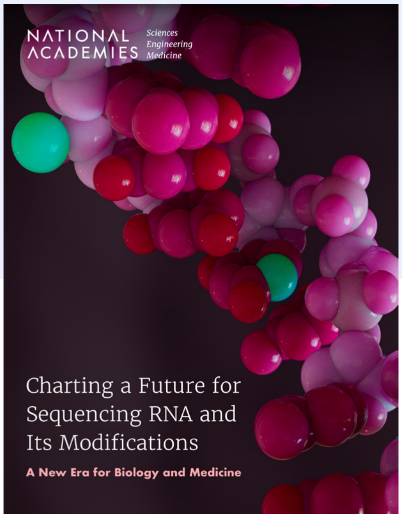
NATIONAL ACADEMIES *Sciences Engineering Medicine*

Consensus Study Report
Highlights

Charting a Future for Sequencing RNA and Its Modifications: A New Era for Biology and Medicine



In recent decades, significant advances in science and technology have greatly enhanced understanding of the many biological molecules that contribute to life's complexity. RNA is one such molecule that has captured attention for its remarkable diversity and important role in critical life processes. DNA passes its information through RNA for delivery to the places where its information is needed. Through natural biological pathways, RNA is edited and revised to give rise to hundreds, in some cases thousands, of distinct RNA molecules for each gene. RNA also acquires modifications during its life cycle, further expanding the repertoire of possible RNA molecules that can be derived from a single gene. In these ways, RNA allows for the diversification of information encoded by DNA, which is essential for the maintenance and survival of complex organisms, such as humans. It follows that disruptions of the cellular machinery responsible for editing and modifying RNA can lead to a wide range of human diseases and disorders, including neurological disorders, heart disease, autoimmune diseases, cancer, and diabetes.

Developing a deep understanding of these processes and the central role of RNA modifications will reveal much about basic biology. But it will also be extraordinarily useful—as it has already begun to be—in advancing human health; ameliorating disease; controlling pathogens; improving crop yields; and pushing the boundaries of synthetic biology, including nanotechnology applications. The most recent and prominent example of health-related applications for RNA modifications (**Box 1**) is the vaccines that saved millions of lives worldwide during the COVID-19 pandemic. Beyond health and medicine, RNA modifications show exciting promise for enhancing agricultural productivity. Preliminarily, engineering of RNA modifications has demonstrated improved crop yields and drought resistance in potatoes. Such engineering has the potential to improve food security for billions of people across the globe.

Comprehensively sequencing RNA and all of its modifications is also expected to contribute to the U.S. economy and reinforce the nation's competitive stance in global scientific and technological innovation. Despite notable progress and economic value in this growing field, much about how RNA modifications affect the fate and function of RNA molecules in living systems is still unknown. Existing technologies cannot currently discover all RNA modifications, let alone comprehensively sequence them on every RNA molecule. This limitation significantly hampers the ability to study and leverage RNA modifications to address current and emerging societal issues.

BOX 1.
RNA MODIFICATIONS AND HEALTH:
From COVID-19 to Cancer

The RNA modification "N1-methylpseudouridine" was instrumental in the development of highly effective and safe messenger RNA (mRNA) vaccines against COVID-19. The 2023 Nobel Prize in Physiology or Medicine was awarded to the researchers whose early work studying RNA modifications for use in mRNA vaccines laid the foundation for this critical breakthrough. Undoubtedly, RNA modifications will continue to be used to expand mRNA vaccines for other pathogens, such as HIV, influenza, and bacteria. Understanding how bacteria and viruses use RNA modifications to evade the human immune response and cause disease will also help unlock new therapies. For example, antivirals and antibiotics that target or exploit these evasive features hold great promise for protecting human lives from harmful infections. Prevention of infectious diseases is just one example of a valuable outcome resulting from research dedicated to understanding RNA modifications. Using technology similar to that of the COVID-19 vaccines, mRNA vaccines against cancer are currently undergoing clinical trials. In addition, RNA-based therapeutics that incorporate RNA modifications are used to treat rare diseases, such as spinal muscular atrophy.

This report proposes a roadmap of innovation and advances that will enable any RNA from any biological system to be sequenced with all of its modifications. Ultimately, with this capability, the committee envisions that RNA modification profiles for diseases will lead to more personalized and targeted treatments and instigate transformative changes across various sectors, beyond health and medicine.

KEY COMPONENTS OF A ROADMAP TO UNLOCK ANY EPITRANSCRIPTOME

The Human Genome Project aimed to provide a complete reference genome for humans and model organisms. This goal was appropriate, given the DNA genomes of different individuals are nearly identical, differing by about 0.4 percent. While every cell in an individual generally has the same genomic sequence, the processing of RNA from each gene is amazingly diverse and dynamic. The collective set of RNA molecules and their modifications, or the "epitranscriptome," varies between cell types and tissues so that the RNA can meet specific demands—for example, to specify muscle or skin. Further diversity arises from factors such as age, sex, and environment. Because there are many epitranscriptomes to determine, even for a single organism or individual, the ultimate and most impactful goal for an epitranscriptome initiative will be to enable sequencing of *any* epitranscriptome by developing the necessary technologies and associated infrastructure. This advance in capabilities would allow for any epitranscriptome, under any cellular condition or context, to be generated well into the future.

Establishing the capabilities to unlock any epitranscriptome will require several efforts to occur in parallel (**Figure 1**). This report outlines the steps to achieve the technological and infrastructural advances necessary to enable the comprehensive sequencing of RNAs in human cells and other organisms, marking a pivotal advance in the understanding and practical application of RNA science.

FIGURE 1: Key efforts needed to unlock any epitranscriptome.

LAUNCHING A LARGE-SCALE INITIATIVE

Even as the importance of epitranscriptomics for addressing a range of challenges across sectors has become clear, progress has been hampered by gaps in sequencing technology and other areas. A focused, large-scale effort is essential to accelerate technological innovation and realize the full promise of the field. U.S. global leadership in this space will hinge on a significant whole-of-government effort and proactive identification of areas for international cooperation. Dedicated funding to key federal entities—such as the National Science Foundation (NSF), the National Institutes of Health (NIH), the National Institute of Standards and Technology (NIST), the Department of Defense (DOD), and the Department of Energy (DOE)—is critical to enhance their ability to work with academia, industry, philanthropic organizations, and international partners in driving innovation towards sequencing RNA and its modifications and ensuring translation of the resulting scientific breakthroughs into advancements including new, effective biotechnology products.

RECOMMENDATION 1: An established oversight body, such as the Office of Science and Technology Policy or a similar entity with appropriate breadth and authority, should catalyze and coordinate efforts supporting a large-scale epitranscriptomics initiative to ensure effective use of resources and minimize duplication. Expertise from the health, agriculture, commerce, energy, national security, and defense sectors will be required. Both research and regulatory agencies should be included as a part of the effort. An implementation plan should be developed and include support for agencies to work with partners in academia, industry, scientific societies, private foundations, international partners, and other relevant groups. The coordinating body should be responsible for strategic coordination of government, academic, and industry partners.

Other key recommendations to address challenges in the focus areas shown in Figure 1 are summarized below.

EXPANDING RESEARCH

Ongoing research in the field of RNA modifications needs to continue and expand. Increased recognition of the importance of RNA modifications in health, and their broad application potential for diagnosis, treatment, and prevention of disease, will fuel technological advances that can benefit other fields.

ADVANCING TECHNOLOGY

Federal funders of research, such as NIH, NSF, DOD, and DOE, should invest in and prioritize closing gaps in the existing tools, exploring new technologies, and centralizing resources for available tools and methods. (*Recommendation 2*)

DEVELOPING STANDARDS AND CENTRALIZING DATA

NIST should develop, curate, and promote standards to support the field, especially RNA reference materials, which should be developed with a focus on accessibility. NIH should establish and maintain a sustainably funded and centrally managed database that maintains up-to-date, curated information about RNAs and their modifications. NIH should collaborate with international partners, and the National Center for Biotechnology Information should then establish and promote standards for databases, data exchange, and nomenclature for RNA modifications. (*Recommendations 3, 4, 5*)

CULTIVATING A WORKFORCE

To develop a strong workforce, institutions and funding agencies, in partnership with education experts, scientific societies, and industry groups, should build upon existing educational materials and training opportunities for students and the public. The materials and opportunities should be age appropriate and engaging for the interests of different groups, while covering the basic biological and chemical principles of RNA modifications, the tools available for their study, and their potential application in future medicines and useful biotechnologies. (*Recommendation 6*)

POTENTIAL OUTCOMES AND BROADER IMPACTS

The following lists some of the potential outcomes and associated broader impacts that are anticipated to arise from a 15-year investment in this space:

- Enhanced fundamental understanding of RNA modifications in living systems, leading to the discovery of new links between RNA modifications and genetic disorders.
- Improved understanding of RNA modifications used by viral pathogens affecting humans, animals, and plants, leading to improved disease control, prevention, and preparation for inevitable future pandemics.
- Better understanding of RNA modifications used by viruses or tumor cells, leading to the development of better vaccines to fight viruses and new immunotherapies to treat cancer.
- Better understanding of RNA modifications in disease-causing bacteria, fostering the development of new antibiotics.
- Discovery of new, previously unrecognized RNA modifications that expand the tools for enhancing efficacy of RNAs used in gene therapies.
- Discovery of new, previously unrecognized RNA modifications that enable new diagnostic protocols for viral detection, tumor testing, and detection of inherited diseases.
- New methods for improving crop yields and drought resilience, thus enhancing agricultural production and greater global food security.
- Discovery of RNA modifications that will bolster synthetic biology capabilities.

- Advances in computer science resulting directly from efforts to create robust and accessible RNA modification databases.

- Application of technological achievements resulting from the epitranscriptomics project to technologies that impact diverse fields.

- An increased public awareness and interest in RNA modifications.

In its essence, the goal of all biomedical science is to relieve human suffering and maintain human health. Time, effort, and money invested in this epitranscriptome initiative directly relates to this goal and will provide information helpful to numerous enterprises, including those listed above. Without knowing the exact composition of all RNA molecules that derive from each gene, the ability of researchers to understand the underpinnings of health and disease is severely limited. Furthermore, if insufficient capabilities exist to directly sequence and study full-length RNA molecules and their modifications, then the ability to leverage that information for biotechnology applications suffers. All major sectors, including health and medicine, agriculture, energy, commerce, defense, and national security stand to benefit from a better understanding of RNA modifications. More broadly, the associated activity across these numerous sectors may positively impact the bioeconomy. The report charts a future for sequencing RNA and its modifications, toward a new era of biology and medicine.

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