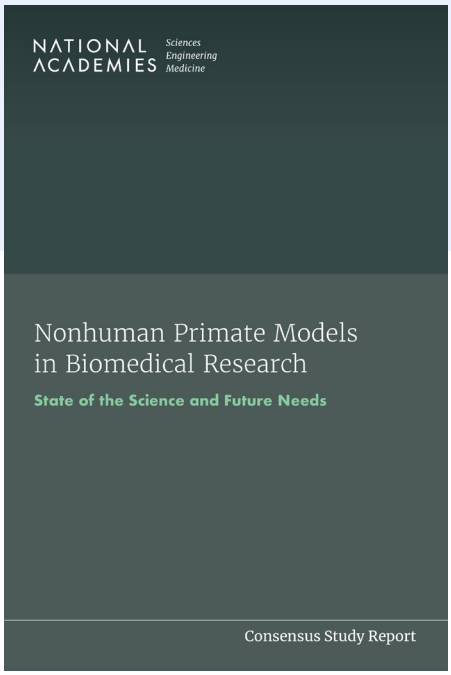
Nonhuman Primate Models in Biomedical Research



State of the Science and Future Needs

OVERVIEW

Biomedical research relies on animal, cellular, and in silico models, with the appropriate choice of a model system being dictated by the question(s) being asked. Although nonhuman primates (NHPs) represent a small proportion—an estimated one-half of 1 percent—of the animals used in biomedical research, they remain important animal models due to their similarities to humans with respect to genetic makeup, anatomy, physiology, and behavior. Remarkable biomedical breakthroughs, including successful treatments for Parkinson's and sickle cell disease, drugs to prevent transplant rejection, and vaccines for numerous public health threats, have been enabled by research using NHP models. However, a worsening shortage of NHPs, exacerbated by the COVID-19 pandemic and recent restrictions on their exportation and transportation, has had negative impacts on biomedical research necessary for both public health and national security. Additionally, there is continued interest in understanding whether and how nonanimal models can be used to answer scientific questions for which NHPs are currently used.

In its Consolidated Appropriations Act of 2021, Congress directed the National Institutes of Health (NIH) to commission an independent National Academies study to explore the current and future use of NHPs in intramural NIH research, as well as existing and anticipated future opportunities for alternatives to reduce NIH's reliance on NHP models. As directed by NIH, the committee's Statement of Task expanded the scope of the study to include both intramural and extramural NIH-supported biomedical research using NHPs. It also charged the committee with determining the status of research, development, and validation efforts for new approach methodologies

(in vitro and in silico models) that can be used to complement or reduce reliance on NHP models in biomedical research.

CONCLUSIONS

Contribution of NHP Models to Advances in Human Health

While no model, animal or otherwise, can fully mimic the complexities of the human body, there remain research questions that currently cannot be answered outside of the context of a living organism. In some cases, NHPs may be the best available animal model in terms of translational relevance to humans. Their use in fundamental basic and translational biomedical research across many domains (e.g., infectious disease; immunology; social, cognitive, and behavioral research; reproduction; regenerative medicine; aging; neuroscience), has contributed to and continues to inform the understanding of human biology and the development of vaccines, therapeutics, and other treatment strategies.

Conclusion 2-1: Nonhuman primates have contributed to numerous human health advances that have improved and preserved countless lives, demonstrating a track record of unique predictive relevance critical for supporting ongoing fundamental basic and translational research missions of the National Institutes of Health.

Conclusion 2-2: Nonhuman primate research resources continue to be vital to the nation's ability to respond to public health emergencies, such as the recent COVID-19 pandemic.

Current Use and Availability of NHPs for NIH-Supported Biomedical Research

In examining the state of NHP use in NIH-supported biomedical research, the committee used as a starting point the 2018 report of the NIH Office of Research Infrastructure Programs, ***Nonhuman Primate Evaluation and Analysis***, which provides a snapshot of NHP research priorities and NHP supply and demand from fiscal years 2013 to 2017. However, supply and demand for NHPs for biomedical research have changed dramatically in the past few years, necessitating a reevaluation of the state of NHP resources and their ability to support current and future priorities for NIH-funded research.

Conclusion 3-1: The shortage of nonhuman primate resources for National Institutes of Health (NIH)–supported biomedical research has continued to worsen, extending beyond concerns raised in the 2018 report of the NIH Office of Research Infrastructure Programs. This resource shortage has been exacerbated by export and transportation restrictions and global public health emergencies.

Conclusion 3-2: Without decisive action and a national commitment to a comprehensive plan for nonhuman primate (NHP) availability, the ability of National Institutes of Health (NIH)–supported extramural program investigators to conduct studies requiring the use of an NHP model will become a function more of access to NHPs than of a concerted response to national public health priorities. The core tenet of NIH that the most meritorious research should receive the highest priority will thereby be threatened.

Conclusion 3-3: Inadequate nonhuman primate (NHP), physical, financial, and human resources, along with the high costs of NHPs, severely limit the ability of National Institutes of Health–supported research programs to respond adequately to public health emergencies, as well as to carry out high-impact biomedical research requiring NHP models.

Conclusion 3-4: Biomedical and public health research in the United States is threatened by dependence on imported nonhuman primates (NHPs). This reliance on external resources is unsustainable and undermines the security of the U.S. biomedical research enterprise. To ensure that NHP resources are available to respond to public health threats, the United States needs to prioritize expansion of domestic NHP breeding programs.

Conclusion 3-5: The National Institutes of Health (NIH) has no central data management or reporting structure across its intramural and extramural programs to provide accurate tracking of the numbers of nonhuman primates (NHPs) required to meet current and future research needs. NIH thus has no way to collect the quantitative data needed to implement a comprehensive strategic management plan for its NHP research and resource portfolio.

Conclusion 3-6: Inadequate coordination of nonhuman primate (NHP) resources and research programs at the national

level contributes to missed opportunities and diminished opportunities for efficient use of limited NHP resources.

Conclusion 3-7: Although the 2018 report of the National Institutes of Health Office of Research Infrastructure Programs (ORIP) identified a serious shortage of nonhuman primate (NHP) resources that was likely to worsen in the future, support for the ORIP-funded national NHP resource infrastructure remains inadequate.

Conclusion 3-8: Inadequate support for national nonhuman primate (NHP) resources by the National Institutes of Health (NIH) Office of Research Infrastructure Programs represents a major threat to NIH-supported NHP research programs nationwide. Funding will have to address current and future needs and the infrastructure required to support them.

Potential of New Approach Methodologies to Complement or Reduce Reliance on NHP Models

New approach methodologies have been used to answer diverse questions of biomedical relevance. Ongoing research efforts continue to explore the potential of in vitro and in silico models to improve the translatability of nonclinical research, extend knowledge of human diseases, and address shortages of and/or replace NHPs. However, in the absence of qualification or validation, enthusiasm for new technologies and approaches must be tempered to avoid overpromising their capabilities as valid replacements for necessary and proven experimental systems. The establishment of collaboration opportunities for investigators developing and using different model systems, including NHP researchers, bioengineers, and computational biologists, could reduce barriers to the adoption of new approach methodologies.

Conclusion 4-1: Based on the current state of the science, there are no alternative approaches that can replace nonhuman primate (NHP) models to answer research questions that require complete multiorgan interactions and integrated biology. Thus, NHPs continue to be essential for the conduct of National Institutes of Health–supported biomedical research.

Conclusion 4-2: Select new approach methodologies (in vitro and in silico models) can replicate certain complex cellular interactions and functions. As such, these new approach methodologies may be used to answer specific research questions that contribute to understanding human biology to prevent and treat human disease. Although there currently exist no alternatives that can fully replace nonhuman primates, it is reasonable to be optimistic that this may change in the years ahead as new approach methodologies continue to advance.

Conclusion 4-3: Furthering the adoption of new approach methodologies (including in vitro and in silico model systems and approaches) with the intent of reducing reliance on nonhuman primate models will require planning and support for studies that can demonstrate adequate performance for specific contexts of use or intended purposes. Expectations for qualification or validation of new approach methodologies depend on the decisions to be made using the data derived from their use and the potential human health consequences of those decisions.

Conclusion 4-4: While nonhuman primates have been regarded as preeminent models for the evaluation of human safety and efficacy, recent guidance demonstrates that the Food and Drug Administration and other regulatory agencies are supportive of the use of new technologies and approaches for regulatory decision making once they have been adequately qualified or validated.

Conclusion 4-5: Efforts to reduce reliance on nonhuman primates (NHPs) in biomedical research will require investment in opportunities to facilitate direct interaction and collaborative research among investigators using NHP models and those developing in vitro and in silico approaches to expand the applicability of new approach methodologies to research questions for which NHPs are currently needed. At present, however, few mechanisms for fostering such interaction and collaborative research are available.

Future Needs and Opportunities for NHP Models in NIH-Supported Biomedical Research

The future needs and opportunities for NHP models in NIH-supported biomedical research will be driven by many of the same factors that have shaped the current landscape, including public health needs, preparedness for unknown future threats, the evolving state of science and public policy, and the availability of NHP

research resources and infrastructure. Prohibiting the continued use of NHPs in NIH-supported biomedical research or imposing insurmountable barriers on their use could result in significant delays in the discovery and development of effective treatment strategies and interventions for human diseases and increase the potential for harm.

Conclusion 5-1: Given the nation's most pressing public health needs and the evolving state of the science, specific domains of research—including neuroscience and neurodegenerative disorders, preparedness for unanticipated communicable infectious threats, immunotherapy, reproduction, aging, and chronic inflammatory diseases—are likely to require increased use of nonhuman primates in the future. The species distribution of future need for such research is likely to remain weighted toward macaques (particularly rhesus and cynomolgus), with increased use of marmosets.

Conclusion 5-2: The 2018 report of the National Institutes of Health (NIH) Office of Research Infrastructure Programs, Nonhuman Primate Evaluation and Analysis, *included recommendations for improving communication and collaboration within the nonhuman primate (NHP) research community, increasing domestic NHP supply capabilities, addressing limitations in NIH funding mechanisms, promoting training in NHP care and research, and enhancing the utility and value of existing NHP resources. These solutions and recommendations have not yet been fully implemented and remain critically important.*

Conclusion 5-3: Addressing the challenges posed for the national research infrastructure by a persistent lack of nonhuman primates (NHPs) will require a commitment and comprehensive national effort focused on expanding domestic NHP resources.

Conclusion 5-4: The creation of a national plan for allocation and expansion of nonhuman primate resources is necessary to optimize the use of this critical scientific resource. Such a plan will require adequate monetary, physical, and personnel resources, as well as a centralized tracking system to match need to investment in a data-driven fashion.

Conclusion 5-5: Continued development and validation of new approach methodologies (in vitro and in silico model systems) is critically important to support further advances in biomedical research. This may reduce the need for nonhuman primate (NHP) models in the future, and/or enhance their utility. Additionally, this may help to mitigate shortages in NHP supply and the high cost of NHP research.

Conclusion 5-6: Given the limited numbers of nonhuman primates (NHPs) available for research, it is incumbent upon investigators and the National Institutes of Health (NIH) to make the best use of each animal through cooperative efforts, data sharing, purposeful planning, and use of data-driven care and management methods for the long-term care and use of NHPs in research. Examples of successful cooperative efforts from the community of NIH-funded NHP researchers—including collaborative working groups; data-sharing resources for clinical and clinical pathology data, gene expression profiling, and genotype data; and biospecimen repositories—can serve as models for broader adoption.

Conclusion 5-7: A system for consistent reporting is needed to adequately capture the life, scientific, and medical history, including experimental treatments and procedures, of individual nonhuman primates (NHPs). The need for complete NHP life histories further supports the development of increased domestic breeding capacity in the United States to maximize the accurate and complete sharing of clinical and experimental data. Currently, the incentives, mandates, and infrastructure within the National Institutes of Health research enterprise are insufficient to support uniform data management and reporting across all NHP research programs.

Conclusion 5-8: Recent advances in genomics, bioinformatics, imaging, digital biomarkers (e.g., noninvasive home enclosure neural and behavioral recordings), extended reality, and artificial intelligence/machine learning have revealed opportunities to understand normal biology and the mechanisms of disease. Such technologies and approaches have the potential to augment the scientific knowledge that can be gained from individual nonhuman primate (NHP) studies and, in some cases, enable less invasive use of NHPs. Leveraging these opportunities for NHP research will require tracking the genotype, phenotype, and history of each animal used, as well as transdisciplinary interactions.

Conclusion 5-9: Additional investments will be needed to implement, maintain, train, and use current and emerging

technologies (such as digital biomarkers, artificial intelligence/machine learning, imaging, extended reality, and laparoscopy), as well as data-driven husbandry practices, with the potential to enhance nonhuman primate research funded by the National Institutes of Health.

LOOKING FORWARD

NHPs are likely to remain a limited and high-cost resource—even with the necessary further investment in domestic breeding to address current shortages. Development of a strategy on the use of new approach methodologies in conjunction with NHP models is needed to optimize the application of NHP research and to answer pressing biomedical research questions in the future. In the meantime, it is important to reiterate that NHP resources demand strong stewardship and research conducted in a way that maximizes the knowledge and actionable insights that can be obtained from each individual animal in every study.

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FOR MORE INFORMATION

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