Science Advancement & Outreach
A DIVISION OF PETA

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REQUEST FOR INFORMATION: NICHD Strategic Plan 2025

Notice number: NOT-HD-24-028

Submitted via email to NICHDStrategicPlan@nih.gov

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We are writing on behalf of People for the Ethical Treatment of Animals—PETA—regarding the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) strategic plan update for 2025–2029.

Recognizing the failure of animal-based research results to translate into human-relevant knowledge, **we recommend that NICHD conduct and fund research using only human biology-based systems and not those that use other species**.

We also take this opportunity to share our Research Modernization Deal, a plan of action with detailed recommendations for advancing biomedical research in the U.S. through non-animal methods, applicable across various research domains. This plan can be accessed at https://www.peta.org/wp-content/uploads/2023/01/peta-research-modernization-deal.pdf. We are happy to meet with NICHD for any questions related to this response or the topics covered in the Research Modernization Deal.

In the following pages we expand on other recommendations for this request for public comment and provide examples of cutting-edge technologies that are advancing our knowledge of human health.

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Research Goal #1: Understanding the Molecular, Cellular, and Structural Basis of Development

Advancing our understanding of *human* development, rather than relying on outdated animal models, is crucial for meaningful scientific progress. The NICHD can develop programs that follow individuals from the early stages of pregnancy and design studies to investigate the molecular, cellular and structural basis of human development. By establishing a collaborative

network with hospitals across the U.S., the institute can increase the collection of patient samples and data to perform more robust analyses and increase its efforts to address health disparities. The NICHD should also foster multidisciplinary collaboration between developmental biologists, geneticists, bioengineers, and computational scientists working with human tissues and data.

In parallel, the NICHD must leverage modern research tools that authentically replicate human development; these tools have evolved substantially in recent years and would continue to improve with greater support. According to the Non-Animal Alternatives Testing Global Market Report 2024, non-animal methods grew 11% in 2024 compared to 2023 and are expected to continue growing globally.[1] In a recent study, Hendriks, et al. described novel brain organoids that replicate key aspects of human development.[2] Their model retains genetic characteristics of their human donors, allowing researchers to create a brain tumor and screen drug responses, which are impossible to address using rodent fetuses.

Investing in shared research infrastructures with institutions and private industry can also advance tool development and reduce costs while helping generate and analyze translatable data on human development. For example, data analytics companies can increase partnerships with healthcare providers

[1] Non-Animal Alternatives Testing Market Definition and Segments. Accessed September 18, 2024. https://www.thebusinessresearchcompany.com/report/non-animal-alternatives-testing-global-market-report

[2] Hendriks D, Pagliaro A, Andreatta F, et al. Human fetal brain self-organizes into long-term expanding organoids. *Cell*. 2024;187(3):712-732.e38.

to obtain real-world patient data to improve outcomes, analyze market trends, and more.[3] Such thorough assessment can guide future research innovation and implementation of effective health strategies. It can also support the identification of new biomarkers, especially those related to extrinsic factors that may affect human development and health disparities in the U.S., both cross-cutting topics of the NICHD's interest. To understand critical developmental features and develop early diagnostics interventions for congenital anomalies, **NICHD must shift funds from animal-based research to modern human-based approaches, like human vitro models, that hold the potential to bridge the gap between molecular discoveries and clinical applications.**

Research Goal #2: Promoting Gynecologic, Andrologic, and Reproductive Health

By helping individuals to manage their fertility and addressing the impact of reproductive health conditions, NICHD is driving progress to transform lives. Several strategies can be pursued to tackle this goal. First, research should focus on deepening our understanding of key reproductive stages such as puberty, andropause, and perimenopause, emphasizing typical and atypical patterns. Women's health faces a critical gap due to scarce funding opportunities[4] for human studies, with a preference for mixed-sex cohorts[5] and reliance on poor animal models that cannot replicate the unique human reproductive system.[6]

The estrous cycle, which dictates the menstrual cycle over an individual's lifetime, differs considerably between humans and non-human primates or rodents in both length and hormonal regulation by the hypothalamus.[7, 8, 9] As mentioned in this Goal 2, the characterization of reproductive aging and its outcomes is critical, given the physiological and neurological alterations women experience during

[3] Trusted Partners in Driving Change. Blue Health Intelligence. Accessed September 19, 2024. https://bluehealthintelligence.com/about-bhi/
[4] Carneiro MM. Four billion reasons to include women's health in the research agenda. *Women & Health*. 2023;63(2):71–72.
[5] Hankivsky O, Springer KW, Hunting G. Beyond sex and gender difference in funding and reporting of health research. *Res Integr Peer Rev*. 2018;3:6.
[6] Women's Health, Research, and Sex as a Biological Variable. Public Responsibility in Medicine and Research. Published February 23, 2023. Accessed September 18, 2024. https://blog.primr.org/womens-health-research/
[7] Acevedo-Rodriguez A, Kauffman AS, Cherrington BD, Borges CS, et al. Emerging insights into hypothalamic-pituitary-gonadal axis regulation and interaction with stress signalling. *J Neuroendocrinol*. 2018;30(10):e12590.
[8] Takahashi A, Kanda S, Abe T, Oka Y. Evolution of the Hypothalamic-Pituitary-Gonadal Axis Regulation in Vertebrates Revealed by Knockout Medaka. *Endocrinology*. 2016;157:10:3994–4002.
[9] Koebele SV, Bimonte-Nelson HA. Modeling menopause: The utility of rodents in translational behavioral endocrinology research. *Maturitas*. 2016;87:5-17.

menopause.[10, 11] However, **the NICHD must shift away from research using rodents and other animals, as these species do not experience a fertile cycle that mimics humans, nor do they naturally undergo menopause.**[12, 13]

As stated by neurologist Aysha Akhtar, "[R]epeatedly, researchers have been lured down the wrong line of investigation because of information gleaned from animal experiments that later proved to be inaccurate, irrelevant, or discordant with human biology."[14] Consequently, findings from animal-based research are mostly extrapolated to humans and ultimately fall short of translating into clinical benefit. Investigating the biological and environmental factors contributing to idiopathic infertility by longitudinal studies, and using innovative animal-free methods, like organs-on-chips and *in silico* modeling, can bridge this gap and provide human-relevant results.

Improving diagnostic methods and treatments for gynecologic conditions, including the mechanisms behind pelvic pain usually a symptom of endometriosis,[15] will help physicians and patients obtain proper management. Wang and colleagues (2022) utilized ultrasonographic data to create the first 3D bioprinted endometrium as a diagnostic tool for congenital uterine anomalies.[16] Similarly, addressing reproductive aging and its impact on fertility can lead to better interventions for both fertility and contraception. A multicellular model by Ahn et al. (2021) effectively simulates the hormonal fluctuations of the menstrual cycle, enabling studies on endometrial permeability to contraceptives.[17] Additionally, this vascularized endometrium provides a proof-of-concept model for studying human embryo implantation—something that animal models cannot replicate.

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[10] Mosconi L, Nerattini M, Matthews DC, *et al.* In vivo brain estrogen receptor density by neuroendocrine aging and relationships with cognition and symptomatology. *Sci Rep.* 2024;14:12680.
[11] Fang M, Zhang P. Regulation of exercise on heart rate variability in perimenopausal and postmenopausal women. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2024;49(4):516-525.
[12] Le Page M. Most mammals go through the menopause - if they live long enough. New Scientist. Published October 26, 2023. Accessed August 29, 2024. https://www.newscientist.com/article/2399813-most-mammals-go-through-the-menopause-if-they-live-long-enough/
[13] Herrera-Pérez JJ, Hernández-Hernández OT, Flores-Ramos M, Cueto-Escobedo J, et al. The intersection between menopause and depression: overview of research using animal models. *Front Psychiatry*. 2024;15:1408878.
[14] Akhtar A. The flaws and human harms of animal experimentation. *Camb Q Healthc Ethics*. 2015;24(4):407-419.
[15] Vercellini P, Viganò P, Bandini V, Buggio L, Berlanda N, Somigliana E. Association of endometriosis and adenomyosis with pregnancy and infertility. *Fertil Steril*. 2023;119(5):727-740.
[16] Wang L, Chen XJ, Liang JH, Zhang ZK, Cao TS, Zhang L. Preliminary application of three-dimensional printing in congenital uterine anomalies based on three-dimensional transvaginal ultrasonographic data. *BMC Womens Health*. 2022;22(1):290.
[17] Ahn J, Yoon MJ, Hong SH, et al. Three-dimensional microengineered vascularised endometrium-on-a-chip. *Hum Reprod*. 2021;36(10):2720-2731.

Research Goal #3: Setting the Foundation for Healthy Pregnancies and Lifelong Wellness

This goal is crucial for advancing maternal and child health. The NICHD's emphasis on interdisciplinary collaborations and a comprehensive approach integrating diverse data types—genomic, social, and behavioral—to tackle complex pregnancy complications is needed. Factors such as age, lifestyle, and genetic makeup impact offspring but the underlying mechanisms are frequently overlooked or inaccessible. Here, patient-derived models, such as organoids, offer valuable opportunities for patient-centric research, enabling the study of unique developmental processes during pregnancy using human tissues. In contrast, animal models—primarily rodents—face significant limitations due to fundamental differences in cell signaling, genetics, and anatomy compared to humans.[18, 19, 20] These disparities make rodents particularly poor for studying congenital conditions. For example, therapeutic targets for fragile X syndrome identified in mouse models have failed to translate in clinical trials involving teens and adults due to interspecies differences in brain development between humans and mice that mislead findings.[21, 22] For these reasons, **NICHD must fully divest from failing animal models to free up resources for human-based pregnancy research.**

The placenta is the main organ supporting oocyte development,[23] yet the key fundamental mechanisms governing its development and function remain elusive, largely due to a lack of appropriate research models.[24] While developmental biologists agree on conserved steps across mammalian embryogenesis, they recognize striking differences between humans and mice. In humans, the blastocyst undergoes more cellular replication cycles before invading the endometrium, whereas in mice, implantation is faster and outside the uterine cavity, with subsequent fetal maturation following divergent pathways.[25] As Knöfer et al point out, "remodelling of uterine arterial vessels largely depends on maternal factors," making mice "an imperfect model of human placentation."[24]

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[18] Mestas J, Hughes CCW. Of mice and not men: Differences between mouse and human immunology. J Immunol. 2004;172(5):2731-2738

[19] Li Z, Zheng W, Wang H, et al. Application of Animal Models in Cancer Research: Recent Progress and Future Prospects. Cancer Manag Res. 2021;13:2455-2475.

[20] Krafft PR, Bailey EL, Lekic T, et al. Etiology of stroke and choice of models. *Int J Stroke*. 2012;7(5):398-406.

[21] Hagerman RJ, Berry-Kravis E, Hazlett HC, et al. Fragile X syndrome. *Nat Rev Dis Primers*. 2017;3:17065.

[22] Berry-Kravis E, Des Portes V, Hagerman R, et al. Mavoglurant in fragile X syndrome: Results of two randomized, double-blind, placebo-controlled trials. *Sci Transl Med*. 2016;8(321):321ra5.

[23] Tutar R, Çelebi-Saltik B. Modeling of Artificial 3D Human Placenta. *Cells Tissues Organs*. 2022; 211(4):527–536.

[24] Knöfler M, Haider S, Saleh L, *et al.* Human placenta and trophoblast development: key molecular mechanisms and model systems. *Cell. Mol. Life Sci.* 2019;76:3479–3496.

[25] Rossant J. Mouse and human blastocyst-derived stem cells: vive les differences. *Development*. 2015;142(1):9–12.

There is an urgent need for both basic and translational research models that can authentically replicate human embryonic processes, replacing these ineffective animal-based approaches. Modern 3D and self-renewing placenta models, derived from human induced pluripotent stem cells (hiPSCs), along with placentas-on-a-chip, have been developed to study placental barriers, diffusion, and human-specific signaling pathways.[23, 24, 26,27] However, these innovative technologies require greater infrastructural and financial support for their use—an opportunity for the NICHD to explore. The training of professionals and researchers, as emphasized in the cross-cutting themes of this strategic plan, is equally important to ensure the successful adoption and implementation of these non-animal methods in future research.

Finally, the focus on community-informed research to address health disparities—another cross-cutting theme—is vital for ensuring equitable care for all. The NICHD can draw inspiration from international initiatives like the UK's Newborn Genomes,[28] a genetic screening program, and Born in Bradford,[29] the largest longitudinal study of families and communities in the UK. As another example, a multinational prospective study investigated the link between maternal hemoglobin concentrations during pregnancy and the risk of adverse outcomes for the mother and offspring, showing that both high and low levels hemoglobin levels pose significant risk factors for complications.[30] These programs offer valuable models for fostering inclusive, research-driven health interventions to improve health and well-being

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Research Goal #4: Improving Child and Adolescent Health and the Transition to Adulthood

This NICHD goal is vital for advancing our understanding of child and adolescent health by addressing key areas such as infant mortality, childhood illness, and the transition from adolescent to adult healthcare. The emphasis on understanding how social and environmental factors influence development —referred to as exposomics—combined with efforts to improve trauma and injury prevention, demonstrates a forward-thinking, holistic approach to enhancing health outcomes. To achieve truly

[26] Lermant A, Rabussier G, Davidson L, Lanz HL, Murdoch CE. Protocol for a placenta-on-a-chip model using trophoblasts differentiated from human induced pluripotent stem cells. *STAR Protoc*. 2024;5(1):102879.
[27] Li Z, Kurosawa O, Iwata H. A Novel Human Placental Barrier Model Based on Trophoblast Stem Cells Derived from Human Induced Pluripotent Stem Cells. *Tissue Eng Part A*. 2020;26(13-14):780-791.
[28] Genomics England. Newborn Genomes Programme. Copyright 2024. Accessed September 21, 2024. https://www.genomicsengland.co.uk/initiatives/newborns.
[29] Born in Bradford. About Bradford. BorninBradford.nhs.uk. Copyright 2024. Accessed September 21, 2024. https://borninbradford.nhs.uk/.
[30] Ohuma EO, Jabin N, Young MF, et al. Association between maternal haemoglobin concentrations and maternal and neonatal outcomes: the prospective, observational, multinational, INTERBIO-21st fetal study. *Lancet Haematol*. 2023;10(9):e756-e766.

translatable findings**, the NICHD should prioritize evidence-based studies utilizing human data and establish long-term, dedicated grants for this purpose.**

Longitudinal studies, such as the UK examples mentioned above, along with *in silico* data interpretation, are particularly well-suited for assessing variables within the human context—something that cannot be replicated in animal models. Multicenter retrospective studies involving children and teenagers are also valuable for understanding specific conditions and their long-term impact on adulthood. Current care models for children, adolescents, and their parents or caretakers often fail people living in unfavorable circumstances and overlook risk factors.[31] For example, mental health disorders such as depression and PTSD in pediatric cancer patients are closely linked to age, so in this context, age-appropriate trauma interventions are necessary.[32]

These human-based approaches are key to identifying factors that affect childhood development, which has a well-defined social-emotional trajectory.[33] Implementing timely interventions that target cognitive, emotional, and social growth can ensure a smoother transition into successful adulthood.[33, 34] However, achieving this ambitious mission will require a concerted effort to train healthcare professionals, educators, and researchers in innovative diagnostic methodologies in both preclinical and clinical scenarios. Building interdisciplinary teams and fostering partnerships between institutions, industries, and experts in data analysis and monitoring can create a solid foundation for shaping a healthier future for the next generations of adults.

Research Goal #5: Advancing Safe and Effective Therapeutics and Devices for Pregnant and Lactating Women, Children, and People with Disabilities

These populations have unique medical needs often underrepresented in clinical and large-scale research which is not well funded.[35] When pregnant individuals, children, and people with disabilities are excluded from research studies, it raises concerns about the external validity of findings and risks skewing data

[31] Papageorghiou A. Maximising health outcomes. *BJOG*. 2022;129(7):1013-1014.
[32] Al-Saadi LS, Chan MF, Al Sabahi A, *et al.* Prevalence of anxiety, depression, and post-traumatic stress disorder among Omani children and adolescents diagnosed with cancer: a prospective cross-sectional study. *BMC Cancer*. 2024;24:518.
[33] Malik F, Marwaha R. Developmental Stages of Social Emotional Development in Children. Updated Sep 18, 2022. StatPearls. Treasure Island: StatPearls Publishing. Available: https://www.ncbi.nlm.nih.gov/books/NBK534819/
[34] Drago F, Scharf RJ, Maphula A, *et al.* Psychosocial and environmental determinants of child cognitive development in rural south africa and tanzania: findings from the mal-ed cohort. *BMC Public Health.* 2020;20:505.
[35] Krahn GL, Walker DK, Correa-De-Araujo R. Persons with disabilities as an unrecognized health disparity population. *Am J Public Health.* 2015;105(suppl 2):S198–S206

toward “healthier,” standardized populations.[36] These groups lack sufficient preclinical models in fundamental research. Attempts to replicate "human-like" conditions in other mammals, such as transgenic non-human primates (NHP)[37, 38] and mice,[39] face significant limitations. First, due to evolutionary divergence,[40] NHPs' social behavior relies heavily on visual and vocal communication, while mice depend on chemical and olfactory signals,[41] which are often disrupted in laboratory settings. These species fail to replicate pathogenesis and contextual conditions requiring clinical diagnosis, especially in the case of neurological conditions with different penetrance spectra, like autism.[40] Moreover, ethical concerns surrounding animal experimentation further highlight the need for change.

To address these challenges, it is crucial to prioritize foundational research using human-based models for biomarker identification and the development of approaches specifically tailored to these underrepresented populations. A model for "accessible research design" has been proposed, encompassing universal design, accommodations, and modifications to ensure the enrollment of people with disabilities.[36] For example, one study found that nearly 90% of developmental research articles excluded children with disabilities, despite 63% of those studies being able to include them with accommodations without compromising research integrity.[42] This issue likely extends to other groups, such as lactating individuals and children.

Additionally, leveraging data science to assess outcomes and utilizing wearable devices for real-time data collection will be key for creating scalable, accessible solutions. Individuals with Down syndrome, the largest genetic cohort at risk for early-onset Alzheimer's disease, face critical opportunities in clinical studies.[43] Challenges like these pushed the establishment of the Down Syndrome Biobank Consortium,[43] a

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[36] Rios D, Magasi S, Novak C, Harniss M. Conducting Accessible Research: Including People With Disabilities in Public Health, Epidemiological, and Outcomes Studies. *Am J Public Health*. 2016;106(12):2137-2144.
[37] Zhao H, Wang Q, Yan T, et al. Maternal valproic acid exposure leads to neurogenesis defects and autism-like behaviors in non-human primates. *Transl Psychiatry*. 2019;9(1):267.
[38] Liu Z, Li X, Zhang JT, et al. Autism-like behaviours and germline transmission in transgenic monkeys overexpressing MeCP2. *Nature*. 2016;530(7588):98-102.
[39] Delling JP, Boeckers TM. Comparison of SHANK3 deficiency in animal models: phenotypes, treatment strategies, and translational implications. *J Neurodev Disord*. 2021;13(1):55.
[40] Zhao H, Jiang YH, Zhang YQ. Modeling autism in non-human primates: Opportunities and challenges. *Autism Res*. 2018;11(5):686-694.
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[42] Feldman MA, Battin SM, Shaw OA, Luckasson R. Inclusion of children with disabilities in mainstream child development research. *Disabil Soc.* 2013;28(7):997–1011.
[43] Aldecoa I, Barroeta I, Carroll SL, et al. Down Syndrome Biobank Consortium: A perspective. *Alzheimers Dement*. 2024;20(3):2262-2272.

multinational brain tissue bank, and other ethical biobanks[44] for human-focused research purposes. However, real progress will only occur when research policy evolves alongside these scientific advances. The NICHD must implement comprehensive measures by actively collaborating with, training, and engaging health organizations dedicated to these communities. Therefore, the institute can create inclusive and equitable therapeutics while, in parallel, tackling health disparities, closing nutrition gaps, and adopting modern animal-free tools to improve overall health.

[44] BocaBio. Drive Science Forward with the Premier Selection of Biospecimens for Research. Assessed September 24, 2024. https://www.bocabio.com/biospecimens/