NATIONAL INSTITUTE OF MENTAL HEALTH

STRATEGIC PLAN FOR RESEARCH

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National Institute of Mental Health

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Message from the Director

It is an exciting time to be at the helm of the National Institute of Mental Health (NIMH), the lead federal agency charged with setting and supporting the national agenda for mental health research. Scientific advances are rapidly transforming neuroscience and mental health care. Just in the last five years, we have made considerable progress. In basic science, the genetic revolution has begun to pay off for mental health research—after facing some challenges, we have now identified hundreds of places in the genome irrefutably linked to mental illnesses such as schizophrenia, autism, and depression. Thanks to the NIH Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, we have new tools and resources that allow unprecedented insight into the exquisite complexities of the living brain. In translational sciences, we celebrated the U.S. Food and Drug Administration (FDA) approval of two of the first truly novel antidepressants in decades—esketamine for treatment-resistant depression, and brexanolone for postpartum depression. And in intervention research, NIMH-sponsored studies proving the effectiveness of coordinated specialty care for first episode psychosis led to nationwide implementation of this evidence-based care model through state-supported mental health clinics.

The future is bright. Looking forward, we've enacted the new NIMH Strategic Plan for Research, aiming to build on these advances. Over the next few years, we look forward to further implementation of suicide prevention efforts based on recent NIMH findings. These findings include studies demonstrating the benefit of universal screening in emergency departments for suicidality, and the benefits and challenges of predicting suicide risk using electronic health records and other digital tools. NIMH is also investing in practice-based research that examines mental health care delivery in real-world settings. For example, NIMH is pioneering the Early Psychosis Intervention Network (EPINET), a research network that will use data from community-based first episode psychosis clinics to enhance the delivery, evaluation, and continual improvement of evidence-based care. These continuous advances drive the enthusiastic and energetic efforts of the research workforce devoted to our mission. And, more importantly, they offer hope and solutions to individuals with mental illnesses, as well as their families and communities.

Since the advent of this plan in 2020, we have faced significant challenges. During the coronavirus disease 2019 (COVID-19) pandemic, symptoms of depression, anxiety and substance use have increased for many. Underserved and minoritized communities are disproportionately impacted by greater rates of illness and death tragically due to SARS-CoV-2 infection as well as with broader mental health consequences of the social, behavioral, and economic impacts of the pandemic. Regardless of direct infection, reports of worsened mental health symptoms have remained elevated compared to pre-pandemic data. In communities of color, systemic racism and its pernicious effects, starkly evidenced by the death of George Floyd at the hands of the police, continue to compound these challenges.

NIMH has relied on its strategic plan to adapt to these challenges. We have collaborated with other Institutes, Centers, and Offices across NIH to fund over 40 projects to understand the mental health impacts of the pandemic, including the impact of public health mitigation approaches and critically to

evaluate scalable, deployable interventions that are desperately needed to respond to the increased mental health needs of diverse populations. All of these efforts are in line with our strategic priorities, particularly in the context of ongoing mental health disparities.

As NIMH Director, I am committed to dismantling structural racism in biomedical research. At NIMH, we aim to identify and address the extent to which our policies, procedures, and culture serve to perpetuate the status quo and are working to promote anti-racist ideas and actions. We started by examining how our application review process affects the diversity of our scientific workforce. For example, some of our early efforts are focused on understanding and employing solutions to reduce disparities in award rates for grant applications supporting Black investigators. With recommendations from the Anti-Racism Task Force (comprised of staff from across the Institute), we are also making changes to improve diversity, equity, inclusion, and accessibility within the NIMH workplace. I recognize that these efforts, among others in line with NIH, such as the UNITE initiative, are just the start to making lasting change.

The NIMH Strategic Plan for Research maps our path. From basic research aimed at understanding how the brain produces behavior, to translational efforts to uncover novel treatment targets, to clinical studies testing novel approaches in community settings, we have charted numerous routes linking these challenges and opportunities. Each has the potential to deliver significant advances in mental health care. NIMH's broad portfolio aims to ensure that our research will have public health impacts across a range of timeframes—from the near-term to the far-off future. At NIMH, we are proud of how far we have come, humbled by the distance yet to be traveled, and empowered by the hope that drives us forward.

Joshua A. Gordon, M.D., Ph.D.

Director, National Institute of Mental Health

Overview of NIMH

The National Institute of Mental Health (NIMH) is the lead federal agency for research on mental illnesses. NIMH is one of the 27 Institutes and Centers that make up the National Institutes of Health (NIH), the largest biomedical research agency in the world. The mission of NIMH is to transform the understanding and treatment of mental illnesses through basic and clinical research, paving the way for prevention, recovery, and cure.

To carry out this mission, NIMH, as established by the Mental Health Act of 1946 and in accordance with Title IV of the Public Health Service Act, conducts and supports biomedical and behavioral research, health services research, research training, and health information dissemination with respect to the causes, diagnosis, treatment, management, and prevention of mental illnesses. As mental health is an important part of overall health, NIMH invests in research on adaptive and maladaptive behaviors to better understand mental function and dysfunction.

NIMH supports research and research training through extramural activities and conducts research and research training through intramural activities. Through its extramural program, NIMH supports more than 3,000 research grants and contracts annually at universities, academic health centers, and other research institutions across the country and around the world. The NIMH Extramural Research Program is organized into four scientific funding Divisions—the Division of Neuroscience and Basic Behavioral Science, the Division of Translational Research, the Division of Services and Intervention Research, and the Division of AIDS Research. NIMH staff manage and administer the extramural research grants and contracts that support cutting-edge scientific discovery in basic, translational, comparative effectiveness, and implementation science that aims to transform understanding, prevention, and treatment of mental illnesses across the lifespan, from prenatal development to late life.

Staff in the NIMH Intramural Research Program (IRP) plan and conduct basic, clinical, and translational research to advance understanding of the diagnosis, causes, treatment, and prevention of psychiatric disorders. NIMH IRP investigators utilize the unique resources of the NIH to conduct state-of-the-art research in an environment conducive to the training and development of clinical and basic scientists that often complements extramural research activities. The NIMH IRP supports approximately 600 scientists, who work on the NIH campus in Bethesda, MD. NIMH intramural scientists range from molecular biologists working in laboratories to clinical researchers working with patients in the NIH Clinical Center, the world's largest hospital dedicated to clinical research. The variety of scientific expertise facilitates interdisciplinary studies and promotes translational research, linking basic research discoveries to clinical care.

To deliver high quality, impactful research and promote translation of such research into clinical practice, services delivery, and policy, NIMH developed the Strategic Plan for Research to advance our mission and guide research over a five-year period. The NIMH Strategic Plan for Research builds on the successes of previous NIMH Strategic Plans, provides a framework for research to leverage new

opportunities for scientific exploration, and addresses new challenges in mental health. In this Strategic Plan for Research, NIMH outlines four high-level Goals as follows:

- **Goal 1: Define the Brain Mechanisms Underlying Complex Behaviors**
- **Goal 2: Examine Mental Illness Trajectories Across the Lifespan**
- **Goal 3: Strive for Prevention and Cures**
- **Goal 4: Strengthen the Public Health Impact of NIMH-Supported Research**

These four Goals form a broad roadmap for the Institute's research priorities over the next five years, beginning with fundamental science of the brain and behavior, and extending through evidence-based services that improve public health outcomes.

Please Note: The terms "mental illnesses," "mental disorders," and "psychiatric disorders" are used interchangeably throughout this document. These terms are meant to include an array of disorders within NIMH's scope of interest. Reference to a specific disorder (i.e., as an example or a highlight) or research area does not imply prioritization, unless otherwise noted. Furthermore, NIMH respects the known comorbidity and heterogeneity of symptoms across mental disorders and recognizes that knowledge gained from studying one may inform understanding of and treatment for others.

Serving as an Efficient and Effective Steward of Public Resources

Scientific Stewardship

Setting Research Priorities

At the agency level, NIH sets research priorities by managing a dynamic balance among existing and emerging public health needs, scientific opportunities, budgetary considerations, and the range of science in its portfolio. At the institute level, priorities are outlined within the NIMH Strategic Plan for Research. At NIMH, a balanced portfolio starts with excellent science that includes diverse subject matter (basic, translational, and applied sciences), diverse timeframes (research with potential impact in the short-, medium-, and long-terms), diverse study populations, and a diverse workforce. NIMH research priorities are also informed by strategic planning. Strategic planning at NIMH is comprehensive, responsive, and adaptive to the often serendipitous nature of biomedical scientific progress. Planning also includes input from a variety of stakeholders, including NIMH leadership and staff, the National Advisory Mental Health Council, as well as federal and private partners, both domestic and global.

NIMH also sets priorities in accordance with NIH-wide strategic plans and research plans of partnering organizations. Such plans include the *NIH-Wide Strategic Plan*, the *Advancing Science for the Health of Women: The Trans-NIH Strategic Plan for Women's Health Research*, the *NIH Minority Health and Health Disparities Strategic Plan*, the *NIH Strategic Plan for Tribal Health Research*, the *Office of Disease Prevention Strategic Plan*, and the *NIH Strategic Plan for Data Science*, among others. NIMH also has a substantial investment in supporting HIV research; this investment is guided by the *NIH Strategic Plan for HIV and HIV-Related Research*, coordinated through the NIH Office of AIDS Research. Additionally, NIMH has contributed to the creation of several strategic plans and reports that include more detail on specific topics, which also inform NIMH priorities. These documents include but are not limited to: the *National Research Action Plan (NRAP)*; the *Interagency Autism Coordinating Committee (IACC) Strategic Plan for Autism Spectrum Disorder*; the *Interdepartmental Serious Mental Illness Coordinating Committee Report to Congress;* the *Grand Challenges in Global Mental Health* Initiative; *A Prioritized Research Agenda for Suicide Prevention: An Action Plan to Save Lives*, a collaboration with the National Action Alliance for Suicide Prevention; and, the Brain Research through Advancing Innovative Neurotechnologies® (BRAIN) Initiative strategic plan, *BRAIN 2025: A Scientific Vision*, and Working Group reports and plans, including the *BRAIN Initiative 2.0: From Cells to Circuits, Toward Cures* and the *BRAIN Initiative and Neuroethics: Enabling and Enhancing Neuroscience Advances for Society*.

Monitoring and Measuring Programs

NIMH continuously reviews and evaluates its scientific research and training programs to ensure responsible management of public funds and measure progress toward accomplishing our mission. For example, NIMH regularly conducts portfolio analyses to identify research gaps and opportunities.

NIMH's monitoring and evaluation efforts continue to evolve to keep pace with changing methods to analyze information, and new requirements mandated by NIH, the Department of Health and Human Services (HHS), and Congress. Program monitoring and evaluation informs the development, implementation, and reporting of NIMH efforts and accomplishments.

Emphasizing Rigor and Reproducibility

Funding excellent science is essential to the research enterprise. As such, NIMH emphasizes the importance of both rigor and reproducibility. Research studies must have a sufficiently rigorous design and be sufficiently powered, such that they can be replicated. This means NIMH ensures the sample sizes within studies are appropriate so they are adequately powered for real-world effect sizes; ensures the statistical analysis plans included in grant applications contain sufficient information for reviewers to properly evaluate them; ensures expertise in review sections and program staff to properly assess statistical methodologies; and, encourages the use of data sharing platforms that can enable third-party confirmation and mega-analyses that consolidate data from multiple studies.

Fostering Resource and Data Sharing

Access to biospecimens and data sharing efficiently expands research capacity and maximizes NIMH's investments by promoting hypothesis generation, increasing the potential for testing novel questions by integrating and harmonizing existing data, and encouraging reproducibility. In concordance with the NIH Data Sharing Policy, NIMH continues to support programs that provide access to biospecimens, such as the NIH NeuroBioBank, a national resource for investigators utilizing human post-mortem brain tissue and related biospecimens. NIMH also strongly encourages investigators to use common data elements, such as those available in the PhenX Toolkit, and requires the use of a small set of common data elements for NIMH-funded mental health research. NIMH expects investigators to share data through databases and repositories, such as the NIMH Data Archive.

Enhancing Oversight and Monitoring of Clinical Trials

NIMH is committed to responsible stewardship, accountability, oversight, and transparency of clinical trials. NIMH continues to enhance oversight and monitoring of clinical trials to strengthen clinical research, ensure compliance, uphold inclusion standards, and safeguard research participants and their data. For example, to ensure studies are meeting their recruitment goals, NIMH expanded the Policy for the Recruitment of Participants in Clinical Research to apply to all clinical trials, regardless of size.

Creating and Strengthening Partnerships

Collaborations and partnerships across the research pipeline are vital components of NIMH efforts to achieve its public health mission. NIMH collaborates with other NIH Institutes and Centers, as well as

HHS (e.g., the Centers for Disease Control and Prevention (CDC), the Centers for Medicare and Medicaid Services (CMS), the U.S. Food and Drug Administration (FDA), the Health Resources and Services Administration (HRSA), the Substance Abuse and Mental Health Services Administration (SAMHSA), the Indian Health Service (IHS), the Administration for Community Living (ACL), the Office of the Assistant Secretary for Planning and Evaluation (ASPE), the Administration for Children and Families (ACF)), and other federal agencies (e.g., the Department of Defense (DoD), the Department of Veterans Affairs (VA)). NIMH also works with public, private, non-profit, and research partners, both domestic and international, including those in the biotech and pharmaceutical industries. To broaden the dissemination and impact of research, NIMH works with external stakeholders—policymakers, advocacy groups, providers, and people with lived experience, including family members—who are also committed to the prevention, treatment, recovery, and cure of mental illnesses. Collaboration, communication, and coordination occur at various stages of research and continue to improve dissemination and implementation of evidence-based strategies, practices, and programs.

Management and Accountability

Cultivating a Respectful and Inclusive Workplace at NIMH

The contributions of each and every member of the NIMH community are vital to transform the understanding, prevention, and treatment of mental illnesses. An environment where all people feel welcome, respected, valued, and heard is essential for individuals to contribute to their fullest potential. As such, NIMH is committed to creating and maintaining a work environment that celebrates and promotes diversity, equity, inclusion, and accessibility, and is free of harassment and other inappropriate conduct. The Institute is actively engaging with staff, including the NIMH Anti-Racism Task Force, to identify opportunities to improve workplace culture and climate. Further, NIMH supports efforts, such as the NIH UNITE initiative, to identify and take actions to address structural racism within the NIH and across the biomedical research community.

Promoting Innovation

The fields of science and technology are constantly evolving. Beyond scientific innovation, NIMH also embraces innovative administrative management practices to ensure the Institute can adapt rapidly to changing needs and requirements while managing existing resources in a complex environment. In addition, NIMH is committed to encouraging a diverse research and scientific support workforce equipped with the knowledge and skills required to execute NIMH's mission.

Enhancing Risk Management

NIMH proactively identifies and mitigates internal and external risks to support the Institute's mission. Working with HHS and NIH leadership, NIMH continues to improve procedures to develop standardized, automated, metric-oriented, and consistent business practices to mitigate risk. NIMH will leverage the values of collaboration, transparency, and accountability throughout our functional areas to proactively adapt risk-management mitigation procedures when confronted with emerging issues.

Improving Administrative Processes

NIMH is committed to innovative and agile process improvement and aims to optimize, automate, and streamline business processes to ensure quality and consistency. As an example, NIMH regularly conducts internal workflow analyses to identify opportunities to reduce administrative burden. NIMH strives to implement business process management initiatives to maintain accountability and support our staff. NIMH will also continue to support efforts aimed at leveraging data to manage the needs of the Institute and drive decision-making processes.

Promoting Workforce Development and Diversity

To keep pace with advancing science, the NIMH workforce needs resources and training to ensure it has the knowledge, skills, and technologies to support its activities. NIMH encourages and supports the development of an inclusive, diverse, and well-trained research workforce. In addition, to preserve institutional knowledge, NIMH employs innovative approaches to encourage career development, retain expertise, and reward outstanding performance with an eye toward achieving equity and inclusion.

Accomplishing the Mission

NIMH developed the Strategic Plan for Research to advance the Institute's mission and guide research over a five-year period. The sections of this plan specifically address areas of crucial importance as NIMH strives to accomplish its mission. First, Challenges and Opportunities confronts the challenges that may lie ahead and describes some of the unique opportunities for scientific exploration to overcome these challenges and advance the understanding of mental illnesses. Second, Cross-Cutting Research Themes are topics that are integral to the Goals of the Strategic Plan for Research and will influence the direction of mental health research as we move forward. Finally, the four Goals of the Strategic Plan for Research form a broad roadmap for the Institute's research priorities, beginning with the fundamental science of the brain and behavior, and extending through evidence-based services that improve public health outcomes. Each of the four Goals include Objectives, followed by Strategies, which include research areas of specific interest that will help drive progress toward achieving our mission. The topics throughout the plan are not exhaustive. Prior to submitting an application, investigators are encouraged to contact NIMH program staff to discuss proposed aims and relevance to the overall Goals.

NIMH will assess and monitor its performance in achieving the Goals presented in this Plan by gathering and analyzing metrics associated with its core mission. Findings will be integrated to inform and refine the direction of the Plan over time. The Institute will share these findings and updates to the Plan with stakeholders regularly.

In the context of prioritizing excellent science, the overall strategy for funding science is to support a broad spectrum of both investigator-initiated and institute-solicited research across the NIMH portfolio. Full implementation of the NIMH Strategic Plan for Research will help transform the prevention, diagnosis, and treatment of mental illnesses.

Challenges and Opportunities

The urgency of NIMH's mission stems from the significant burden mental illnesses impose on individuals, their families, and society. In any given year, nearly one-fifth of all U.S. adults struggle with a mental illness[1] and the burden of mental illness is predicted to rise worldwide in coming decades.[2,3] Mental illnesses cut across age, sex, race, ethnicity, and socioeconomic status. Mental illnesses occur more commonly in people with other chronic illnesses, such as heart disease, diabetes, cancer, and HIV.[4,5] In fact, people with a mental illness may have an increased risk for chronic illnesses,[6] and effective treatment for mental illnesses can reduce that risk.[7] Individuals with mental illnesses are also disproportionately represented among homeless and incarcerated populations.[8] Furthermore, serious mental illnesses significantly impair one's ability to function in daily life, are associated with personal loss of earnings,[9] have a negative global financial impact,[10] and are among the leading causes of poor health and early mortality worldwide.[4,11] Tragically, suicide remains an urgent public health crisis in the United States.[12] Although suicide prevention efforts are helping to lower the national suicide rate, health disparities among certain minoritized groups persist. The burden of mental illnesses demands that we harness scientific knowledge and tools to achieve better understanding, prevention, and treatment of these disabling conditions. In this section, we outline our plans to leverage considerable research opportunities to address the many challenges of mental health and mental health research.

Coronavirus Disease 2019 (COVID-19) Pandemic

To address the ongoing challenges that SARS-CoV-2 and the secondary impacts of the COVID-19 pandemic pose to our health and well-being, NIH is working urgently in unprecedented ways to understand and mitigate health threats. The NIH Strategic Plan for COVID-19 Research provides a framework for funding research across the scientific spectrum, primarily focusing on the direct testing, therapeutic, and preventive approaches needed to address SARS-CoV-2 and its long term consequences. As part of the strategic response to COVID-19, NIMH is actively engaged with the NIH Researching COVID to Enhance Recovery (RECOVER) initiative, which seeks to understand, prevent, and treat post-acute sequelae of SARS-CoV-2 infection. NIMH is also participating in multiple Rapid Acceleration of Diagnostics (RADx) initiatives, including the RADx® Underserved Populations (RADx-UP) program, which aims to lay the foundation to reduce disparities for those underserved and vulnerable populations who are disproportionately affected by the COVID-19 pandemic. NIMH is also involved in several other NIH-wide efforts, including the Social, Behavioral, and Economic Impacts of COVID-19 and Maternal and Child Health workgroups. Emerging data indicate that people with serious mental illness have been hard hit by the pandemic. Individuals with schizophrenia or depression are more than seven times more likely to contract COVID-19 and are more than twice as likely to die from it if they do fall ill, compared with individuals who do not have a mental illness.[13-15] NIMH-supported researchers are examining the effects of COVID-19 on mental health and developing and testing ways to improve delivery of care and treatment of mental illnesses in the context of a pandemic. This work is critical to meet the increased

mental health needs for all who have been impacted by the pandemic, particularly as access to mental health services remain insufficient for the demand. In addition, NIMH staff continue to develop resources and share coping strategies to help people during the pandemic. More information about NIH's response to the COVID-19 pandemic and guidance for researchers can be found on the NIH COVID-19 webpage.

Suicide Prevention

Given the troubling rise in the national suicide rate in the past decades, suicide prevention research remains an urgent priority for NIMH. From 1999 through 2018, U.S. suicide rates had shown small but consistent increases. However, in 2019, the age-adjusted suicide rate (13.9 per 100,000) was significantly lower than the 2018 rate (14.2 per 100,000), a trend that continued in 2020 (13.5 per 100,000).[12] This decrease did not occur across minority racial and ethnic groups, and explanations for these disparities are being explored.[16] NIMH's portfolio includes projects aimed at identifying individuals and populations most at risk for suicide, understanding the causes of suicide risk, developing suicide prevention interventions, and testing the effectiveness of these interventions and services in real-world settings. NIMH intramural and extramural research efforts have resulted in the development of screening tools and clinical pathways for implementation in real-world settings to identify those at risk for suicide. Our current collaborative efforts are testing the benefits of risk detection and interventions. Because many suicide decedents in the United States have accessed health care services in the 12 months preceding death, health care systems can play a vital role in identifying individuals at risk and preventing suicide attempts.[17] NIMH research has focused on emergency departments as a critical focal point, demonstrating that brief screening tools can improve providers' ability to identify individuals at risk for suicidal behavior.[18,19] Pairing this screening with a low-cost intervention, such as safety planning and follow-up phone calls, results in significant decreases in subsequent suicide attempts in the following year.[18] NIMH-supported research has also led to the development of a computerized adaptive screener, which may make it easier for providers to screen more people and could help emergency departments quickly facilitate a connection with mental health services. NIMH continues to support research to identify how and why these screening and follow-up interventions work, and how these evidence-based tools can be scaled up for broader implementation to prevent suicide attempts and deaths. In addition, accumulating evidence suggests that various preventive interventions delivered early in life can change children's mental health and substance use trajectories in a positive manner, including decreased risk for suicidal ideation and behaviors in adolescence and adulthood. NIMH continues to focus on understanding how disparities in suicide arise and can be addressed including among sexual and gender minority youth and adults who have elevated rates of suicide ideation and attempts across age, race, and ethnic groups.[20] Understanding disparities in suicides among Black, American Indian and Alaska Native, and Asian youth, as well as pre-teens, older adults, and rural residents, continues to be an important area of focus.

Early Intervention in Psychosis

In 2008, NIMH launched the Recovery After an Initial Schizophrenia Episode (RAISE) project, a large-scale research initiative with the goal to help reduce the likelihood of long-term disability that people with schizophrenia often experience and help them lead productive, independent lives. The RAISE studies aimed to answer questions about the feasibility, effectiveness, and scalability of early intervention services for people experiencing first episode psychosis in the United States, with an emphasis on coordinated specialty care (CSC), a team-based, integrated, multi-element treatment approach to early psychosis. Baseline findings from the RAISE studies documented areas in need of improvement, including the long duration of untreated psychosis,[21] variable adherence to treatment guidelines,[22] and poor attention to comorbid medical conditions associated with premature mortality.[23] In addition, the RAISE studies demonstrated that early intervention improves clinical outcomes among youth and young adults with first episode psychosis, and that CSC is a feasible and cost-effective approach to early intervention in first episode psychosis.[24,25,26] Through collaborations with other federal agencies, NIMH transformed these findings into real-world change.[27,28] CSC is now the standard of care for early psychosis, with more than 360 CSC programs across the country. In 2019 alone, CSC programs helped over 22,000 young people confronting the tremendous challenge of a first episode of psychosis by ensuring they had access to the best possible evidence-based care.

NIMH leveraged this expansion of CSC programs in the U.S. through the Early Psychosis Intervention Network (EPINET). The goal of EPINET is to accelerate advances in early psychosis care, recovery outcomes, and scientific discovery through a national early psychosis learning health care partnership. In this "learning health care system," data that are routinely collected in CSC programs, as part of clinical practice, drive continuous improvement in client care and further scientific inquiry. Through EPINET, NIMH supports eight regional scientific hubs that include more than 100 CSC clinics in 17 states, as well as a national data coordinating center that standardize, collect, and aggregate data across community clinics and use computational methods to study CSC quality and treatment effectiveness. By studying large, nationally representative data sets, EPINET may offer crucial insights into how best to tailor early psychosis care for individuals and provide information to guide improvements in diagnosis and intervention.

NIMH has joined the Accelerating Medicines Partnership® (AMP®) to form a public-private partnership between the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), the European Medicines Agency, and multiple public and private organizations to establish the AMP Schizophrenia (AMP SCZ) initiative. AMP is managed through the Foundation for the National Institutes of Health (FNIH). The goal of the initiative is to generate tools that will improve success in developing early-stage pharmacologic interventions for patients who are at risk of developing schizophrenia. AMP SCZ has established a research network focused on identifying biological markers of disease progression, outcome measures and clinical endpoints. The initiative has also established a Data Processing, Analysis, and Coordinating Center to allow researchers to integrate and analyze data from new and key existing cohorts at clinical high risk for psychosis, with all data and analyses made publicly available through the

NIMH Data Archive. Findings from these studies may enable researchers to develop algorithms that predict the course of illness for individuals with clinical high risk for psychosis and allow clinical trials to test new pharmacologic interventions to prevent the onset of psychosis.

Mental Health Equity

Racial and ethnic minorities, sexual and gender minorities, socioeconomically disadvantaged populations, and underserved rural populations experience striking disparities in burden of mental illness, access to and engagement in care, and recovery. Moreover, people from minoritized and marginalized communities are disproportionately affected by existing disparities that have been exacerbated by recent acts of racism and discrimination and converging public health crises (e.g., COVID-19, HIV, and opioid epidemics).[29] In accordance with the 21st Century Cures Act, NIMH staff work closely with the National Institute on Minority Health and Health Disparities (NIMHD), the Office of Research on Women's Health (ORWH), and other NIH Institutes, Centers, and Offices to ensure activities take into account the health needs of minorities and women and are focused on reducing health disparities. In our efforts to achieve mental health equity, NIMH developed an Approach to Mental Health Disparities Research, which outlines five priority research areas to address mental health disparities. NIMH supports research that addresses the needs of individuals and communities across age, race, ethnicity, language, gender identity, sexual orientation, geography, and social determinants of health (e.g., education, economic stability, quality of housing, access to health care, experience of discrimination), as well as their intersectionality (a framework that addresses the multiple dimensions of individuals' identity and social systems as they intersect with one another and relate to inequality).[30] Of particular priority is research that identifies mechanisms contributing to the persistence of mental health disparities, and tests interventions aimed at reducing disparities, improving outcomes, and promoting equity. Further, to build a valid evidence base for effective prevention, treatment, and mental health services, NIMH strives to foster a culture of inclusion that values and fosters partnerships between study participants, communities, and researchers from all backgrounds.

HIV Research

The prevalence of mental illnesses is higher in people with or at risk for HIV compared to the general population. Mental illnesses can be a barrier to HIV prevention, testing, linkage to treatment, treatment engagement, and retention in care. Mental illnesses are associated with poor health outcomes such as lower medication adherence, higher HIV incidence rates, and increased disease burden. There are also many co-occurring biological, psychosocial, and structural factors, as well as social determinants such as stigma, violence, and stress, that influence the development and course of mental illnesses and HIV. Mental health research is an integral component of HIV-related research across the lifespan. As such, NIMH supports a broad research portfolio in the U.S. and around the world to prevent HIV acquisition in high incidence populations and improve treatment and care among people with HIV, including those with comorbid mental and substance use disorders.

NIMH utilizes basic science to understand the pathogenic mechanisms of HIV-associated central nervous system (CNS) disorders, while translational research supports the development of therapeutic strategies to treat HIV-CNS comorbidities, including cognitive disorders and mental illnesses. In addition, NIMH supports efforts focused on eradicating the virus from the CNS, a prerequisite to finding a safe, effective, and complete cure for HIV. To complement efforts in basic and translational science, NIMH also advances behavioral and social science research to examine individual, interpersonal, community, institutional/health system, and environmental factors; peer and community-based strategies; structural and psychosocial determinants; and, data science, methodologies, and technological approaches critical in HIV prevention and treatment. NIMH supports implementation science to enable researchers to bring evidence-based interventions to the greatest number of people who may benefit, and develop innovative communication and dissemination approaches that facilitate trust and use of those interventions, particularly among people with HIV in resource-limited settings. NIMH also places a high priority on HIV research that can impact individuals from high-incidence populations across the lifespan, both domestically and globally, including racial and ethnic minorities, sexual and gender minorities, mobile populations, adolescents, women, and infants.

Digital Health Technology

Recent advances in technology continue to evolve and create new opportunities to improve access, availability, utilization, and quality of mental health care services. The pace of research and clinical use of digital health approaches has been dramatically accelerated by the COVID-19 pandemic. The growth of digital health technologies, which blend mobile health and health information technology (such as smartphones, wearable sensors, electronic health records), gives the public, health care providers, and researchers new ways to access information and to measure and manage health and productivity. Ongoing NIMH-supported research leverages mobile and other emerging technologies to develop, test, and deliver targeted preventive and treatment interventions for disorders such as anxiety, insomnia, and depression. Approaches include just-in-time interventions that can be pushed out using smartphones or other technology based on information about the person's current state and needs. Additional innovations employ patient- and clinician-facing digital monitoring devices, smartphones, and other applications or dashboards that facilitate monitoring and early detection of changes in patient status that might signal the need for additional or more intensive services to forestall relapse or hospitalizations. NIMH is also interested in digital biomarkers and outcome assessments for inclusion in clinical trials for monitoring responses to interventions. While the technology frontier offers promising opportunities for drug development and mental health care, much work remains to address questions about efficacy and effectiveness, bias, regulation, privacy, and additional ethical considerations. As technology is increasingly utilized in mental health research and care, innovation is needed to bridge the digital divide and ensure that lower resourced settings are included.

Genetics

Tremendous progress has been made in psychiatric genetics. Genome-wide association studies (GWAS) as well as rare variant association analyses, both of which required global-scale collaborations to assemble immense sample sizes, uncovered statistically rigorous and fully-replicated genetic links to schizophrenia, autism, depression, and other psychiatric disorders. In considering the complexity of the genetic landscape, the *Report of the National Advisory Mental Health Council Workgroup on Genomics* provided recommendations for the future of genomics research: 1) utilize statistically rigorous, unbiased, and well-powered studies; 2) harness innovative approaches that address both common and rare genetic variants; and, 3) leverage universal data sets that capture genetic and phenotypic variation across diverse human populations. NIMH is focused on expanding the ancestral diversity of genetic samples, and increasing our understanding of the genetic determinants of mental illnesses like obsessive-compulsive disorder, anorexia nervosa, and other disorders where additional work is needed. A significant goal is to better understand how molecular, neural, environmental, and psychosocial mechanisms interact with the genetic and epigenetic links that have been identified. Acquiring this new knowledge will likely cross levels of analysis, from genes to cells to circuits to behavior.

Neural Circuits

Neuroscience has provided us with the tools to look deeply into the function of neural circuits, and directly test hypotheses about brain-behavior relationships using noninvasive brain stimulation technologies. Over the past decade, technologies—such as optogenetics, chemogenetics, viral tracing, and high-resolution optical imaging—aimed at measuring and modulating the activity of specific circuits, have facilitated the attainment of a vast knowledge base about the circuits that control behavior and mental processes. Noninvasive neuromodulation devices allow scientists to change function within circuits for therapeutic benefit, and this approach led to the U.S. Food and Drug Administration (FDA) approval of transcranial magnetic stimulation (TMS) for the treatment of depression and obsessive-compulsive disorder. This knowledge, in turn, may enable the development of diagnostic and treatment strategies that detect and normalize circuit dysfunction in people with mental illnesses. In addition, invasive neural recording devices (e.g., deep brain stimulation with dual stimulation and recording electrodes) that are used to treat a variety of clinical conditions in humans may enable researchers to explore neural circuity underlying complex human behavior and mental illnesses. To drive progress in circuit neuroscience, NIMH, in part through the NIH Brain Research Through Advancing Innovative Neurotechnologies® (BRAIN) Initiative, aims to reveal how complex neural circuits dynamically interact to influence mental functions. NIMH is committed to understanding which circuits are altered in mental illnesses and how; which circuit elements can be changed to reverse or compensate for these alterations; and, at which points in time during the course of illness these manipulations are most effective.

Cross-Cutting Research Themes

Several significant research themes cut across and are integral to the Goals of the NIMH Strategic Plan for Research. These themes highlight areas where NIMH-funded science may have the greatest impact, bridge research gaps, and offer novel approaches to accelerate advances in mental health research. This section summarizes these major themes that, along with the challenges and opportunities facing the mental health field, inspired this Strategic Plan for Research.

A Comprehensive Research Agenda

Excellent and comprehensive science requires an inclusive approach focused on varied topic areas, extending research participation and partnerships, and advancing the research agenda across multiple timeframes. To ensure there is the potential to improve clinical care over the short-, medium-, and long-term, study designs should engage diverse populations and perspectives, methods, tools, and models. Diversity in these areas of research, such as engaging multiple perspectives, enables us to address complex basic, translational, and applied questions, including those at the intersection of the brain, behavior, and community. All vertebrate animal and human studies should factor sex as a biological variable into research designs and reporting. Depending on the research question, researchers should consider how genetic background will advance the quality and interpretability of the outcomes. Clinical research studies should include participants from diverse racial and ethnic backgrounds, and across gender identities, geographical context, socioeconomic status, neurotype, and age—offering meaningfully representative samples best suited to address public health concerns and provide the most rigorous foundation to inform care and policy.

Prevention

NIMH has a developmentally focused, theory-based prevention research program that spans the life course from prenatal though late-life, at different levels of intervention (e.g., universal, selective, indicated, tiered), and in different settings (e.g., families, schools, health care, communities). While the targeted developmental stage may change, the primary focus of interventions is on reducing risk and increasing protective factors that can modify proximal outcomes (e.g., parenting, self-regulation, skill development) and long-term, distal outcomes (e.g., depression, anxiety, suicide ideation and behaviors). Transition periods (e.g., biological, normative, social) offer important opportunities for the implementation of prevention interventions at different developmental stages. NIMH supports research examining the efficacy and effectiveness of prevention interventions conducted in a variety of contexts and settings, and the implementation of effective interventions at scale in communities in a sustainable manner.

Global Mental Health

Mental illnesses are a global concern, presenting shared opportunities to advance science across international boundaries. NIMH investments in effectiveness and implementation research in low- and middle-income countries are producing innovative strategies for expanding access to mental health care and improving care quality and outcomes in a range of settings worldwide. Notably, several researchers are taking interventions developed for low resource settings in the global context and applying them in the United States to address the tremendous burden of illness and limited health care capacity during the COVID-19 pandemic. At the same time, new global opportunities are emerging to advance our understanding of how genetics (or population genetics), cultural backgrounds, societal and familial structures, and environmental exposures can be integrated within basic and translational mental health research. Findings from this research will enhance our knowledge of mental health and illness; point to new targets for better preventive and treatment interventions; and, lead to novel approaches for addressing mental health needs worldwide, including those of currently underserved populations. NIMH also supports research on the implementation of new and evolving tools and technologies to facilitate and improve mental health screening, assessment, prediction, prevention, and treatment across systems of care. International collaborations with researchers, providers, advocates, individuals living with mental illness and their families, and global health and development agencies are also improving NIMH's ability to address mental illnesses in the United States, especially for those from geographically, socioeconomically, and culturally diverse populations.

Environmental Exposures

Numerous factors in the environment can influence the development of mental illnesses. The environment includes natural and built components, individual factors such as the microbiome, and social factors such as, family interactions, peer relationships, and social determinants of health. Social determinants may include structural racism, housing instability, food insecurity, socioeconomic status, and others. These environmental factors, which vary within and across populations and settings, can affect biological systems important in regulating functions of the body and mental processes. We are making significant strides toward understanding how environmental factors affect brain development and shape behavior. For example, as part of the Adolescent Brain Cognitive Development (ABCD) study, which has enrolled over 10,000 children across the country, researchers are examining how biology and environment interact and relate to developmental outcomes, such as physical health and mental health. NIMH also continues to vigorously support efforts to study the biological and psychological impacts of trauma, mechanisms of prenatal risk, and numerous other environmental factors that may contribute to mental illnesses. In collaboration with the NIH Helping to End Addiction Long-term® (HEAL) Initiative, NIMH supports the HEALthy Brain and Child Development (HBCD) Study to understand the impact of prenatal and postnatal exposure to drugs and other adverse environmental conditions and on brain development and development of substance use, mental disorders, and other developmental outcomes. NIMH is also participating in the NIH Climate Change and Health Initiative, an urgent, cross-cutting effort

to reduce health threats from climate change and build health resilience in individuals, communities, and nations around the world, especially among those at highest risk.

Comorbidities

Comorbidities—the co-occurrence of mental and/or other physical disorders, including substance use disorders—may affect both the development and clinical course of mental illnesses through their effects on basic biological processes. For example, some treatments for people with HIV may affect inflammation in the CNS, metabolism, and the microbiome—factors that also impact the development of mental illnesses. Examining the interactions between mental illnesses and co-occurring conditions will provide additional insight into the causes and facilitators of mental illnesses, as well as provide pathways to improve the provision of interventions and services to ultimately prevent and treat mental illness and comorbidities and achieve better outcomes for people with mental illnesses. NIMH works with other NIH Institutes and Centers to support research to address treatable medical comorbidities linked to premature mortality associated in people with serious mental illness. For example, through the NIH HEAL Initiative®, NIMH leads a portfolio of research to help improve the provision of services for people with co-occurring opioid use disorder and mental disorders and/or suicide risk.

Translation

***Engaging Novel Frameworks for Studying Mental Disorders*.** High rates of psychiatric comorbidity and heterogeneity of symptoms occur when patients are characterized using solely the current diagnostic categories, which rely on self-reported or observable symptoms. To extend research beyond diagnostic boundaries, NIMH's evolving Research Domain Criteria (RDoC) framework integrates many approaches and levels of information to advance our understanding of mental illnesses. These levels of information span from cellular to behavioral measures, with attention to developmental trajectories and the impact of environmental and social factors. The RDoC framework is also well-suited to computational approaches, such as those described below, which incorporate multiple multimodal sources of information to improve mental health outcomes. Through the RDoC framework, NIMH encourages the identification of neurobehavioral mechanisms of specific domains of function. Beyond improving research sample characterization using objectively measurable factors, this approach holds promise for uncovering mechanisms of mental illnesses, identifying putative therapeutic targets, and paving the way for novel preventive and treatment interventions.

Advancing Interventions. Historically, novel prevention and treatment development has been slow, expensive, and high risk. To speed progress across the basic-to-clinical research pipeline, NIMH employs an experimental therapeutics approach to clinical trials requiring studies to define intervention targets and milestones. With NIMH's experimental therapeutics approach, studies not only evaluate the clinical effect of an intervention, but also generate information about the mechanisms contributing to a disorder or an intervention response.

***Accelerating Public Health Impact*.** The translation of new interventions into routine practice and population-level benefits has also been far too slow. To accelerate the adoption and implementation of evidence-based interventions and strategies into routine mental health care and other settings, NIMH invests in studies that anticipate real-world implementation during intervention development. Additionally, NIMH takes an experimental approach to testing mechanisms of effective care delivery in real-world settings, engages stakeholders throughout the research process, and attends to pragmatic questions about implementation like financing, scalability, and sustainability. This is especially important when considering the challenges of delivering care to underserved communities and in low-resource settings.

Computational Approaches

Computational approaches are aimed at developing mathematical and modeling frameworks to improve the understanding, prevention, and treatment of mental illnesses. Computational approaches can allow us to mechanistically describe and empirically test how high-level behavioral phenotypes emerge from complex neurobiological processes at the micro-, meso-, and macro-scale levels of the brain. For example, computational models can put into explicit mathematical terms testable hypotheses regarding how alterations in genes might causally affect circuit function through disruptions of neuronal and synaptic dynamics. Similarly, computational models can suggest how circuit dysfunction impacts neural development and plasticity, and how that dysfunction manifests in behavior leading to progressive, chronic disorders. In addition to modeling frameworks incorporating biophysical realism, more data-driven computational approaches can take advantage of large data sets, categorizing brain dysfunction in ways that can lead to better diagnoses, improved biomarkers, and tailored preventive and treatment interventions. Using big data and theoretical approaches in clinical research can help bridge the gap between integrative multi-omics (e.g., epigenomics, transcriptomics, proteomics), neuroimaging, and digital phenotyping to traverse the complex path from genomics to therapeutics. Using computational approaches to assist in the development of explanatory theoretical models that integrate information across diverse experimentally tested domains (such as biological, psychological, social, and cultural environments; see the RDoC framework) can help define a critical path forward for understanding mechanisms and advancing new treatments. Within clinical research, computational methods (e.g., data mining, machine learning, predictive analytics) may also be used to analyze electronic health records or other clinical data to identify modifiable risk factors, derive quantitative predictions to inform the optimal timing of interventions, and evaluate the outcomes of treatment trajectories. For instance, mathematical modeling approaches may identify how mental health and HIV transmission dynamics impact HIV prevention and treatment. NIMH is dedicated to supporting computational approaches that integrate knowledge gained at genetic, molecular, cellular, circuit, behavioral, and health care system levels, and ask high-impact basic neuroscience, translational, and service and intervention questions.

Harnessing the Power of Data

Advances in data acquisition and the availability of aggregated, harmonized data sets, coupled with new computational modelling tools like machine learning, are revolutionizing the efficiency with which researchers turn data into knowledge. These advances will ultimately help us better understand the complex factors affecting prevention and treatment outcomes, and will optimize mental health care quality and effectiveness. NIMH is committed to providing modernized data infrastructure for use by the research community, capitalizing on advances in data science and information technology; setting policies to address storing data efficiently and securely for productive and ethical data use; and, connecting with the NIH data ecosystem and other data systems to make NIMH data usable to the broader community, consistent with findability, accessibility, interoperability, and reusability (FAIR) principles. In addition to providing the infrastructure, NIMH is working with other major mental health research funders around the world to establish a set of measures that all mental health researchers may use as they collect data. This effort is expected to allow researchers to better integrate data from different laboratories. Further, the development, validation, optimization, and expansion of digital mental health tools will improve our understanding of mental illnesses in real time, help track the course of illness, and improve mental health care. NIH's Data Sharing Policy encourages widespread data sharing and collaborations with experts in other areas of science, including behavioral and social scientists, implementation scientists, ethicists, engineers, informaticists, and computer scientists, to add significant value to research and accelerate the pace of discovery.

Research Workforce

Scientific advancement requires investment in future generations of mental health researchers. Indeed, research shows that diverse teams working together and capitalizing on innovative ideas and distinct perspectives outperform homogenous teams. As such, NIMH encourages investigators to consider diverse perspectives in designing their investigative teams, and emphasizes the importance of the diversity of perspectives across all phases of career development.

Training. Supporting outstanding scientists who will advance the field of mental health research is a priority for NIMH. NIMH uses institutional and individual funding mechanisms to support research training, education, and career development across a range of career stages from undergraduate education through early-stage faculty positions. The Institute maintains a robust investment in the career development of investigators in all priority research areas described in NIMH's Strategic Plan for Research and is committed to the inclusion of individuals who enrich the diversity of perspectives in research.

Inclusion and Diversity. By prioritizing inclusion and diversity, NIMH remains steadfast in its commitment to improving recruitment, training, advancement, and retention of researchers from diverse backgrounds, including those from groups underrepresented in the biomedical and behavioral sciences, across areas of research funded by NIMH. For example, at the institutional level, NIMH

supports the NIH Blueprint Program for Enhancing Neuroscience Diversity through Undergraduate Research Education Experiences (BP-ENDURE) that is focused on preparing undergraduates to enter and successfully complete neuroscience Ph.D. programs. Likewise, NIMH participates in the Maximizing Opportunities for Scientific and Academic Independent Careers (MOSAIC) effort to enhance diversity within the academic biomedical research workforce by providing support and mentorship to facilitate the transition of promising postdoctoral researchers from diverse backgrounds into independent faculty careers in research-intensive institutions. NIMH also encourages the neuroscience community to take advantage of the new NIH-wide Faculty Institutional Recruitment for Sustainable Transformation (FIRST) Program, supported by the NIH Common Fund. Further, NIMH is participating in the BRAIN Initiative effort to support the establishment of facilities at minority-serving institutions and Institutional Development Award-eligible institutions for improved access to key neuroscience research resources. NIMH is also participating in an effort to evaluate the impact of the recent Plan for Enhancing Diverse Perspectives (PEDP), a required element for some NIH applications to outline strategies to advance the scientific and technical merit of the proposed project through expanded inclusivity. In addition, NIMH offers several funding opportunities and supplement programs to enhance the diversity of the workforce. To better understand barriers and facilitators to achieving racial and ethnic equity in funding success, NIMH also hosted virtual listening sessions during which extramural researchers shared their experiences navigating the NIH grant application process.

Goal 1: Define the Brain Mechanisms Underlying Complex Behaviors

Through basic science, researchers endeavor to answer fundamental questions about the mechanisms (e.g., brain, behavioral, environmental, psychosocial) that contribute to cognition, perception, motivation, and social behavior. We have seen extraordinary progress in basic science over the past several years, including in neuroscience. New tools have enabled precise mapping and the ability to modulate brain circuits across model systems, from cells in a dish to the human brain. New techniques have improved the resolution of structural and functional imaging in humans. New sensor technologies are transforming the study of behavior. These new tools, techniques, and technologies will help us piece together the many complex connections among genes, the brain, and behavior. Researchers are also exploring how these aspects of mental function become altered in mental illnesses.

The vast number of cells and connections in the brain make understanding its function in complex behavior particularly challenging. New tools and technologies are helping us create a detailed map of the circuits involved in complex behavior, including those associated with mental illnesses. For example, to address the range of individual variation in brain circuits, the Human Connectome Project provided a reference atlas of neuronal connectivity—or a connectome—of 1,200 healthy brains. Researchers are now mapping long-distance brain connections and looking at their variability in unprecedented detail. These efforts are underway across development and across mental illnesses.

The genomics revolution, fueled by technological advances, has revealed insights into the genetic architecture of mental illnesses. Over the past several years, large, replicated genomic studies have revealed many common and rare variants associated with the most heritable conditions (e.g., schizophrenia, bipolar disorder, autism). We are also making strides in identifying the genetic and nongenetic factors that control gene expression and play other roles in mental health and illness. While we have gone from few clues to many, we still cannot fully explain the root causes of mental illnesses. Researchers have begun the task of sorting through the complex patterns of genomic variation and environmental moderators to define and elucidate how these variations confer risk and resilience. We now know hundreds of identifying locations in the genome where genetic variation raises risk for psychiatric disorders. Because most participants in these studies have been of European descent, the findings may not be applicable to all. NIMH is expanding efforts to increase the diversity of the study participants across our genomics research to better benefit people of all racial and ethnic groups. Researchers are also exploring the role of nongenomic factors (e.g., the environment, experience, the microbiome) and their impact on the risk for mental illnesses, including their impact on gene expression.

We seek to understand how the interplay of molecular, cellular, circuit-level, genetic, and environmental factors influence the development of mental illnesses through animal and human studies. Multidisciplinary approaches integrating statistics, mathematics, physics, computer science, and engineering will help us begin to explain how our brain predicts, interprets, alters, and responds to a complex world. Through basic science, we will achieve a more refined understanding of the brain

mechanisms underlying complex behaviors, which will drive progress toward the novel interventions of tomorrow.

The following Objectives further define this Goal:

Objective 1.1: Elucidate the brain mechanisms underlying cognitive, affective, and social processes

To truly transform our understanding of mental illnesses, we need to identify the roles of all brain cell types and circuits in the myriad aspects of mental processes. Knowing how brain cells work together in circuits to drive cognitive, affective, and social processes will inform future circuit-based preventive and treatment interventions. New tools and techniques that span units of analysis (e.g., genes, molecules, cells, circuits, physiology, behavior) will transform our understanding of the brain, thus fostering our understanding of mental illnesses.

To better elucidate the brain mechanisms underlying cognitive, affective, and social processes, NIMH will support research that employs the following Strategies:

Strategy 1.1.A: Characterizing the genomic, molecular, cellular, and circuit components contributing to brain organization and function

Interest areas include:

1. Determining the phenotypic properties and dynamic interactions of neurons, astrocytes, oligodendrocytes, microglia, immune cells, and other cell types and how they contribute to brain organization and function.
2. Exploring the genomic, molecular, and physiological factors in cell-to-cell variation and determining the functional consequences of this variation.
3. Applying advanced neuroanatomical and functional approaches to map neural circuits at micro-, meso- and macro-scales.

Strategy 1.1.B: Identifying the developmental, functional, and regulatory mechanisms relevant to cognitive, affective, and social domains, across units of analysis

Interest areas include:

1. Elucidating the developmental processes that lead to the establishment of functional brain networks subserving these domains, including modifying factors (e.g., genomic, experiential) affecting these trajectories.
2. Identifying the mechanisms that mediate normal cellular communication and plasticity at the level of molecular control, signal transduction, synapses, circuits, and/or behavior. Examining how alterations of these mechanisms may disrupt function; such mechanisms may involve non-neural components (e.g., immune system, microbiome).

3. Developing and validating experimentally grounded theories for how the brain computes within these domains across spatiotemporal scales and levels of neurobiological abstraction (e.g., coordinated neural activity patterns and network state changes).
4. Applying novel behavioral assays of the domains that are causally linked to specific mechanisms at multiple units of analysis (e.g., genetic, molecular, cellular, circuit, physiological, behavioral, and/or systems). These approaches will be prioritized over studies relying on traditional behavioral tests that presume congruence with human symptoms of mental illnesses and do not give insight into the function of the circuit(s) under investigation.
5. Evaluating the preclinical utility of modifying cellular, synaptic, or circuit function for therapeutic benefit.

Strategy 1.1.C: Generating and validating novel tools, techniques, and measures to quantify changes in the activity of molecules, cells, circuits, and connectomes

Interest areas include:

1. Developing novel assays that can be used to interrogate key regulators of cellular communication using *in situ* and circuit-based models for screening, target discovery, and development of novel probes of cell function.
2. Advancing human cell-based assays using induced pluripotent stem cells (iPSCs) for studying the molecular factors in mental illnesses, with an emphasis on optimizing robustness, reproducibility, and fidelity to *in vivo* human cell phenotypes, maturation, three-dimensional organization, and/or circuit function.
3. Developing novel, age-appropriate imaging assays with higher spatial and temporal resolution for visualization and analyses of brain structure, maturation, connectivity, and function, with particular emphasis on advancing real-time measurement approaches.
4. Developing innovative computational tools for the analysis and interpretation of neural activity including single unit, local field potentials, and other electrophysiological temporal dynamic patterns.
5. Developing and validating novel, objective physiological and behavioral measures as research tools to assess synaptic plasticity and circuit function in experimental systems, and as assays for assessing therapeutic targets in humans.
6. Advancing objective, quantitative assays to track, manipulate, and analyze behavior at high temporal resolution in a range of species, ages, and settings, and across multiple modalities and systems.
7. Developing noninvasive assays for interrogating and manipulating brain circuit function for therapeutic purposes.
8. Advancing novel assays to develop biomarkers of disease and for therapeutic discovery.

Objective 1.2: Identify the genomic and non-genomic factors associated with mental illnesses

A full understanding of the multifaceted contributors to risk for mental illnesses requires examination of genomic, epigenomic, and other factors, including the environment and experience, worldwide. Understanding how these factors contribute to adaptive and maladaptive behaviors, mental function and dysfunction, and mental illnesses is critical for developing improved diagnostics and interventions that are effective for diverse individuals and populations. The genetic architecture of mental illnesses is extraordinarily complex. While the field of genomics has achieved remarkable advances in the past few years, the exact mechanisms that place certain individuals and populations at higher risk than others remain unknown. We need comprehensive approaches to understand genomic and non-genomic risk factors, and such investigations must consider diverse populations from around the world. To facilitate the transition of knowledge to practice, we need novel study designs, advanced genomic technologies, and innovative statistical and bioinformatic methods. These approaches will help us to revolutionize the analysis and interpretation of genetic associations and will speed the transition of this knowledge to practice.

To more effectively identify the genomic and non-genomic factors associated with mental illnesses, NIMH will support research that employs the following Strategies:

Strategy 1.2.A: Discovering gene variants and other genomic elements that contribute to the development of mental illnesses in diverse populations

Interest areas include:

1. Performing large, well-powered, whole genome and exome-, epigenome-, and other “ome”-wide studies in appropriate tissues.
2. Elucidating genetic architecture and heritability across the full allele frequency spectrum.
3. Mapping and identifying causal variants within risk loci.
4. Analyzing co-heritability and shared genetic risk architecture using cross-trait analyses.
5. Collecting and genomically characterizing ancestrally diverse cohorts.

Strategy 1.2.B: Advancing our understanding of the complex etiology of mental illnesses using molecular epidemiologic approaches that incorporate individual genetic information in large cohorts

Interest areas include:

1. Conducting robust, well-powered, and unbiased genome-wide x phenome-wide association studies by leveraging large-scale genetic and phenotypic/exposure data from biobanks, health systems, and other population-scale cohorts.
2. Conducting Mendelian randomization studies that identify modifiable exposures mediating or mitigating risk for mental illnesses.

3. Developing epidemiologic studies that incorporate individual polygenic risk scores, and other genetic markers of risk, and leveraging existing large, population-based cohorts, including ethnically and ancestrally diverse cohorts, registries, and/or health systems to conduct analyses that advance understanding of the complex etiologies, trajectories, comorbidities, and treatment responses of severe mental illnesses.

Strategy 1.2.C: Elucidating how human genetic variation affects the coordination of molecular, cellular, and physiological networks supporting higher-order functions and emergent properties of neurobiological systems

Interest areas include:

1. Creating human molecular reference maps from defined cell types and circuits.
2. Elucidating the relationship between genomic features, such as gene regulatory elements and chromatin structure, and the spatiotemporal dynamics of gene and protein expression in healthy individuals and those with mental illnesses.
3. Assembling reference, multi-omic molecular maps (e.g., epigenomic, transcriptomic, proteomic) across development, regions, and cell types of the human brain.
4. Mapping quantitative trait loci (e.g., expression, methylation, histone acetylation, chromatin accessibility) across development, regions, and cell types of the human brain.
5. Identifying the developmental periods, signaling pathways, cell types, and neural systems driving disease pathogenesis in humans.

Strategy 1.2.D: Developing novel tools and techniques for the analysis of large-scale genetic, multi-omic data as it applies to mental health

Interest areas include:

1. Increasing the power and reliability of association studies including whole genome, exome-, epigenome-, phenome-, and other “ome”-wide studies.
2. Integrating multi-omic data sets from tissues and single cells.
3. Integrating phenotype data spanning multiple units (e.g., genetic variation, gene expression, electrophysiology, neuroimaging, behavior).
4. Focusing on robust genome-wide and brain-wide association studies, genome x phenome-wide interaction studies, and genome-wide epistasis detection.

Objective 1.3: Identify and characterize the neural circuit mechanisms contributing to human behavior and their disruption in mental illnesses

Most of what we currently know about human brain circuits comes from studying healthy functioning. To understand changes in neural structure and function related to mental illnesses, we must apply the research tools we have in hand to characterize the neural circuits implicated in mental illnesses across diverse populations. It is becoming increasingly possible to map both proximal and distal neural

connectivity in the brain, enabling an understanding of the relationships between neuronal structure and function at the systems level. To develop comprehensive understanding of neural connectivity in mental illnesses, we must extend existing structural and functional mapping to the cellular level. Connectomic studies of the brain are bringing us innovative tools and technologies. Emerging developments include robust molecular markers for synapses, new tracers for identifying circuit inputs and outputs, high density electrode arrays, and novel microscopy techniques to reconstruct brain circuits. New technologies are faster, less expensive, and scalable for anatomic reconstruction of neural circuits at all biological scales. Focused studies of circuit disruption in mental illnesses will be essential to translate knowledge gained from these technologies into novel targets for therapeutics.

To better characterize and analyze the neural circuit mechanisms involved in mental illnesses, NIMH will support research that employs the following Strategies:

Strategy 1.3.A: Utilizing connectomic approaches to identify brain networks and circuit components that contribute to various aspects of mental function and dysfunction

Interest areas include:

1. Conducting brain-wide analyses to determine which neural circuits drive network patterns associated with a pathology.
2. Characterizing network components at the molecular, single-cell, morphological, microenvironmental, or circuit level that contribute to risk for mental illnesses.
3. Conducting connectomic studies during brain development, from prenatal to late adulthood.

Strategy 1.3.B: Determining through brain-wide analysis how changes in the physiological properties of molecules, cells, and circuits contribute to mental illnesses

Interest areas include:

1. Investigating how molecular, cellular, and/or circuit-level changes in the brain, or changes in response to environmental factors, affect the coordination of neural activity patterns (very large-scale samples) during cognitive function, emotional regulation, and social cognition at one or more stage of development, from prenatal to late adulthood.

Strategy 1.3.C: Developing molecular, cellular, and circuit-level biomarkers of impaired neural function in humans

Interest areas include:

1. Validating biomarkers using analysis of neural circuits; combining approaches, such as those that assess or detect synaptic integrity, plasticity, and function; as well as immune signaling activity and cells that affect neural circuits.
2. Integrating molecular and genomic data from large-scale multi-omic studies with connectomics and functional approaches in humans to formulate multilevel hypotheses regarding circuit function and dysfunction in mental illness.

3. Testing the causal nature of circuit-based hypotheses in animal, computational, and human experimental systems.

Strategy 1.3.D: Developing innovative technologies—including new imaging, computational, electrophysiological, pharmacological, and genetic tools—to interrogate and modulate circuit activity and structure altered in mental illnesses.

Interest areas include:

1. Creating or improving methods to investigate the connectivity of brain networks, at total or very large scale and during one or more stages of development that are relevant to mental illnesses, including age-appropriate, novel imaging tools for visualization and analyses of brain structure and function.
2. Pioneering strategies to use circuit-based technologies to identify circuit-specific intervention targets.
3. Developing novel technologies to modulate specific circuit elements with the potential for translation into humans.

Goal 2: Examine Mental Illness Trajectories Across the Lifespan

Many mental illnesses first present in childhood, adolescence, or young adulthood, yet mental illnesses are likely the late behavioral manifestations of changes that began years earlier. These early alterations may influence the course of brain and behavioral development and establish the trajectories of mental illnesses. To better understand these trajectories, we need to develop a comprehensive picture of typical and atypical brain and behavioral development across the lifespan. At the same time, novel biomarkers and behavioral indicators hold promise for identifying who is at risk at the earliest possible point, when development or aging is going off course, or which preventive and treatment interventions will produce the best outcomes for which individuals. We also need to understand the factors contributing to risk of, resilience to, and protection from development of mental illness.

Examining biological and behavioral processes in animals and humans across the lifespan, starting at the earliest possible point, will transform our understanding of the neurodevelopmental origins and progression of mental illnesses through late life. Research to identify the earliest markers or signs that distinguish typical from atypical brain and/or functional development will be instrumental in predicting illness trajectories and outcomes decades later. Equally important is how these markers differ in meaningful ways across individuals, developmental stages in the lifespan, diverse populations (e.g., age, sex, gender, race, ethnicity), varied experiences, social determinants, environmental factors, and their intersectionality.[30]

As we chart developmental and aging trajectories across the lifespan, it is important to identify sensitive periods—critical timepoints to intervene to reduce risk for and to prevent the onset of mental illnesses and improve outcomes. Further, to provide new therapeutic avenues to prevent and treat mental illnesses, we must identify a broad range of relevant factors, such as social and environmental influences (including but not limited to violence and trauma), and molecular-, cellular-, and system-level mechanisms affecting typical and atypical development.

The following Objectives further define this Goal:

Objective 2.1: Characterize the trajectories of brain, cognitive, affective, and behavioral development across the lifespan and in diverse populations

Across the lifespan, the brain and the cognitive, behavioral, and affective functioning it supports undergo dramatic changes, in part as a result of myriad experiences. Yet, our understanding of how biology, psychological development, and experience interact to affect brain development—and, ultimately, social, behavioral, medical, and other outcomes—is still incomplete. Discoveries through basic and translational research further our fundamental understanding of how mental illnesses develop early or later in life and through the course of illness. By characterizing the trajectories of typical and atypical brain, cognitive, affective, and behavioral development across the lifespan and in diverse populations and contexts, we can identify factors that protect from, increase risk for, or give rise to

mental illnesses. Greater understanding is needed to determine periods when the brain is at increased sensitivity to biological and environmental influences, and optimal periods for intervention. It is important to also consider the dynamic and non-linear nature of development and aging, simultaneously evaluate multiple domains of function, and incorporate maturational influences.

To better understand developmental and aging trajectories and the progression of mental illnesses, NIMH will support research that employs the following Strategies:

Strategy 2.1.A: Elucidating the mechanisms contributing to the trajectories of brain development and behavior

Interest areas include:

1. Characterizing the interdependence and functional development of simultaneously occurring, yet unevenly progressing, trajectories in different brain regions and circuits across the lifespan.
2. Determining the biological and psychological mechanisms by which experience and environment affect neural and behavioral development.
3. Examining individual differences and the inter-relatedness of biological, behavioral, and environmental (including social, cultural, and structural) contributors to heterogeneity in risk for and resilience from mental illnesses across the lifespan, trajectories of illnesses, prevention, and treatment interventions. Studies may use multi-level modeling to incorporate an intersectionality framework in mental health research.
4. Developing novel statistical, computational, and analytical techniques to integrate behavioral, genomic, multi-modal imaging, clinical, environmental, and other data types across repeated assessments and across independent data sets.

Strategy 2.1.B: Characterizing the emergence and progression of mental illnesses, and identifying sensitive periods for optimal intervention

Interest areas include:

1. Conducting longitudinal studies that track changes in behavior with changes in brain development, psychosocial development, and other normative maturational processes, to characterize the progression from early markers to subsequent impairment in domains of functioning. NIMH encourages the use of large and diverse samples, adequately sampled for underserved, minority, and underrepresented groups and with sufficient power to examine mediators and moderators including race, ethnicity, sex, gender, and sexual orientation.
2. Identifying the biological mechanisms (e.g., molecular, cellular, circuit-level) involved in healthy and dysfunctional neurodevelopmental trajectories, including the functional consequences of sex and gender differences that have shown empirical associations to mental illnesses.
3. Identifying and characterizing sensitive periods for brain, cognitive, social, and affective development during which core facets of functioning (e.g., RDoC constructs) can be targeted for optimal intervention to prevent, pre-empt, and/or effectively treat mental illnesses across diverse populations.

4. Translating knowledge about sensitive periods and their critical mechanisms to manipulate developmental trajectories of neural circuits and associated behaviors to prevent or minimize disease trajectories and promote optimal outcomes.

Objective 2.2: Identify and understand risk factors, biomarkers, and behavioral indicators of mental illnesses and of intervention responses across the lifespan

The best time to address a mental illness is before the appearance of symptoms. Preventive interventions will rely on biomarkers and other indicators that give health care providers the ability to predict the onset of illness for individuals, not just populations, at risk. Currently, the mental health field lacks predictors that could inform a diagnosis, guide intervention, or predict response to intervention and the future course of illness. Further, understanding the mechanisms involved in risk and protective factors may shed light on novel intervention targets. Targets can include molecular processes; synaptic- and circuit-level regions or networks; neural systems; psychological, cognitive, emotional, or behavioral processes; and, environmental phenomena. We need to identify clinically useful biomarkers and behavioral indicators with high predictive value to guide the use of preventive interventions across diverse populations, environments, and developmental processes.

To lay the foundation for predicting outcomes and optimizing preventive and treatment interventions, NIMH will support research that employs the following Strategies:

Strategy 2.2.A: Determining early risk and protective factors, and related mechanisms, to serve as novel intervention targets

Interest areas include:

1. Identifying early manifestations of core functional domains (see RDoC framework) particularly during infancy, early childhood, and adolescence that predict the onset and course of mental illnesses.
2. Examining mechanisms of sequential, additive, and/or interactive combinations of risk, resilience, and protective factors that span modalities and units of analysis and predict progression along the illness trajectory.
3. Identifying novel intervention targets based on knowledge of neurobehavioral, psychological, and contextual mechanisms and trajectories, and the optimal time points for intervention.

Strategy 2.2.B: Developing reliable and robust biomarkers and assessment tools to predict illness onset and course, across diverse populations

Interest areas include:

1. Identifying specific, clinically relevant, developmentally appropriate, and validated biomarkers (including neural and behavioral indicators) of risk, onset, progression, recovery, and relapse phases of illnesses.

2. Using multiple modalities and standardized methods to identify robust mediators, moderators, and predictors of resilience, illness course, and differential trajectories.
3. Harnessing computational approaches to define and refine biomarkers, and to demonstrate potential clinical utility.
4. Developing fine-grained, objective, and quantitative behavioral assessment tools in animals and humans to evaluate dysfunction in domains relevant to the trajectories of mental illnesses.
5. Developing evidence-based risk assessment instruments that encompass multiple domains, are sensitive to developmental and aging stages, and have high predictive power for the onset or recurrence of mental illnesses.
6. Developing, testing, and refining tools and methodologies that integrate multimodal clinical, behavioral, and biological risk factors to prevent the onset of chronic conditions and optimize outcome.

Goal 3: Strive for Prevention and Cures

We need to develop better ways to prevent and treat mental illnesses. To achieve that goal, we need validated targets for interventions; new methods of intervention; improved methods to match interventions to individuals and populations, including marginalized and underserved communities; and, strategies for scaling interventions for the greatest public health impact. Interventions may encompass prevention and treatment, consider all therapeutic modalities (e.g., pharmacologic, psychosocial, behavioral, device-based, biologics), and include structural changes (e.g., policies).

Robust clinical studies require testable hypotheses on how an intervention will engage a relevant target. Targets can include molecular processes; synaptic- and circuit-level regions or networks; neural systems; cognitive, emotional, and interpersonal processes; and, provider behavior, decision-making, and organizational policies and behaviors. Interventions should aim to modify targets, based on a hypothesis that such modification will result in improved symptoms, behavior, or functional outcomes. Evaluating the relationship between modification of targets and clinical outcomes allows us to fine-tune our understanding of mental illnesses and helps us to prioritize the most promising interventions. This idea underlies NIMH's experimental therapeutics approach by which interventions serve not only as potential therapies or preventive strategies, but also as probes to generate objective information about mechanisms of illness and/or resilience. Through the experimental therapeutics approach, information from a research study has scientific value, irrespective of the intervention's success.

Precision in mental health care means that individuals and populations will receive preventive and treatment interventions that are optimally matched to their characteristics and needs, across disease stages, diagnostic categories, cultures, and the lifespan. Optimizing interventions will not only require consideration of symptoms and functioning, but also a broader consideration of etiologies, intervention, preferences of patients and families, and the contexts of intervention delivery.

NIMH supports the development and testing of preventive as well as treatment interventions, recognizing that many mental illnesses begin well before adulthood and often before symptoms appear or daily functioning is impaired. We need preventive interventions for delivery early in the course of illness and early in life for at-risk individuals, plus treatment interventions to mitigate mental illnesses and associated dysfunction at the earliest possible opportunity. NIMH encourages the development and testing of preventive and early interventions that can be delivered in a developmentally appropriate manner (e.g., at known sensitive periods and at key transitions) as early in life as possible and early in the illness course, to prevent or forestall mental illnesses and associated dysfunction.

The following Objectives further define this Goal:

Objective 3.1: Develop new interventions based on discoveries in genomics, engineering, neuroscience, and behavioral science

The experimental therapeutics approach focuses not only on testing whether new interventions show clinical benefit, but, more importantly, on a staged approach where researchers initially establish confidence that the intervention is acting on the presumed target in humans, through a dose-dependent mechanism. If successful, larger clinical trials would serve to reconfirm target engagement and further assess clinical impact of the potential intervention. If the interventions do not work in the expected manner, negative results are likewise scientifically informative and fundamental. In the case of an intervention engaging the target but failing to demonstrate a clinical effect, the target would be disqualified. If the intervention fails to adequately engage the target, the intervention would be disqualified from further consideration.

The experimental therapeutics framework also recognizes that clinical targets may differ qualitatively and quantitatively throughout the life course. Therefore, there needs to be a strong scientific premise for selecting clinical targets within a particular age range. Additionally, the dose of an intervention that is safe and effective for target engagement may be age- or developmental stage-dependent and should be systematically established in advance of efficacy testing. It is also recognized that multiple targets may need to be engaged to exert beneficial outcomes.

To more effectively develop new preventive and treatment interventions based on novel genomic, engineering, neurobiological, and behavioral advancements, NIMH will support research that employs the following Strategies:

Strategy 3.1.A: Developing novel interventions using a mechanism-informed, experimental therapeutics approach

Interest areas include:

1. Enhancing the predictive value of preclinical assays used to select targets, drug candidates, circuit-based or cognitive/behavioral interventions, devices, and biologics for clinical development.
2. Identifying preventive and treatment intervention targets appropriate to an individual's age and stage of illness, and testing interventions to modify those targets to prevent or improve symptoms. Putative targets should be based on scientific discoveries that advance our understanding of the mechanisms and trajectories of mental resilience and illnesses.
3. Developing promising preventive and treatment intervention strategies that target specific molecular, cellular, neural circuit, or psychological mechanisms driving core domains of cognitive, behavioral, and affective function that are disrupted in mental illnesses, including those that cut across diagnostic categories. Strategies may include pharmacological, psychosocial, device-based, or biologic therapeutic candidates that engage the target of

interest. Studies may also evaluate the functional impact of target engagement and determine the optimal dose needed to achieve functional impact.

4. Developing novel preventive interventions based on an understanding of risk and protection at the level of the individual and within a developmental and environmental context, and testing whether targeting proximal risk and protective factors, or intervening factors that reduce risk, result in promoting health and preventing illness.

Strategy 3.1.B: Developing and implementing measurement strategies to facilitate mechanism-based intervention development and testing

Interest areas include:

1. Developing and validating quantitative behavioral and neurophysiological measures of target engagement in humans and animals as translational assays linked to functional domains disrupted in and across mental illnesses.
2. Developing and optimizing reliable and objective measures of target engagement and intervention on brain (molecular, cellular, circuit) function, side effects, clinical symptoms, and functional outcomes that can be implemented in clinical trials.
3. Testing novel behavioral markers and their associated neural activity patterns as potential stratification measures. Such testing might include computational and bioinformatics approaches and remote sensors.
4. Optimizing and validating real world outcome measures, including participant-reported outcomes, for use across clinical and non-clinical populations. Such measures may take into account illness phase, age, sex, race, ethnicity, culture, education, socioeconomic background, and other factors.
5. Developing and assessing novel mobile technology and digital health tools to enable objective measurement of behavior and intervention effects on symptom expression, functional outcomes, and quality of life in naturalistic environments.
6. Developing valid proxy measures or markers that are relatively brief and cost-effective for use in outcomes research.
7. Applying quantitative methods, algorithms, and metrics to assess the value and efficiency of intervention strategies.

Objective 3.2: Develop strategies for tailoring existing interventions to optimize outcomes

Clinical trials have traditionally focused on diagnostic status and symptom severity. Inattention to the complex topography of intervention targets, and to individual differences in psychopathology and intervention needs and preferences, can limit the value of findings and their potential uptake in routine practice. Strategies should focus on functional outcomes, considered within the context of an individual's development stage, environment, and culture.

Personalized mental health interventions mean that people should receive preventive and treatment interventions optimally matched to their needs. Optimizing interventions will not only require consideration of symptoms and functioning, but also a broader consideration of genetic, developmental, psychosocial, cultural, and environmental factors, and functional deficits and needs. Optimal care will also require consideration of the characteristics of population stratification or the candidate interventions and characteristics of providers and settings. Efficient research designs are needed to examine approaches for optimizing interventions for individuals, families, communities, populations, and settings.

To better tailor existing interventions to optimize outcomes, NIMH will support research that employs the following Strategies:

Strategy 3.2.A: Investigating personalized intervention strategies across disease progression and development

Interest areas include:

1. Investigating heterogeneity in, and mechanisms of, response to existing efficacious preventive and treatment interventions to inform personalized interventions that address specific outcomes.
2. Investigating strategies for sequencing or integrating interventions that are optimal for individuals in the context of phases of disease progression, stages of development, and other characteristics.
3. Establishing the safety and efficacy of efficacious therapeutic interventions developed for adult populations in children and the elderly, as well as women at various phases of the reproductive cycle (including menarche, the menstrual cycle, all stages of pregnancy, and menopause), while testing targets and target engagement specific to these populations.
4. Running prospective studies of known efficacious interventions to identify moderator variables and objective biomarkers, digital phenotypes, composite biomarkers, and/or multi-modality derived biotypes.
5. Developing multi-modal intervention strategies that combine the simultaneous application of established or novel pharmacological, psychosocial, biologic, and/or neuromodulation interventions to selectively access specific therapeutic targets through synergistic action.

Strategy 3.2.B: Developing and refining computational approaches and research designs that can be used to inform and test personalized interventions

Interest areas include:

1. Developing and refining research methods that can be used to advance personalized interventions, including computational algorithms for prescriptive approaches and innovative trial designs.

2. Reanalyzing or conducting meta-analyses using individual or aggregated clinical trials, patient registries, electronic health records, or other existing clinical data sets to identify moderators that might serve as tailoring variables for interventions.
3. Applying innovative computational approaches (e.g., machine learning, artificial intelligence, pattern classification techniques, predictive analytics) to multiple streams of data (e.g., routinely collected standardized measures in electronic health records, sensor-based data, social media/device use metrics, community-level data) using existing data sources to inform targets and timing for interventions and to facilitate clinical decision-making.
4. Developing and using innovative trial designs and data collection strategies to test personalized strategies that incorporate tailoring variables (e.g., clinical data, biomarkers, behavioral markers derived from passive sensing of naturalistic behaviors, patient response history) into participant assignment.
5. Promoting research designs that address the needs of underserved, minoritized, and marginalized groups. Such studies may include computational approaches that address biases in the data used to develop models (e.g., systemic under diagnosis in certain racial or ethnic groups), and use gold standard data that are diverse, appropriately over-sampled for minority groups, and that do not train the model to perpetuate existing health disparities.

Objective 3.3: Test interventions for effectiveness in community practice settings

Effectiveness research aims to generate information about the implementation of interventions and services in real-world settings. Effectiveness research is most useful for informing practice or policy decisions when it addresses a condition that has substantial public health significance; when it justifies the practical benefit of the intervention over existing approaches; when it is conducted in diverse, representative populations and contexts; when interventions are potentially scalable and could be disseminated into current practice; and, when it assesses a broad array of stakeholder-relevant outcomes.

Effectiveness research is best implemented through efficient and innovative platforms and designs that advance treatment personalization in community settings. Deployment-focused models of intervention and services research, which consider the key characteristics of the settings and providers where interventions and services will be implemented, are critical. Consistent with the NIMH experimental therapeutics approach to intervention development and testing, there is a need for effectiveness trials that contribute to our overall understanding of intervention change mechanisms. Not only are these effectiveness trials beneficial when they test the impact of interventions on clinical endpoints; they are beneficial when they explicitly examine whether the intervention engages the targets that mediate the clinical benefit.

To better test intervention effectiveness in community practice settings, NIMH will support research that employs the following Strategies:

Strategy 3.3.A: Developing and testing approaches for adapting, combining, and sequencing interventions to achieve the greatest impact on people's lives and functioning

Interest areas include:

1. Developing and testing approaches for implementing new indications and developing and testing adaptations or augmentations of evidence-based interventions when research suggests that a moderator or negative prognostic factor can be targeted to improve response substantially for a readily identifiable refractory subgroup.
2. Testing integrated and sequenced approaches to optimize effectiveness and safety, while minimizing unnecessary or off-label use of devices or psychotropic medications among children, adolescents, and adults.
3. Developing and testing broadly relevant preventive/early interventions that target shared modifiable risk and protective factors and/or key domains of functioning (e.g., emotion regulation, cognitive systems, and social processes) and thereby change life trajectories and reduce risk for multiple mental illnesses.
4. Focusing on strategies that address the needs of individuals and populations at risk for relapse/recurrence and manage chronic disorders (e.g., post-acute phase interventions/service strategies that are matched to the stage of illness both in terms of the goals and approaches to maximize the chances of complete recovery and sustained remission).
5. Developing and testing approaches that employ mobile health (mHealth) and other emerging technologies to boost the effectiveness of evidence-based interventions and to monitor health.
6. Using community-engaged research approaches to ensure that mental health interventions align with the needs of underserved, minoritized, and marginalized populations; that community stakeholders are involved in all phases of research; and, that community-based intervention studies employ rigorous designs to address health disparities questions.

Strategy 3.3.B: Conducting efficient pragmatic trials that employ new tools to rapidly identify, engage, assess, and follow participants in the context of routine care and other settings

Interest areas include:

1. Conducting effectiveness trials that leverage practice-based research and other research investments to inform intervention development and increase the efficiency and relevance of effectiveness research, including identifying targets and optimal timing for intervention.
2. Supporting refinement of preventive and treatment interventions for mental illnesses, while capitalizing on efficiencies to facilitate participant recruitment and data collection.
3. Supporting practice-based research aimed at refining and testing efficacious preventive interventions (including universal, selective, indicated, and tiered approaches), so that they are scalable and can be sustainably implemented in settings (e.g., primary care, schools, communities) where preventive services are delivered to youth.
4. Externally validating practice-based research across diverse populations and contexts to enhance the relevance and translation potential of trial results.

Strategy 3.3.C: Enhancing the practical relevance of effectiveness research via deployment-focused, hybrid effectiveness-implementation studies

Interest areas include:

1. Encouraging deployment-focused intervention and service models and effectiveness testing that consider the perspective of relevant stakeholders and key characteristics of intended intervention settings, to increase the likelihood that the interventions/services are feasible and scalable, and the research results will have utility for end users.
2. Emphasizing hybrid effectiveness-implementation research that goes beyond examining the effect of interventions on symptomatic or functional outcomes and designing studies to address questions regarding how client-, provider-, community-, and organizational-level factors impact clinical outcomes, implementation, and scalability of research-generated interventions.
3. Encouraging hybrid effectiveness-implementation trials across diverse settings to identify setting characteristics (e.g., workforce capacity, case mix) that impact intervention delivery and test strategies to sustain intervention effectiveness and quality of implementation in diverse settings.
4. Examining novel applications of technology that can generalize across indications, target populations, and operating platforms, to facilitate the delivery of interventions and enhance their reach and therapeutic value.

Goal 4: Strengthen the Public Health Impact of NIMH-Supported Research

Through mental health services research, investigators seek generalizable strategies for increasing access to and continuity with evidence-based interventions, fostering high quality equitable care, and improving clinical and recovery outcomes for millions of people with mental illnesses. To increase the public health impact of services studies, investigators test ways to develop or adapt, implement, scale-up, and sustain effective service delivery strategies and interventions for varied populations across multiple service and community settings in a cost-effective manner. This work requires new research designs, measures, and statistical approaches for evaluating system-wide interventions and measuring population-level effects, and may benefit from stakeholder input. New models of health care financing and delivery of care, along with evolving technologies such as electronic health records, health informatic systems, and multipurpose mobile computing devices, present unique opportunities for conducting deployment-focused services research in real-world settings. Such research may help to improve mental health care by determining the effectiveness of service strategies and optimizing the organization and sustained delivery of evidence-based preventive and treatment interventions; speeding the implementation of research-informed innovations in community settings; and ultimately ensuring optimal outcomes for individuals at risk for and affected by mental illnesses, particularly those from underserved communities and underrepresented minority groups.

The following Objectives further define this Goal:

Objective 4.1: Improve the efficiency, effectiveness, and reach of mental health services through research

Practice-based research, conducted within primary, specialty, and non-traditional health care and other community settings, is uniquely suited to address questions concerning clinical epidemiology; access to care, quality, effectiveness, and continuity of services; and clinical, functional, and societal outcomes associated with mental health interventions. Weaving systematic data collection into routine care is an efficient means for capturing information about clinical populations, provider behavior, system-level performance, and outcomes for key subgroups. In addition, NIMH recognizes a need for more research on the impact of various financing strategies to ensure care for all, especially children and adolescents at risk for and with developmental precursors of mental illnesses and people with serious mental illness, neurodevelopmental conditions, and complex health needs.

To test approaches for improving the efficiency, effectiveness, and reach of mental health services, NIMH will support research that employs the following Strategies:

Strategy 4.1.A: Employing assessment platforms within health care and other relevant systems to accurately assess the distribution and determinants of mental illnesses and to inform strategies for improved services

Interest areas include:

1. Examining mental illness prevalence, service use, intervention response, and relapse events via data from large, diverse, and representative population samples or practice-based research networks, to identify new opportunities for individual-, provider-, organizational-, community-, or system-level interventions.
2. Promoting data-driven approaches for improving screening and detection of low base-rate events (e.g., suicidal behavior, first episode psychosis); monitoring real-time trends in incidence, prevalence, and severity; and, identifying novel targets for preventive interventions or treatment engagement.

Strategy 4.1.B: Optimizing real-world data collection systems to identify strategies for improving access, quality, effectiveness, and continuity of mental health services

Interest areas include:

1. Developing pragmatic, valid, and reliable measures of engagement, intervention fidelity and quality, and outcomes that can be applied at the person, clinic, system, community, and/or population level to advance measurement-based care.
2. Comparing performance feedback methods and quality improvement processes for adoption across a range of systems and age groups to advance the principles of learning health care.
3. Applying computational modeling and data analytics to electronic health records, administrative claims data, and information from other sources to study mental health needs, social determinants, and services over time, and to identify mutable targets for improving service access, delivery, quality, and outcomes.

Strategy 4.1.C: Comparing alternative financing models to promote effective and efficient care for individuals with serious emotional disturbance and serious mental illness

Interest areas include:

1. Comparing alternative financing mechanisms that promote high quality, clinically effective, affordable, and efficient mental health care across settings and populations and discourage low-value services.
2. Optimizing public and commercial financing mechanisms that cover integrated care packages for individuals with complex needs (e.g., combination psychopharmacology, psychotherapy, rehabilitative therapy, care coordination interventions).
3. Studying the impact of national, state, provincial/county-level, or other health care system rules and regulations on participation in provider reimbursement and/or waiver programs.
4. Understanding the role of financing and economic factors on developing and supporting a highly qualified mental health workforce.

5. Understanding the impact of economic factors affecting patients' access and ability to seek high-quality mental health services on mental health outcomes.

Objective 4.2: Expedite adoption, sustained implementation, and continuous improvement of evidence-based mental health services

The delay between research findings and implementation in real-world settings is often lengthy, and delayed uptake of effective mental health interventions and services is widespread. NIMH recognizes the need for research to develop and test strategies that speed dissemination, adoption, and implementation of evidence-based interventions and sustain these practices over time. Strategies that reduce the lag between research discovery and science-driven practice could radically alter the quality and outcomes of care provided for all individuals with mental illnesses.

To accelerate deployment-focused intervention and services research, NIMH encourages strong partnerships among scientists, those who directly benefit from evidence-based approaches (e.g., service users, providers, caregivers), and public and private stakeholders. Effective partnerships among these stakeholders are crucial for identifying salient services research questions, developing realistic interventions and services, and testing adoptable, scalable, and sustainable approaches that promote continuous improvement of mental health care.

To speed adoption, implementation, and continuous improvement of evidence-based mental health services, NIMH will support studies that employ the following Strategies:

Strategy 4.2.A: Strengthening partnerships with key stakeholders to develop and validate strategies for implementing, sustaining, and continuously improving evidence-based practices

Interest areas include:

1. Conducting dissemination and implementation studies that reflect active partnerships between scientists and key stakeholders across all phases of the research process.
2. Investigating strategies that promote rapid incorporation of practice-based research findings into health and other system decision making, clinical practice guidelines, and reimbursement policies for mental health services.
3. Addressing workforce issues related to implementation and sustainment of evidence-based approaches in health care and other settings (e.g., training providers in new treatment models and technologies; maintaining provider competence; involving paraprofessionals and peer providers; retaining qualified providers; managing staff turnover without compromising the quality of services; and, studying policies that impede or facilitate high quality care).

Strategy 4.2.B: Building models to scale-up evidence-based practices for use in public and private primary care, specialty care and other settings

Interest areas include:

1. Examining and monitoring client, caregiver, provider, organizational-level, and community factors, including social determinants of health, that affect the usability and transportability of interventions and services (i.e., the degree to which the evidence-informed intervention can be implemented with fidelity).
2. Adapting interventions and services with demonstrated effectiveness in one setting to determine fit for use in other contexts such as non-specialty community/practice settings where mental health care is or could be delivered (e.g., primary care, schools, child and adult welfare, criminal and juvenile justice settings, long-term care facilities, geriatric service programs).
3. Employing hybrid effectiveness-implementation designs to enhance the delivery of evidence-based mental health practices and improve implementation outcomes (e.g., fidelity, acceptability, feasibility, appropriateness, penetration, and sustainability of services).

Strategy 4.2.C: Developing decision-support tools and technologies that increase the effectiveness, implementation, and continuous improvement of mental health interventions in public and private primary care, specialty care, and other settings

Interest areas include:

1. Developing and validating novel tools, smart technologies, real-time analytics, and ecologically valid measures to monitor the engagement of intervention targets in services interventions.
2. Examining and adapting the attributes of evidence-based interventions (e.g., intensity, duration, frequency) and implementation (e.g., fidelity, feasibility, acceptability) that affect their generalizability to practice settings.
3. Developing and testing decision-support algorithms for matching services within a health system (e.g., pharmacotherapy, psychotherapy, rehabilitation, care coordination, transition planning) to clients' needs over time, including stepped-care algorithms that span non-specialty and mental health specialty services.
4. Developing and testing strategies (e.g., shared decision making or behavioral economic approaches to behavior change) to enhance prevention and treatment engagement and adherence.

Objective 4.3: Develop innovative service delivery models to dramatically improve the outcomes of mental health services received in diverse communities and populations

Service delivery models provide a framework for mental health care, which account for various settings, providers, and resources. Available data indicate that many current service delivery models are inadequate to meet the mental health service needs in the United States and around the globe. To provide high quality care to populations in need, researchers may need to adapt evidence-based models to account for moderators, including social determinants of health, known to impact intervention

effectiveness among underrepresented, underserved, vulnerable, and minority groups. Services research and implementation science strategies that test adaptations should be designed to determine whether the adapted strategy counteracts moderators that have been shown to impede effectiveness and clinical outcomes.

NIMH is committed to supporting research that reduces disparities and advances equity in mental health services and outcomes. As such, we need innovative and sustainable service delivery models that address disparities that stem from historical, social, and economic inequities that disproportionately affect marginalized populations and people with serious mental illness, to include people experiencing instability in housing, employment, income, and food. People with serious mental illness are among the first and most disproportionately affected by these social and economic insecurities. We must develop and test novel components of care across multiple settings where mental health services are needed and use developmentally and culturally appropriate tools to better reach populations in need and substantially improve the delivery of evidence-based mental health care.

To improve the outcomes of individuals receiving mental health services and to ensure equity of outcomes in all populations, NIMH will support research to develop innovative services delivery models that employs the following Strategies:

Strategy 4.3.A: Adapting, validating, and scaling-up programs currently in use that improve mental health services for underserved populations

Interest areas include:

1. Testing innovative approaches for reducing empirically documented disparities in care access, quality, and outcomes for racial and ethnic minority groups; individuals limited by English language proficiency, educational, or cultural barriers; sexual and gender minorities; individuals living in rural areas; socioeconomically disadvantaged persons; and, other underserved groups.
2. Combining data from multiple sources of information (e.g., electronic health records, administrative claims data, epidemiologic surveys, census data, qualitative methods) to identify underserved groups and to explore novel approaches for coordinating health/community service resources and improving overall health outcomes.
3. Conducting research to better understand, predict, and reduce mental health workforce shortages across pediatric, adolescent, adult, and geriatric services; reduce the shortage of culturally and linguistically competent care providers for racial and ethnic minorities; reduce the workforce shortages in certain geographic areas (e.g., rural and underserved communities); and, promote care that is respectful and affirming of individual's sexual orientation and gender identity.

Strategy 4.3.B: Developing and validating service delivery models that provide evidence-based care for individuals throughout the course of mental illness

Interest areas include:

1. Developing and testing innovative strategies to promote early identification and engagement in prevention and mental health services for children, adolescents, and adults, especially for those experiencing early symptoms of mental illness.
2. Characterizing care pathways to identify mutable barriers and facilitators to improving access to care across the lifespan, including children at risk for autism or mental illnesses, transition-age youth with autism or emerging mental illnesses, and adults with autism or mental illnesses.
3. Defining and testing the specific mechanism(s) of action (i.e., targets) in service delivery approaches purported to improve mental health outcomes across developmental stages. When paraprofessionals or peer providers are delivering services, the research should make clear the intended purpose for involving nontraditional staff (e.g., addressing work force shortages, instilling hope and re-moralization, improving client engagement) and then test whether engagement of these targets mediates outcomes, with consideration for scalability of strategies that prove effective.

Strategy 4.3.C: Developing and validating systems-level strategies, using technology and other approaches, to identify, support, optimize, and monitor the effectiveness of evidence-based care throughout the course of illness

Interest areas include:

1. Using technology to improve prevention and early detection of mental illnesses, connect clients across all ages to evidence-based care, increase reach of and engagement with services for underserved populations, and improve client-level outcomes.
2. Developing and testing clinician-facing “dashboards” or other system-level technologies that can be used to support providers in their use of measurement-based care, to facilitate and optimize system-level quality monitoring and improvement, and to improve clinical workflows.
3. Developing and testing implementation strategies for evidence-based practices (e.g., ensuring availability, accessibility, effectiveness, scalability, sustainability) in non-specialty settings where significant unmet need exists (e.g., the criminal/juvenile justice system, employment settings, military or veteran organizations, schools, and the child welfare system).
4. Building novel service delivery models that capitalize on systems that are already engaging individuals with mental health needs (e.g., schools, social services, or other community-based settings, online/virtual communities).

Strategy 4.3.D: Developing and validating decision-making models that bridge mental health, medical, and other care settings to integrate the appropriate care for people with serious mental illness and comorbid medical conditions

Interest areas include:

1. Developing and testing service delivery models for people with comorbid conditions (e.g., medical comorbidities, co-occurring substance use disorder), such as care decision models that integrate treatment for mental illnesses and medical conditions, and service delivery

interventions to reduce modifiable health risks associated with premature mortality in people with serious mental illness. These innovative service delivery models should be feasible in a wide range of settings and acceptable to a wide variety of health disparity populations, since racial and ethnic minorities have greater prevalence of comorbidities.[31]

2. Developing and validating decision-support tools to assess mental health and functional needs, medical risk factors, and mental health/medical treatment availability in non-specialty settings where children and adolescents are served, and to facilitate treatment planning.
3. Using existing and developing novel technologies (e.g., mobile devices, information systems) to significantly improve access, engagement, quality, effectiveness, and efficiency of integrated mental health services, while making sure that these advances benefit people with a wide range of backgrounds, socioeconomic status, ethnicity, race, and geographical area of residence.
4. Investigating strategies for active symptom management that reduce the symptom burden in individuals with serious mental illness and multiple chronic conditions.

Strategic Planning Process

The National Institute of Mental Health (NIMH) updates its Strategic Plan for Research every five years to keep pace with scientific advancements and the changing landscape of the mental health field. NIMH uses the Strategic Plan to communicate our priorities and help guide future mental health research efforts at the Institute. The new 2020 Plan retains core elements of previous NIMH Strategic Plans, and has been revised, updated, and expanded in response to the many discoveries and changes in the field over the past five years.

We began by updating the Institute's four overarching Goals (referred to as Strategic Objectives in the 2015 Strategic Plan for Research). To accomplish this, we sought input from NIMH leadership, subject matter experts, and other staff to identify knowledge gaps and opportunities for research advancement. The four Goals are intended to be broad and capture the diversity of topics the Institute must focus on to achieve its mission. The Goals successively build in scale from basic neuroscience and behavioral science to research on delivery of mental health services. These four Goals are:

1. Define the Brain Mechanisms Underlying Complex Behaviors
2. Examine Mental Illness Trajectories Across the Lifespan
3. Strive for Prevention and Cures
4. Strengthen the Public Health Impact of NIMH-Supported Research

Updating the Plan was an iterative process, with opportunities for NIMH staff, advisory boards, and the public to contribute. NIMH presented a framework for the 2020 Plan to the Interdepartmental Serious Mental Illness Coordinating Committee (ISMICC), and cross-walked the Institute's priorities with ISMICC focus areas and recommendations. The framework was also presented to the National Advisory Mental Health Council (NAMHC) and a draft Plan was reviewed by the NAMHC members. We incorporated their feedback and published a revised draft Plan for public comment; members of the scientific community, professional societies, advocacy organizations, and the general public were invited to share feedback via a Request for Information (RFI) published in the NIH Guide and in the Federal Register. Comments were submitted via a web-based RFI input tool, email, or mail from December 2, 2019 to January 15, 2020. The Institute received robust feedback from our many stakeholders, including researchers, mental health advocates, and individuals with lived experience. After reviewing comments and making numerous edits, the final Plan was presented to the NAMHC and published on the NIMH website.

The 2020 NIMH Strategic Plan for Research is the product of many authors. We would like to thank everyone who took the time to review and provide feedback and input on the many draft Plans. We look forward to your continued involvement as we support research to transform the understanding and treatment of mental illnesses to pave the way for prevention, recovery, and cure.

Updates to the Plan

The NIMH Strategic Plan for Research is a living document, which means it is updated regularly to keep pace with ever-evolving scientific approaches and research priorities that can lead to new discovery. The most recent update was published in July 2021. Archived PDFs of the previous versions of the Plan are available below.

- NIMH Strategic Plan for Research – 2021 Update – published July 2021 (PDF)
- NIMH Strategic Plan for Research—published May 2020 (PDF)

In addition, on the Progress pages included in the digital version of the Plan, we highlight key contributions of NIMH and NIMH-funded investigators in advancing research toward achieving the four Goals of the NIMH Strategic Plan for Research and the Institute's mission.

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