# National Institute on Alcohol Abuse and Alcoholism Strategic Plan:

## **Fiscal Years 2024–2028**

Advancing Alcohol Research to Promote Health and Well-Being





National Institute on Alcohol Abuse and Alcoholism

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## **Director's Message**

Alcohol-related problems exact an immense toll on individuals, families, and communities. In the United States, more than 178,000 people die per year from <u>alcohol misuse</u>, making alcohol a leading preventable cause of death.<sup>1</sup> From the first year of the COVID-19 pandemic in 2019 through 2021, alcohol-related deaths increased approximately 38%, far outpacing previous increases of around 2% per year.<sup>2</sup> Alcohol-related traffic fatalities increased by 14% from 2020 to 2021, their highest level since 2009.<sup>3</sup>

Alcohol misuse is linked to more than 200 diseases and injury-related conditions—including approximately 50% of liver disease deaths, 5% to 6% of cancer cases, and 4% of cancer deaths—and contributes substantially to health care costs and lost productivity.<sup>4,5</sup> The adverse effects of alcohol are extensive and impact health in



ways that many people may not realize. In addition, nearly 30 million people in the United States have <u>alcohol use disorder (AUD)</u>, and less than 10% of them receive treatment or help.<sup>6,7</sup>

The mission of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) is to generate and disseminate fundamental knowledge about the adverse effects of alcohol on health and well-being and to apply that knowledge to improve the diagnosis, prevention, and treatment of alcohol-related problems, including AUD, across the life course. For more than 50 years, NIAAA has been at the forefront of cutting-edge alcohol research that has significantly expanded our understanding of the factors that contribute to alcohol-related problems and the mechanisms through which they develop.

Thanks to NIAAA-supported research, AUD is widely regarded as a treatable chronic disorder stemming from various genetic and environmental factors, like many other common chronic health conditions. Accumulating evidence demonstrating the health risks of alcohol at all levels, along with the recent cultural shift around sober curiosity in the United States, have provided NIAAA new opportunities to lead the changing conversation around alcohol.

We have developed and promoted materials which help individuals and communities reevaluate their relationship with alcohol, and change how alcohol-related health issues are perceived and addressed in health care. These efforts, supported by advances in basic, translational, and clinical research, are leading to more effective prevention, diagnosis, and treatment of alcohol misuse and are helping to reduce stigma associated with alcohol-related problems as well as the stigma associated with choosing not to drink.

NIAAA's strategic plan charts a course for the next five years as we seek to address alcohol research challenges while maintaining flexibility to address emerging research opportunities and urgent public health needs. Preventing alcohol misuse at all ages, enhancing the diagnosis of AUD, <u>fetal alcohol</u> <u>spectrum disorders (FASD)</u>, and other alcohol-associated pathologies, improving treatment for these

conditions, and addressing health disparities in alcohol misuse and related consequences are just some of NIAAA's most salient goals. I am optimistic that NIAAA-supported research will pave the way for future breakthroughs that will help more Americans live healthier, more productive lives.

#### George F. Koob, Ph.D.

Director National Institute on Alcohol Abuse and Alcoholism

## Introduction to the Strategic Plan Structure of the Strategic Plan

The National Institute on Alcohol Abuse and Alcoholism (NIAAA) Strategic Plan Fiscal Years 2024–2028 describes research goals, themes, and programs that support the NIAAA mission. These goals also support the <u>NIH-Wide Strategic Plan: Fiscal Years 2021–2025</u> and the <u>NIH-Wide Strategic Plan for</u> <u>Diversity, Equity, Inclusion, and Accessibility: Fiscal Years 2023–2027</u>, as well as complement other National Institutes of Health (NIH) strategic plans and U.S. Department of Health and Human Services (HHS) initiatives.

Four <u>research goals</u> represent long-standing pillars of NIAAA-supported research. <u>Cross-cutting</u> <u>research themes</u> represent high-priority concepts and emergent research opportunities that cut across the four research goals. <u>Cross-cutting research programs</u> describe coordinated programs with elements that span the four research goals. In addition to conducting and funding research, NIAAA has established <u>capacity and operational priorities</u> toward sustaining robust research capabilities, practicing good scientific stewardship, and strengthening the reach and impact of NIAAA-supported research.

## National Institute on Alcohol Abuse and Alcoholism Mission

NIAAA's mission is to generate and disseminate fundamental knowledge about the adverse effects of alcohol on health and well-being and to apply that knowledge to improve diagnosis, prevention, and treatment of alcohol-related problems, including <u>alcohol use disorder (AUD)</u>, across the life span.

Today, NIAAA is the world's largest funder of alcohol research. NIAAA provides leadership in the national effort to reduce alcohol-related problems by:

- Conducting and supporting alcohol-related research in a wide range of scientific areas, including neuroscience and behavior, epidemiology and prevention, treatment and recovery, and metabolism and health effects
- Coordinating and collaborating with other research institutes and federal programs on alcohol-related issues
- Collaborating with institutions (including international, national, state, and local), organizations, agencies, and programs engaged in alcohol-related work
- Translating and disseminating research findings to health care providers, researchers, policymakers, and the public

## **Statutory Authority**

As established by the <u>Comprehensive Alcohol Abuse and Alcoholism Prevention</u>, <u>Treatment</u>, and <u>Rehabilitation Act of 1970</u>, NIAAA's mission is to "develop and conduct comprehensive health,

education, training, research, and planning programs for the prevention and treatment of alcohol abuse and alcoholism." Visit the <u>History of NIAAA</u> webpage to learn more about NIAAA's major milestones.

## Institute Organization

NIAAA is one of the 27 Institutes and Centers (ICs) of NIH, a component of HHS. NIH is the foremost federal agency for funding biomedical research in the United States.

NIAAA's <u>organizational structure</u> includes the <u>Office of the Director</u>, which sets research, programmatic, and institute-wide priorities in collaboration with NIAAA offices and research divisions. NIAAA offices include the <u>Office of Extramural Activities</u>, the <u>Office of Science Policy and Communications</u>, and the <u>Office of Resource Management</u>. NIAAA's intramural research division, the <u>Division of Intramural Clinical and Biological Research</u>, conducts cutting-edge alcohol research and promotes research training. NIAAA's four extramural research divisions—the <u>Division of Epidemiology and Prevention Research</u>, the <u>Division of Metabolism and Health Effects</u>, the <u>Division of Neuroscience and Behavior</u>, and the <u>Division of Treatment and Recovery</u>—develop, plan, and coordinate multidisciplinary research and research training in a wide range of scientific areas essential to NIAAA's mission.

## **Strategic Planning Process**

NIAAA's strategic planning process considers the long-term priorities of the field while remaining flexible to adapt to emerging public health needs and scientific opportunities. It also considers a dynamic balance of basic, translational, and clinical research relevant to NIAAA's broad mission. Although NIAAA engages in formal strategic planning, the institute continually assesses and refines priorities as the science and public health landscape evolves.



To initiate its strategic planning process, NIAAA formed a strategic plan working group comprising staff from the NIAAA Office of Science Policy and Communications in 2020. This group convened meetings with NIAAA leadership and all NIAAA offices and divisions to develop an overall framework for the new strategic plan. Additionally, two listening sessions were held with extramural and intramural staff to provide input on the process and utility of the strategic plan. These sessions were followed by meetings with each NIAAA research division, which was asked to identify research needs and opportunities related to its scientific areas. Their feedback, with input from NIAAA leadership, formed the basis of an outline representing the draft strategic plan framework.

A <u>request for information (RFI)</u> inviting public comment on the draft framework was issued in 2021. RFI responses were received from researchers, advocacy groups, professional societies, and others. The results were summarized in a report to the National Advisory Council on Alcohol Abuse and Alcoholism in September 2021. The outline was refined based on the RFI feedback and Council input and was followed by writing of the strategic plan in consultation with NIAAA leadership, offices, and research divisions.

The final NIAAA Strategic Plan: Fiscal Years 2024–2028 represents a collaborative effort of NIAAA leadership, NIAAA staff across the institute, and the National Advisory Council on Alcohol Abuse and Alcoholism.

### Strategic Plan Implementation and Monitoring

Over the next five years, NIAAA will monitor progress on its goals and research priorities. NIAAA's ability to pursue its research goals and priorities is supported by its commitment to building a robust research capacity and serving as a responsible steward of the public's investment. This strategic plan is a living document that is responsive to public health challenges as well as to changes in the scientific landscape.

## **Cross-Cutting Research Themes**

NIAAA has identified cross-cutting research themes, which provide a lens for examining high-priority topics that span two or more of the <u>research goals</u> outlined in this strategic plan. The following themes complement the <u>Cross-Cutting Research Programs</u> and <u>Supporting the Mission</u> sections of this strategic plan.

## Advancing Diversity, Equity, Inclusion, and Accessibility in the Alcohol Research Enterprise

Health equity is the principle underlying the continual process of ensuring that all individuals or populations have optimal opportunities to attain the best health possible.

NIAAA is genuinely committed to true change that is sustainable, propels the NIAAA mission, and capitalizes on the full range of talent in the nation. A deeper understanding of the issues that face <u>underserved and underrepresented populations</u><sup>\*</sup> is essential for promoting health equity and ensuring that NIAAA-supported research benefits all.

NIAAA is pursuing new research opportunities to address gaps in <u>minority health and health disparities</u> <u>research</u>, including research on <u>health determinants</u> such as barriers to treatment that contribute to alcohol-related health disparities. Such studies enrich the understanding of the mechanisms of alcohol-associated disorders and inform novel approaches for prevention, diagnosis, treatment, and recovery.

NIAAA recognizes that the experiences and perspectives of the alcohol research workforce help to guide not only the scientific methods that they use and the solutions that they seek, but also the fundamental questions that they ask. NIAAA requires a plan for enhancing diverse perspectives among <u>Specialized</u> <u>Alcohol Research Centers and Comprehensive Alcohol Research Centers</u> to advance the scientific and technical merit of proposed projects through expanded inclusivity.

<sup>\*</sup> As defined in the NIH-Wide Strategic Plan for Diversity, Equity, Inclusion, and Accessibility, *underserved populations* are populations sharing a particular characteristic as well as geographic communities who have been systematically denied a full opportunity to participate in aspects of economic, social, and civic life. *Underrepresented populations* are populations sharing a particular characteristic, who are underrepresented in the U.S. biomedical, clinical, behavioral, and social sciences research enterprise, including the NIH workforce and research participants.

NIAAA also seeks to initiate and sustain collaborative research partnerships between research centers in minority serving institutions and Alcohol Research Centers to strengthen research capacity and the scientific workforce at these institutions. Supporting and advancing the best science depends on having a diverse and talented scientific and administrative workforce, as NIAAA aims to remain the global leader in scientific discovery and innovation in alcohol research.

## **Advancing Research on Women's Health**

Alcohol use among women is a growing public health concern. Alcohol use is increasing among women older than age 26. For the first time, adolescent and young women (ages 12–20) are drinking—and binge drinking—more than men. A substantial body of evidence suggests that women who drink are at a higher risk of adverse alcohol-related pathology and consequences than men who drink. These include faster progression of AUD, blackouts, liver disease, heart disease, cognitive deficits, and certain cancers, among other effects.

Research also suggests that pathways to alcohol misuse may differ between women and men. Women experience stress and trauma more frequently than men, and alcohol is often used to cope with psychological distress. Unfortunately, health care providers are less likely to screen for alcohol misuse and provide interventions to women compared to men.

To improve the health of women, NIAAA will continue to support biological and behavioral research to more fully understand how alcohol use and misuse impact women and to develop interventions tailored to the unique needs of women. This includes studies on health issues that affect young women, including the etiology, prevention, and treatment of alcohol misuse. Research is needed to elucidate sex differences in the mechanisms contributing to alcohol's adverse effects on the brain, other organs, and body systems, and how these mechanistic differences can reveal novel targets for prevention and treatment of alcohol-related harms. More research is also needed to identify the risk and protective factors that contribute to alcohol-associated health outcomes among women to inform the development of prevention and treatment interventions.

Given the contribution of alcohol to many health conditions, NIAAA will encourage innovative studies to enhance understanding of the relationships between alcohol misuse and common comorbidities, such as mental health conditions and other acute and chronic health conditions. New research to improve implementation and coordination of evidence-based care for alcohol problems across settings, including prenatal care, and across components of health systems will be essential for improving the health and well-being of women. NIAAA is actively participating in the <u>White House Initiative on Women's Health</u> <u>Research</u> and will pursue collaboration with the <u>NIH Office of Research on Women's Health</u> and partners across NIH to advance integrated research in women's health.

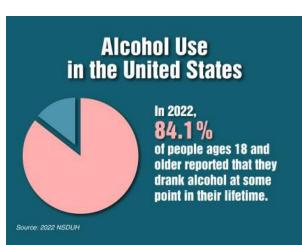
#### Applying a Life Course Approach to Alcohol Research

Biological, behavioral, social, and environmental changes that occur throughout life influence the emergence and progression of alcohol misuse and its associated health consequences. A life course approach that takes these changes into account can inform research on the development of interventions and resources tailored to the specific needs of individuals and populations.

NIAAA encourages research to address critical knowledge gaps about the impact of alcohol misuse unique to each life stage to facilitate improved prevention, identification, and treatment of alcohol-related problems.

## Encouraging a Whole Person, Integrated Approach to Health

Alcohol misuse contributes to many acute and chronic health conditions, and impacts health in ways that individuals and health care providers may not realize. The relationship between alcohol and so many elements of health underscores the importance of addressing alcohol misuse in the context of <u>whole</u> <u>person health</u>. Whole person health looks at the connections across biological, behavioral, social, and environmental domains of health to address disease, and is supported by integrated approaches to care. For example, integrating alcohol screening, brief intervention, and referral to treatment (SBIRT) in routine health care can increase the chances that an alcoholrelated problem is identified and addressed, and can



help clinicians identify other physical and mental health-related issues affected by alcohol misuse.

Integrating treatment for AUD and <u>alcohol-associated liver disease (ALD)</u> holds promise for promoting recovery from both conditions and for contributing to the long-term survival of patients. Using the integration of care between AUD and ALD as an example, future work should emphasize opportunities to integrate care for alcohol misuse and other pathophysiologies exacerbated or caused by alcohol, such as sleep disorders, pain, and stress- and mood-related disorders.

A better understanding of the mechanistic and clinical relationships between alcohol misuse and commonly co-occurring mental and physiological conditions could lead to novel, integrated strategies that improve the prevention of, early diagnosis of, treatment of, and long-term recovery from these conditions. Delving into the health determinants that influence these relationships will also provide valuable insights towards these goals.

NIAAA encourages innovative basic, translational, and clinical research that enhances the understanding of whole person health and facilitates integrated care to improve health outcomes and reduce health care costs.

## Innovating Alcohol Research and Care Through Data Science

In 2019, prior to the mandatory NIH Data Management and Sharing Policy, NIAAA established a new repository for data generated by NIAAA-funded studies in humans, the <u>NIAAA Data Archive</u>, housed within the National Institute of Mental Health (NIMH) Data Archive. This growing archive will eventually

contain data from thousands of NIAAA-funded studies, which will be made available to the research community. In addition to facilitating rigor and reproducibility of research, the NIAAA Data Archive will provide a rich resource for secondary analyses—a strategy that supports the optimal use of research resources.

Artificial intelligence (AI) will be critical for developing new statistical and analytical models for alcohol research. Such new models will be important for real-time data analysis, prediction, automated tools for data harmonization and management, and the generation of interactive tools for the prevention of alcohol misuse, individualized AUD treatment, and guidance of recovery. In particular, multi-omic approaches combined with data science approaches also hold promise for identifying biomarkers or algorithms of biomarkers that could help predict vulnerability to alcohol misuse, individualize AUD treatment, and guide recovery.

## **Cross-Cutting Research Programs**

Cross-cutting research programs are NIAAA-managed research portfolios that include topics spanning multiple research goals outlined in this strategic plan. These programs complement the <u>Cross-Cutting</u> <u>Research Themes</u> and <u>Supporting the Mission</u> sections of this strategic plan.

## **Fetal Alcohol Spectrum Disorders**

<u>Fetal alcohol spectrum disorders (FASD)</u> represent the broad range of neurodevelopmental impairments and other physical effects that result from prenatal exposure to alcohol. NIAAA supports a robust <u>FASD</u> research program to advance study of the causes, mechanisms, diagnosis, prevention, and treatment of FASD.

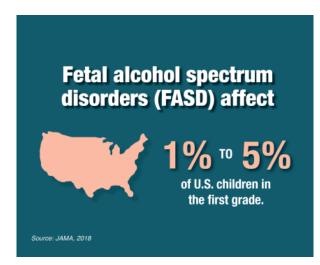
Research to reduce stigma around prenatal alcohol exposure, to increase education and awareness of FASD, and to develop culturally appropriate prevention strategies are important components of FASD prevention. Basic research on the biological mechanisms that underlie prenatal alcohol exposure and contribute to FASD can lead to the identification of diagnostic biomarkers as well as potential treatment targets, paving the way for earlier diagnosis and treatment. NIAAA is also facilitating efforts to reach consensus on a single research classification system for FASD to harmonize research efforts across the globe and accelerate scientific progress.

## **Objective 1: Advance the Prevention of Prenatal Alcohol Exposure**

Preventing and reducing alcohol use during pregnancy is essential to preventing prenatal alcohol exposure and related consequences, including FASD. Studies have shown that alcohol SBIRT approaches are an effective tool for addressing alcohol and other substance use in primary and prenatal care settings.

NIAAA encourages research and other activities to prevent and reduce prenatal alcohol exposure and the prevalence of FASD—for example:

 Designing and evaluating cost-effective models to help women at high risk of having a child with FASD (i.e., who misuse alcohol, have AUD, or



already have another child with FASD) to reduce or abstain from drinking during pregnancy and, consequently, reduce the incidence of FASD

- Developing culturally informed interventions to prevent alcohol-exposed pregnancies
- Improving implementation and enhancing scalability of effective preventive interventions (e.g., alcohol SBIRT) for alcohol misuse and its negative consequences in women
- Identifying the causes of FASD-related stigma and exploring strategies to reduce it in order to improve prevention efforts
- Promoting collaboration with federal and nonfederal organizations to raise public awareness about FASD and advance implementation of prevention interventions in various clinical and nonclinical settings

## Objective 2: Improve Early Identification and Treatment Interventions for Fetal Alcohol Spectrum Disorders

Improved diagnostic techniques for FASD could enable more accurate diagnosis, expand access to assessment for FASD, allow for earlier intervention, and likely reduce costs and overall burden of FASD across the life span. Early identification holds promise for better outcomes, but limited availability of FASD diagnostic services remains a barrier to care.

NIAAA encourages research to enhance FASD screening, diagnosis, and treatment—for example:

 Improving implementation of existing evidence-based FASD diagnostic approaches across the life span as well as early intervention and care for individuals with FASD across a range of populations and settings, such as for children and parents in the child welfare system and individuals in the juvenile justice system

- Developing novel technologies and methods to facilitate earlier identification of children affected by prenatal alcohol exposure, as early as the fetal and newborn periods
- Assessing combinations of evidence-based therapeutic approaches for individuals with FASD
- Understanding and addressing health disparities concerning prenatal alcohol exposure in different populations
- Developing and evaluating novel prenatal and postnatal therapeutic approaches, medications, and dietary supplements to combat prenatal alcohol exposure and FASD
- Pursuing various interventions to mitigate the neurocognitive and behavioral deficits associated with FASD across the life span

## Objective 3: Identify Mechanisms, Diagnostic Biomarkers, and Potential Treatment Targets for Fetal Alcohol Spectrum Disorders

Alcohol can disrupt prenatal development through a variety of mechanisms. Understanding the biological effects of prenatal alcohol exposure that emerge across the life span, from prenatal development to adulthood, can inform preventive and therapeutic strategies to mitigate the consequences of prenatal alcohol exposure.

NIAAA encourages research to advance foundational knowledge of the mechanisms mediating FASD—for example:

- Identifying and characterizing the biological mechanisms underlying the harmful effects of prenatal alcohol exposure across the life span, including health consequences that persist or emerge in adults with FASD
- Further defining periods of susceptibility to alcohol exposure (e.g., periconception, specific months or trimester, entire pregnancy, or time points during postnatal development)
- Elucidating the potential paternal contribution to the etiology of FASD
- Refining and advancing biomarkers of prenatal alcohol exposure
- Defining the long-term health impacts of prenatal alcohol exposure in later adulthood

## **Alcohol and HIV**

Alcohol is an important contributor to the HIV pandemic. In the United States, many people with HIV engage in alcohol misuse or have AUD. Alcohol can affect behaviors that increase the likelihood of

acquiring or transmitting HIV to others. Alcohol may also speed HIV progression in people living with the disease, influence their engagement and retention in HIV treatment, and increase their susceptibility to organ damage and coinfections. These effects may shift across the life span, particularly as people living with HIV enter midlife and older adulthood.

In coordination with the <u>NIH Office of AIDS Research</u> and the <u>NIH Strategic Plan for HIV and HIV-</u><u>Related Research</u>, NIAAA continues to advance basic, translational, and clinical research to improve health outcomes among people living with HIV, including women and underserved populations who experience health disparities. NIAAA will enhance collaboration with partners within and outside NIH to translate and disseminate research findings to maximize the public health impact of NIAAA-supported HIV research, and to strengthen the research and workforce capacity to sustain alcohol-HIV research.

## Objective 1: Understand the Biological and Behavioral Mechanisms of Alcohol Misuse and HIV

The mechanisms through which alcohol misuse interacts with HIV to increase morbidity and mortality are not well understood. While HIV can be treated effectively with antiretroviral medications, alcohol misuse contributes to or exacerbates adverse medication interactions, chronic inflammation, liver and other organ injury, cardiovascular and neurological problems, and other pathologies.

Several biological or behavioral phenotypes of HIV and alcohol have been identified that may have markedly different disease courses, biological underpinnings, and treatment responses. Collaborative, multidisciplinary research will be key to better understanding the interactions between alcohol misuse and HIV.

NIAAA encourages research to better understand the relationship between alcohol misuse and HIV to inform the development of effective interventions—for example:

- Determining how alcohol misuse confers a biological risk for HIV infection
- Determining how current and past alcohol misuse in the context of HIV infection and the use of antiretroviral medications affect HIV disease progression and the development of organ and tissue injury (e.g., gut, liver, lung, and brain)
- Improving the understanding of the biological, clinical, and socio-behavioral aspects of aging through the lens of HIV infection and alcohol misuse

## Objective 2: Prevent Alcohol Misuse and Treat Alcohol Use Disorder Among People Living With HIV or at High Risk of Acquiring HIV

As noted above, alcohol misuse contributes to poor health outcomes among people living with HIV and reduces the effectiveness of strategies designed to prevent new HIV infections. For example, the use of pre-exposure prophylaxis (PrEP) is highly effective in preventing HIV among those at high risk. However, alcohol misuse may reduce a person's likelihood of following PrEP medication regimens.

Alcohol misuse may also affect an individual's adherence to antiretroviral therapy and contribute to HIV transmission. Evidence-based approaches, such as brief interventions, contingency management, risk and harm reduction interventions, and stepped care approaches, have been demonstrated to prevent and reduce alcohol misuse among people living with HIV. Stepped care approaches that integrate treatment for alcohol misuse and HIV have also been shown to improve HIV-related outcomes. Strategies to identify and address alcohol misuse among people with HIV or at high risk for HIV can contribute to improved health and a reduced incidence of HIV.

NIAAA encourages alcohol-related research to prevent and reduce HIV infection, progression, and transmission—for example:

- Enhancing routine alcohol SBIRT to reduce HIV transmission and disease progression
- Developing strategies that address alcohol-related barriers to effective use of PrEP, especially
  among women and other populations with historically low usage rates
- Developing novel interventions and enhancing implementation of existing evidence-based prevention and treatment interventions that address both alcohol misuse and HIV
- Expanding access to and options for AUD treatment for people living with HIV

## **Objective 3: Address Alcohol-Related Comorbidities Among People Living With HIV**

Many comorbidities, coinfections, and medical complications are associated with chronic alcohol misuse and HIV disease progression. These factors combine with the natural processes of aging to increase frailty and present challenges for medical management. Addressing comorbid medical complications is critical for improving quality of life and longevity.

NIAAA encourages research to address alcohol-related comorbidity among individuals with HIV—for example:

- Promoting the integration of care for HIV, alcohol misuse or AUD, and co-occurring health conditions and medical complications in different settings
- Developing a comprehensive model for alcohol misuse or AUD and disease outcomes among older adults with HIV, including expanded biomarker assays
- Evaluating the efficacy and effectiveness of interventions for reducing alcohol misuse in improving co-occurring pain, stress, and other mental health concerns among people living with HIV

### **Research Goals**

This strategic plan includes four major goals, which cover the depth and breadth of research necessary to improve the understanding of and to address the effects of alcohol misuse on individuals and society. These goals complement the <u>Cross-Cutting Research Themes</u>, <u>Cross-Cutting Research Programs</u>, and <u>Supporting the Mission</u> sections of this strategic plan.

## Goal 1: Elucidate the Biological Mechanisms and Consequences of Alcohol Misuse

NIAAA aims to advance research on the effects of alcohol on the brain and other organs, organ systems, and tissues. This research includes an integrative approach to understand the brain cells and circuits that underlie and are altered by alcohol misuse, and the complex relationships between alcohol misuse and physiological effects throughout the body, ranging from liver disease to cancer.

Alcohol misuse has powerful effects on the brain and behavior. Neuroscience research has characterized the short-term impact of alcohol on brain activity and the adaptations in brain structure and function that occur as individuals progress from occasional, controlled alcohol use to alcohol misuse and <u>AUD</u>. This work has made major strides in shedding light on the neurotransmitter

#### **NIAAA's Long-Term Vision**

To comprehensively understand the biological processes affected by alcohol misuse to inform the prevention, diagnosis, and treatment of alcohol-related problems.

systems and neurobiological mechanisms that are altered by alcohol and that contribute to the development of alcohol misuse and AUD. Equally important, neuroscience advances are laying the foundation for understanding the individual differences that drive alcohol misuse across the life span. Innovative research to elucidate the biological mechanisms of alcohol-associated pathology and recovery within a neurobiological framework can reveal novel opportunities for more effective prevention, diagnosis, and treatment of alcohol misuse and AUD.

Alcohol misuse also has powerful effects beyond the brain and can damage nearly every organ system in the human body. While the liver is the primary site of alcohol metabolism and is susceptible to alcoholassociated injury and disease, alcohol misuse is a significant contributor to pancreatitis, cardiovascular disease, cancer, and other health conditions. Additionally, alcohol misuse can negatively impact the complex interactions between organ systems. For example, research demonstrates that alcohol-related neurobiological changes may not be due entirely to the direct actions of alcohol on the brain but may be mediated partially through interactions with the gastrointestinal tract, liver, and endocrine system. Basic, translational, and clinical research is needed to better characterize the mechanisms through which alcohol misuse damages the body's organ systems and leads to, and exacerbates, chronic disease.

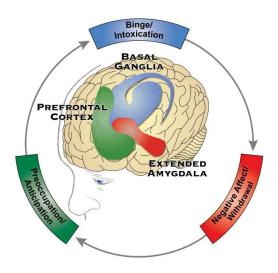
Additionally, understanding the biological mechanisms underlying the effects of prenatal alcohol exposure, from prenatal development to adulthood, and understanding other medical challenges, such as HIV/AIDS, can inform preventive, diagnostic, and therapeutic strategies to improve health outcomes. See the <u>Fetal Alcohol Spectrum Disorders</u> and <u>Alcohol and HIV</u> discussions within the <u>Cross-Cutting</u> <u>Research Programs</u> section for more information on these specific research areas.

Goal 1 research topics are integrally linked to the <u>Cross-Cutting Research Themes</u>. Examples of NIAAA research priorities in this area include the following objectives.

## **Objective 1: Explore the Neurobiological Mechanisms of Alcohol Misuse and Alcohol Use Disorder**

The addiction cycle is a validated heuristic framework for understanding the development, progression, and heterogeneity of AUD. The framework is based on dysregulation in three functional and neurocircuitry domains: incentive salience (reward drinking), negative emotional states (relief drinking), and executive function (loss of control).

Drinking to cope with stress has received renewed attention as a major driver of alcohol misuse and AUD, and has emphasized the role of negative emotionality (also known as hyperkatifeia) as a target for treatment. The COVID-19 pandemic further exacerbated the role of stress in alcohol misuse. NIAAA-supported research on the relationships between alcohol misuse and stress has



yielded new insights into the neurotransmitter and neurocircuit dynamics that underlie excessive alcohol use and relapse, as well as the negative emotional states and executive function deficits associated with the addiction cycle. These studies have also shed light on the role of neuroinflammation and sex differences in mediating AUD and stress-related behaviors, as well as the bidirectional relationship between alcohol misuse and other co-occurring behavioral health disorders.

Life stage is a key factor that influences how alcohol impacts brain function. For example, research has demonstrated that alcohol misuse can impact the delicate balance of brain development that occurs during adolescence and continues into a person's mid-20s. Additionally, with the rapid increase of the older adult population, the impact of alcohol misuse on the aging brain has come into the spotlight. Not only is the prevalence of alcohol misuse and AUD increasing among older adults, but alcohol misuse has been associated with a faster cognitive decline and other aging-related effects. Research to better understand the neurobiological links between alcohol and age-



related effects on brain health could reveal novel targets for prevention and treatment.

NIAAA encourages innovative research and integrated approaches to build on existing knowledge of the biological mechanisms that mediate alcohol misuse across the life span and at all levels of the addiction cycle. Some specific examples of high-priority research gaps include:

• Identifying molecular, cellular, and functional brain connectivity that underlies the development of, maintenance of, return to, and recovery from alcohol misuse and AUD, using animal models, human

imaging studies, and multilevel translational approaches—such multilevel analyses may include modern neurobiological techniques from single-cell physiology to computational neuroscience and AI approaches across species

- Characterizing the dynamic interactions of extraneuronal contributors to alcohol misuse and AUD, including the extracellular matrix, neuroimmune cells, perineuronal cells, and peripheral neuromodulatory targets
- Identifying the roles of interoceptive cues, including autonomic, neuroimmune, and gut microbiome cues, in alcohol misuse and AUD
- Understanding how social determinants of health (e.g., childhood trauma, psychiatric comorbidity, social isolation, socioeconomic challenges, and health care availability) interact with neurobiological mechanisms to mediate alcohol misuse and AUD
- Elucidating the neurobiological mechanisms that mediate the interactions between alcohol misuse and cognitive decline, including cognitive decline related to Alzheimer's disease and other dementias, in the context of aging
- Examining the mechanisms by which sex differences influence individual differences in the brain's response to alcohol as individuals progress from alcohol use to misuse to AUD
- Exploring neuroadaptations as well as other biological measures and/or -omic signatures in combination with data science approaches to develop diagnostic biomarkers for the prevention, diagnosis, and treatment of alcohol misuse and AUD

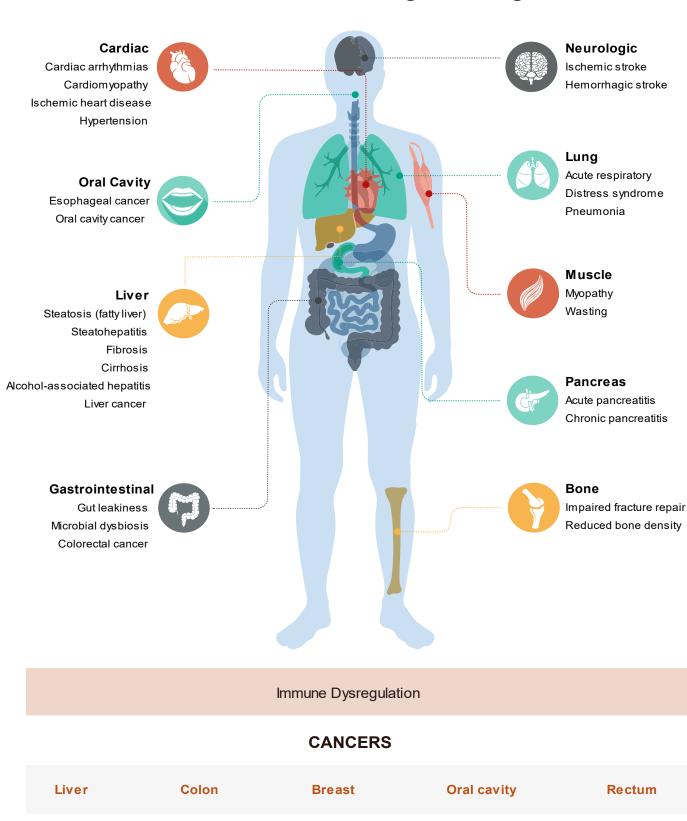
## **Objective 2: Elucidate the Underlying Mechanisms of Alcohol-Induced Tissue and Organ Damage**

Alcohol misuse has devastating effects on organs, systemic health, and life expectancy. <u>Alcohol affects</u> <u>many organs and tissues in the body</u>. Alcohol misuse is associated with increased liver disease, pancreatitis, cardiomyopathy, lung pathologies, skeletal muscle myopathy, diminished bone strength and impaired recovery from trauma, infectious diseases, and several types of cancers (including head and neck, esophageal, liver, breast, and colorectal cancers). Alcohol consumption also disrupts body-wide systems, specifically the immune system, the endocrine system, and the lymphatic system.

Research suggests alcohol damage occurs through both shared and tissue- and organ-specific mechanisms. For example, alcohol-related dysfunction of the immune system and associated inflammation contributes to some, but not all, mechanisms of alcohol-associated organ damage. Understanding features of alcohol damage that are unique to specific tissues or organs will inform focused prevention and treatment approaches. Identifying specific risk and protective factors could also reveal individual differences in targets for prevention and treatment.

NIAAA encourages research to further characterize the biological factors that contribute to alcoholassociated damage to the body's tissues, organs, and organ systems, with an emphasis on research that will identify targets for development of effective therapies to prevent and treat these devastating conditions. Currently, there are no U.S. Food and Drug Administration (FDA)-approved medications for the treatment of alcohol-associated damage to any organ. Examples of NIAAA research priorities in this area include:

- Investigating mechanisms mediating the susceptibility and development of the following clinically significant alcohol-associated conditions with the goal of better prevention and treatment of alcoholassociated conditions: liver disease, pancreatitis, cardiomyopathy, lung disease, skeletal muscle myopathy, disrupted bone homeostasis, infectious diseases, and cancers
- Exploring tissue-specific molecular, cellular, and systemic responses to alcohol misuse and AUD on metabolism, inflammation, tissue repair, regeneration, and homeostasis and their contribution to alcohol-related tissue and organ damage across ages and biological sex
- Characterizing the effects of alcohol's disruption of components of the immune system on the body's defense against infection and related comorbidities
- Exploring alcohol's effects on organ-organ interactions, such as interactions among gut-liver-brain, gut-brain axis, gut-lung, and other organ interactions that are still unexplored but clinically relevant



#### **Alcohol-Associated Organ Damage**

## **Objective 3: Enhance Translation of Basic Research Findings to Clinical Practice**

A mechanistic understanding of the conditions that give rise to alcohol misuse and AUD requires work in model systems where invasive techniques can be used. Major goals are to translate physiological findings derived from preclinical studies into clinical applications for AUD as well as to back translate human findings to validate preclinical models for further research.

Barriers to translation and back translation include different data collection methods, different temporal scales, species-specific approaches to behavioral regulation, and lack of biological homology across species. Predictions derived from computational modeling approaches can be examined through conventional laboratory approaches and provide the basis for developing and testing novel treatment strategies. Identifying similar computations employed across species provides a basis for predictive models that capture pathologies that underlie alcohol misuse and AUD.

NIAAA also supports the development and application of complementary methods, models, and technologies, along with the integration and translation of data across multiple species and levels of analyses, to understand the causes and improve the treatment of AUD and other alcohol-related health conditions. The effects of alcohol on tissue can be investigated with defined cellular systems of stem cells, induced pluripotent cells, and organoids.

Examples of research that NIAAA encourages to advance translation include:

- Developing high-throughput screening models to identify compounds having potential to treat alcohol misuse, AUD, and alcohol-related organ damage
- Expanding the validation of candidate biomarkers in the discovery phase to improve prevention, diagnosis, and treatment of alcohol-associated conditions
- Identifying phenotype-specific multi-omic profiles of AUD in the context of alcohol-associated organ damage that include genomics, proteomics, transcriptomics, metabolomics, and epigenomics to inform cross-organ analyses in understanding alcohol misuse and AUD
- Conducting back translation studies on mechanisms using molecular genetic approaches, such as gene editing and stem cell studies, to understand mechanisms for alcohol misuse or organ injury based on human data for alcohol research
- Expanding computational modeling approaches to provide a basis for predictive models that capture pathologies that underlie alcohol misuse and AUD

## Goal 2: Identify Patterns, Trends, and Public Health Impact of Alcohol Misuse

NIAAA will continue to support epidemiological research to identify and track patterns of alcohol use and misuse, drinking-related outcomes and disparities, and individual and environmental variables that confer risk or resilience.

Epidemiological research is key to addressing the public health impact of alcohol misuse. Identifying and

tracking patterns and trends in alcohol use and related harms convey the scale and burden of alcohol misuse in the nation. Although significant changes in patterns of drinking behavior and consequences have occurred over time, it is important to acknowledge that population-level averages may not reflect the public health impact of alcohol misuse among various sociodemographic groups. As in the <u>Advancing Diversity, Equity, Inclusion, and</u>

#### **NIAAA's Long-Term Vision**

To gain a complete understanding of the patterns and trends of the burden and likelihood of alcohol misuse to inform the diagnosis, prevention, and treatment of alcohol-related problems.

<u>Accessibility in the Alcohol Research Enterprise</u> discussion in the <u>Cross-Cutting Research Themes</u> section of this strategic plan, it is important for epidemiology research to focus on alcohol misuse and related consequences among minority populations as well as the general population.

Epidemiological research also plays a critical role in identifying factors that influence the initiation of alcohol use and the progression to alcohol misuse, including <u>heavy drinking</u> and AUD. Knowledge of risk factors associated with alcohol misuse can inform prevention and intervention efforts. Similarly, epidemiological studies can reveal factors that protect against alcohol misuse and consequences. This information can be used to develop prevention strategies that focus on health promotion.

Goal 2 research topics are integrally linked to the <u>Cross-Cutting Research Themes</u>. Examples of NIAAA research priorities in this area include the following objectives.

### **Objective 1: Identify and Track Trends in Alcohol Misuse and Related Consequences**

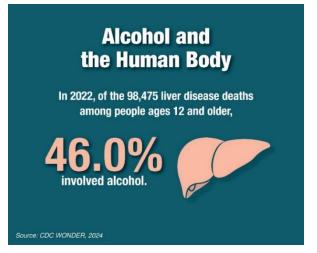
Collection and analysis of national data on alcohol use are essential for surveilling the patterns and impact of alcohol misuse on public health. For example, recent data have revealed some successes, such as declining alcohol use among youth. These studies also indicate, however, that the recent decrease has been slower among females compared to males. Among adults, however, alcohol use is increasing, with larger increases found among women, Black men, and older adults. A growing number of studies have also revealed higher levels of alcohol misuse and harms among adolescents and adults in sexual and gender minority populations.

Each year, approximately 5 million people visit emergency departments for alcohol-related reasons, from injuries to diseases.<sup>8</sup> The rate of alcohol-related deaths in the United States more than doubled between 1999 and 2021. Additional epidemiological reports also indicate that <u>ALD</u>s, such as cirrhosis, are increasing, particularly among women and young adults, and alcohol now accounts for almost half of

liver disease deaths in the United States.<sup>4</sup> Research tracking the patterns and correlates of alcohol involvement in morbidity and mortality can inform decisions about where to direct prevention and treatment efforts.

NIAAA encourages research to understand the scope and scale of alcohol misuse—for example:

 Identifying patterns, trends, and disparities in alcohol misuse, AUD, alcohol-related consequences, as well as treatment access and utilization across demographic groups, including but not limited to age,



race, ethnicity, sex, gender identity, geographic location, socioeconomic status, and career

- Characterizing patterns and trends in co-use of alcohol, cannabis, opioids, and other substances and their contributions to adverse health and social outcomes
- Identifying and characterizing secondhand effects of alcohol misuse (e.g., interpersonal violence, assault, homicide, child maltreatment, and motor vehicle crashes)
- Improving assay methodologies for validated biomarkers of alcohol consumption considering cost, timeliness, and accessibility in clinical settings
- Applying innovative data measurement technologies and approaches for more accurate and/or realtime assessment of alcohol use, related behaviors, and associated changes over time (e.g., ecological momentary assessment, biomarkers, and biosensors)
- Utilizing cutting-edge data collection and analytic approaches, such as AI, social network analyses, and data analytics to study and predict patterns and trends in alcohol misuse to facilitate timely intervention
- Examining the long-term health and societal effects of the increase in alcohol misuse and alcoholrelated consequences due to the COVID-19 pandemic, particularly due to coping with stress

## Objective 2: Explore How Social Determinants of Health Convey Risk for and Resilience to Alcohol Misuse and Associated Outcomes

Structural and social determinants of health, or environmental factors that are associated with general health outcomes, are related to the risk for and resilience to alcohol misuse and related harms in both adolescents and adults. Social determinants include social environment (e.g., discrimination, racism, social isolation, growing up in a home with parental AUD), physical environment (e.g., alcohol outlet density, exposure to violence), health care services (e.g., access to and quality of care), economic stability (e.g., job security, income), and education access and quality (e.g., educational opportunities and support).

Social determinants of health can contribute to accumulating stress. In turn, stress leads some individuals to drink alcohol to cope and results in chronic disease and other adverse outcomes. Exposure to stressors (e.g., job loss) is a key contributor to a return to drinking and plays a role in "deaths of despair," such as alcohol-involved suicides, drug overdoses, and liver disease deaths linked to underemployment and hopelessness.<sup>9</sup> Moreover, adverse childhood experiences (e.g., racial discrimination, parental AUD, and exposure to violence in homes and neighborhoods) are associated with an earlier onset of alcohol use, more frequent binge drinking during adolescence, consuming more drinks per binge occasion during adulthood, and poorer physical and emotional well-being in general.



Source: Healthy People 2030, U.S. Department of Health and Human Services, Office of Disease Prevention and Health Promotion. Retrieved March 12, 2024, from https://health.gov/healthypeople/objectives-and-data/socialdeterminants-health

In contrast, protective factors against the initiation and escalation of alcohol misuse have also been identified. Supportive relationships with parents/caregivers and other adults, for example, are associated with a lower likelihood of adolescent drinking and related harms.

Advancing research on social determinants provides important opportunities to address health disparities and improve overall public health. Such studies can shed light on the underlying factors that contribute to interactions of alcohol misuse with health disparities as well as targets for intervention.

NIAAA encourages research to better understand how social determinants of health contribute to alcohol-related risk and resilience—for example:

- Elucidating the ways in which social determinants of health—such as discrimination, trauma, workplace stress, homelessness, and adverse childhood experiences—influence the risk for alcohol misuse, AUD, and associated harms
- Understanding the effects of economic fluctuations on alcohol misuse and related outcomes
- Characterizing the influence of the family environment, such as parental/caregiver AUD and recovery, on alcohol-related behaviors and consequences among youth
- Exploring the influence of a person's social context, such as social media exposure, social network interactions, and peer networks, on alcohol misuse and associated outcomes, such as recovery from AUD
- Elucidating how social determinants of health interact with biological pathways to contribute to health disparities and adverse health outcomes
- Exploring how social determinants of health confer protection against alcohol misuse and identify ways to strengthen their influence

 Examining the impact of helping young people cope with stress, anxiety, and depression on alcoholrelated attitudes and behaviors

## Goal 3: Prevent and Reduce Alcohol Misuse, Alcohol Use Disorder, and Associated Consequences

NIAAA encourages the development, evaluation, and implementation of culturally appropriate individual, family, school, community, and policy-based strategies to prevent alcohol misuse, alcohol use disorder, and related consequences.

Evidence-based strategies to prevent and reduce alcohol misuse and the associated consequences are critical for lessening the resulting individual, social, and public health impact. Research is revealing opportunities for developing novel prevention interventions and improving the effectiveness of existing ones.

#### **NIAAA's Long-Term Vision**

Develop and implement effective and targeted prevention strategies to prevent all alcohol-related problems.

Alcohol use commonly begins during adolescence, and the earlier a person starts to drink the more likely they are to escalate to alcohol misuse, develop <u>AUD</u>, harm themselves and others while intoxicated, and misuse other substances. As such, prevention strategies that seek to delay and prevent alcohol use among adolescents are a major focus of the NIAAA research portfolio.

Similarly, integration of prevention across a variety of health, community, justice, and social service settings can increase the reach among underserved populations. These interventions typically occur at the individual, family, school, community, and policy levels, and focus on preventing or delaying the initiation of alcohol use or preventing escalation to more serious problems.

Additionally, promoting awareness of <u>FASD</u>, adopting culturally informed prevention strategies, and evaluating policies that also reduce stigma around seeking treatment can support efforts to prevent alcohol use and reduce consequences among individuals who are or may become pregnant. The <u>Cross-Cutting Research Program</u> on FASD explores this research area.

Goal 3 research topics are integrally linked to the <u>Cross-Cutting Research Themes</u>. Examples of NIAAA research priorities in this area include the following objectives.

## **Objective 1: Increase Utilization of Alcohol Screening** and Brief Intervention in Different Settings

The U.S. Preventive Services Task Force recommends alcohol screening and brief intervention (SBI) in primary care settings for adults ages 18 and older. A data analysis from the National Survey on Drug Use and Health showed that although alcohol screening often occurs among people with AUD who have utilized health care in the last year, there is still insufficient use of brief intervention or referral to alcohol treatment. Research also indicates that not all groups of people are equally likely to be screened or receive advice about risks associated with drinking, a practice that may contribute to health disparities.

Barriers to SBI are significant but surmountable. The barriers include lack of health care provider time to ask questions and respond to harmful drinking behaviors, need for health care provider training for efficient and effective alcohol SBI, lack of treatment resources for referral (especially among adolescent and minority populations), and impediments to reimbursement of alcohol SBI and referral to treatment.

For both adolescents and adults, there are relationships between patterns of alcohol use and other risk factors for health. Evidence-based screening tools can uncover these risks. For instance, among adolescents, certain drinking behaviors are related to the likelihood of having depression and misusing opioid pain medications. Thus, in addition to identifying alcohol misuse, alcohol SBI can also help health care providers uncover other issues that impact health and well-being. Studies have also suggested that training health care providers to conduct SBI reduces stigma toward patients with AUD.

NIAAA encourages research to promote improvements in alcohol SBI, including increased utilization and a better understanding of outcomes—for example:

- Collecting additional evidence of the effectiveness of SBI for alcohol misuse among adolescents and older adults
- Assessing the effectiveness of SBI for prevention of alcohol and co-occurring cannabis and other drug use, liver disease, atrial fibrillation, and other conditions caused or exacerbated by alcohol misuse
- Continuing to investigate digital technologies for SBI, evaluate their effectiveness, and assess their impact on uptake of alcohol SBI in various settings
- Identifying barriers and effective strategies for increasing real-world adoption (scaling up) of alcohol SBI and evidence-based preventive interventions among all populations
- Measuring the long-term health care cost savings based on the utilization of SBI in the prevention or exacerbation of alcohol-related conditions

### Objective 2: Develop and Improve Targeted Interventions to Prevent and Reduce Alcohol Misuse Across the Life Course and in Different Settings

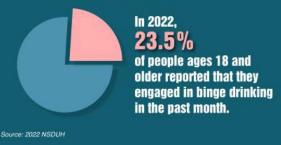
Patterns of alcohol use and misuse vary over the life course. Typically, alcohol use is initiated in adolescence, peaks in young adulthood, and then gradually declines over the course of adulthood. Binge drinking (for a typical adult, this corresponds to consuming five or more drinks for men and four or more drinks for women in about two hours) and high-intensity drinking (defined as alcohol intake at levels twice or more the gender-specific threshold for binge drinking) often begins or escalates in late adolescence or early adulthood.

The earlier in life a person begins to use and misuse alcohol, the greater the likelihood they will go on to develop significant problems with alcohol. Furthermore, early alcohol use has the potential to negatively impact brain development and increases the likelihood of cognitive impairments and AUD. For these reasons, adolescents and young adults remain a central focus of prevention research.

Social and environmental factors contribute to decisions about alcohol use throughout life and offer opportunities for prevention. As young people progress through adolescence and into adulthood, there is considerable variation in life experiences that can increase or decrease the likelihood of alcohol misuse. Examples are related to factors such as home and school environment, social experiences (online and in person), and opportunities and choices related to education and career.

Each of these factors provides opportunities for prevention efforts tailored to connect in meaningful ways with young people who have diverse experiences, beliefs, and access to resources.

#### Binge Drinking in the United States



Examples of research in this area that NIAAA encourages include:

- Creating and tailoring interventions for alcohol misuse for life stage and environment
- Improving prevention and early intervention through the use of validated biosensors and biomarkers, including risk predictions of alcohol-associated disease development and progression using biomarker signatures
- Developing or modifying underage drinking prevention strategies to integrate prevention of combined use of other substances
- Evaluating strategies to prevent and reduce high-intensity drinking
- Evaluating the impact of social media on alcohol use and associated behaviors as well as the use of social media and other digital technologies in the development of "in-the-moment" and other innovative prevention interventions
- Using social media to counter misinformation about alcohol and provide evidence-based information for prevention
- Developing prevention models to reduce family and cross-generational effects of alcohol misuse, such as violence, child maltreatment, and other harms
- Designing and evaluating interventions to mitigate the effects of trauma and childhood adversity on alcohol misuse and alcohol-related conditions, such as AUD
- Evaluating the impact of general health promotion strategies (whole person health, including effective stress management and coping strategies) on alcohol misuse and AUD
- Creating culturally informed interventions to reduce adverse alcohol-related outcomes among different populations

• Creating interventions for people in specific work environments who are at higher risk for alcohol misuse due to work-related stress and trauma, such as first responders and health care providers

## **Objective 3: Determine the Impacts of Policies on Alcohol Misuse, Health Effects, and Acute Harms**

Alcohol-related policies represent a population-level strategy that can affect all individuals within a jurisdiction (e.g., federal, state, local, or institutional). A well-known example of an impactful alcohol policy is the 1984 U.S. National Minimum Drinking Age Act, which led to the adoption of 21 as the legal age to purchase or publicly possess alcohol in all states in the United States. The change in drinking age was associated with reductions in underage alcohol use and related traffic fatalities among young people. Policy research has revealed several other effective environmental-level interventions that reduce alcohol-related harms (see box).

NIAAA encourages ongoing and new efforts to determine the impact of policies on alcohol misuse and harms, such as:

 Examining effects of alcohol policies on alcoholrelated morbidity, mortality, and risk behaviors, including but not limited to intentional and unintentional injuries, child and maternal health outcomes, and chronic conditions

## Environmental-level interventions include:

- Administrative license suspension
- 0.08% blood alcohol concentration law, with zero tolerance for youth
- "Use and lose" laws to suspend or revoke driver licenses for alcohol violations
- Restriction of adult provision of alcohol to underage individuals
- Mandatory assessment for drivers with alcohol-related traffic citations
- Dram shop and social host laws
- Increased alcohol taxes
- Reduced alcohol outlet density
- Responsible beverage service laws
- Laws restricting hours and days of alcohol sales
- Determining the differential effects of alcohol policies, including across population subgroups
- Characterizing the effects of cannabis legalization on alcohol misuse, co-use with other substances, and related risk behaviors
- Evaluating the impact of new policies related to alcohol on alcohol-related behaviors or outcomes these include additional labeling of alcohol containing products and other policies adopted during the COVID-19 pandemic
- Evaluating the effects of social media marketing on underage drinking and related consequences, such as motor vehicle crashes, intentional and unintentional injuries, and other alcohol-related consequences (e.g., poor academic and work performance among youth)

## Goal 4: Improve Diagnosis and Expand Treatment of Alcohol Use Disorder and Alcohol-Related Conditions

To advance the treatment of alcohol-related conditions, NIAAA encourages research to refine diagnosis, enhance treatment, sustain recovery, and ultimately, to reduce the treatment gap.

Alcohol-related health conditions are currently underdiagnosed and undertreated. Less than 10% of people with <u>AUD</u> receive any help despite the availability of evidence-based pharmacological and behavioral treatments.<sup>7</sup> In addition, there are no FDA-

#### **NIAAA's Long-Term Vision**

To develop effective treatments that are accessible to every person with an alcohol-related health problem.

approved medications for <u>ALD</u>, and evidence-based treatment strategies are also needed for other alcohol-associated conditions, such as <u>FASD</u>. Developing, optimizing, and implementing evidence-based treatment strategies for AUD and alcohol-related conditions remain high priorities for NIAAA. Likewise, research to improve the early identification and diagnosis of alcohol-related health issues to enhance treatment effectiveness are also important NIAAA priorities.

As described under the Cross-Cutting Theme on <u>Integrating care for alcohol-related problems</u>, AUD commonly co-occurs with other health conditions, including organ and tissue damage and mental health conditions. Integrating treatment for AUD with treatment of <u>co-occurring conditions</u> related directly or indirectly to alcohol use is an important step toward improving alcohol-related outcomes and overall health.

Moreover, improved diagnostic techniques for FASD would enable more accurate diagnosis and earlier intervention, offering a better chance for improved outcomes. The <u>Cross-Cutting Research Program on</u> <u>Fetal Alcohol Spectrum Disorders</u> explores this research area.

Goal 4 research topics are integrally linked to the <u>Cross-Cutting Research Themes</u>. Examples of NIAAA research priorities in this area include the following objectives.

## Objective 1: Enhance Treatment Options for Alcohol Use Disorder and Related Conditions

Currently, there are three medications for AUD approved by the FDA, and they are effective and important treatment aids. Still, given the multiple biological processes that contribute to AUD, new medications are needed to provide a broader spectrum of treatment options.

Pharmacotherapy, especially when combined with behavioral interventions, is an effective, evidencebased component of AUD treatment. NIAAA encourages research to develop a larger number of pharmaceutical treatments for AUD, because people deserve to choose from a range of evidence-based treatment options that can be tailored to their individual needs. In addition, improving the precision of diagnosis could improve patient outcomes. Because AUD is a complex, highly heterogeneous condition, some individuals may, for example, respond best to a medication that helps with craving and relieves impulsivity, whereas others may respond best to a medication that reverses the negative emotional state of withdrawal or protracted withdrawal symptoms.

ALD, a spectrum of liver diseases caused by <u>alcohol misuse</u>, is the most common alcohol-related cause of death. There are no FDA-approved medications for ALD, and current standard medical treatment, such as steroids, may have significant side effects. Through the NIAAA-supported <u>Alcohol-associated</u> <u>Hepatitis Network</u>, researchers can use and contribute to ALD research and gain insights into the causes and treatments of ALD and integrated treatment of ALD and AUD. Development of drugs that act on multiple molecular targets to reverse and prevent progression of liver damage and to reduce alcohol intake can open new opportunities. Research may identify similar strategies for other alcohol-associated organ damage.

AUD also frequently co-occurs with sleep, pain, and mental health disorders, such as anxiety disorders. Medications to address these co-occurring conditions, in coordination with AUD, could vastly improve health outcomes.

Developing effective pharmacotherapies to address AUD, ALD, and other co-occurring conditions and increasing their uptake continue to be major priorities for NIAAA. NIAAA encourages research to support these priorities, for example:

- Harnessing computational and data science approaches to identify and evaluate biological, cognitive, and behavioral markers, endophenotypes, and clinical characteristics that can be used to predict an individual's response to specific treatments or treatment combinations
- Developing biomarker and biomarker signatures to serve as surrogate endpoints for intervention clinical trials and to improve clinical management of alcohol-associated health conditions
- Validating alternative outcome measures for alcohol pharmacotherapy trials that will be accepted by the FDA for phase II and III trials (i.e., a two-level reduction in the World Health Organization drinking risk levels)
- Developing new or repurposing existing medications to treat AUD, ALD, and other alcohol-associated organ dysfunction such as alcohol-associated pancreatitis and acute respiratory distress syndrome
- Using pharmacoepidemiological approaches to identify potential medication targets to either co-opt existing medications for use in alcohol-related conditions or facilitating the development of new medications, if necessary
- Leveraging high-throughput multi-omics, AI, machine learning, and other statistical approaches to identify molecular signatures and other potential targets linked to pharmacotherapy for AUD
- Developing high-throughput screening platforms for discovery of medications to treat AUD
- Exploring new human laboratory paradigms that will help predict efficacy in clinical trials for AUD/ALD medications development

- Assessing the impact of concurrent use of medications for AUD and other co-occurring disorders on, for example, drug interactions and altered drug pharmacokinetics
- Exploring strategies to design innovative clinical trials to study one or more specific phenotypetargeted therapies in the context of co-occurring disorders in AUD patients

## Objective 2: Improve and Expand Behavioral Health Strategies for Alcohol Use Disorder

NIAAA-supported research has generated an extensive evidence base supporting the effectiveness of AUD behavioral health strategies that are commonly used today. This evidence has also informed the treatment of other substance use disorders. However, at present, little is known about the effectiveness, uptake, and implementation of evidence-based behavioral health strategies for AUD.

Incorporating new scientific discoveries and digital technologies can improve AUD behavioral health strategies, contributing to more widespread use in clinical practice and greater acceptability and accessibility for all patients. An increased focus on whole person health and culturally informed treatment approaches provides opportunities to enhance health and increase the reach of evidence-based therapies. Translating research on the mechanisms and processes through which evidence-based behavioral treatments work for individuals can inform the refinement of current therapies to be more effective as well as inform the development of new behavioral treatments.

NIAAA encourages research to improve and expand behavioral health strategies for AUD—for example:

- Disseminating and implementing evidence-based behavioral health strategies in real-world treatment and clinical practice settings
- Utilizing technologies (e.g., mobile devices, computers, and web-based applications) to enhance the dissemination of evidence-based behavioral treatments
- Considering social determinants of health in AUD treatment, including how the incorporation of empathy and religious or spiritual assessments influences clinical care in alcohol treatment outcomes
- Conducting pragmatic and/or hybrid effectiveness clinical trials that evaluate evidence-based behavioral health treatments in various real-world settings

## **Objective 3: Advance Research on Recovery From Alcohol Use Disorder**

NIAAA is dedicated to supporting research that explores the complex, individualized nature of <u>recovery</u> <u>from AUD</u>. Just as there are varying manifestations of AUD, there is no single path to recovery. Whereas some people with AUD recover quickly and with minimal intervention, others need longer or more intense treatments and support. Research to identify and characterize the risk, resilience, and other factors that contribute to long-term recovery, including factors that allow some people to recover without formal treatment, can inform interventions to reduce the risk of a return to drinking and facilitate sustained recovery.

To bring clarity to the concept of recovery and to improve consistency across recovery research, NIAAA has developed an operational definition of recovery from AUD. The definition involves remission from AUD and cessation from <u>heavy drinking</u>, which are associated with improvements in dimensions of wellbeing, quality of life, and biopsychosocial functioning. NIAAA will continue to support research that evaluates the efficacy and effectiveness of treatment strategies that impact long-term recovery, particularly using components outlined in NIAAA's recovery definition. The generation and analysis of large treatment and recovery data sets that track long-term recovery, with follow-up timepoints after treatment, will be crucial in advancing recovery research.

Continuing care models and other comprehensive recovery support systems hold promise for sustaining longer-term recovery. These systems often include community-based services and supports that aim to improve the overall well-being of individuals and build upon critical strengths and resources of individuals, families, and communities.

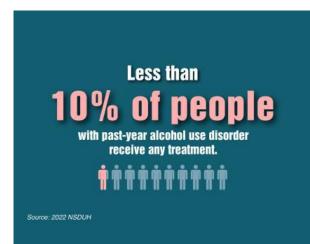
NIAAA encourages research to enhance knowledge about recovery from AUD and to inform the development and implementation of effective strategies to support sustained recovery—for example:

- Identifying the role of different components of short- and long-term recovery programs (e.g., behavioral treatments, medications, inpatient or outpatient treatment, long-term follow-up) using NIAAA's definition of recovery
- Identifying the potential moderating factors in the trajectories of recovery among sub-populations, such as individuals of all races, ethnicities, sexual orientations, gender identities, ages, languages, abilities, socioeconomic statuses, and geographic regions, and individuals with co-occurring health conditions
- Defining and assessing dimensions of functioning, quality of life, and well-being that are integral to sustained recovery, as well as identifying reliable and valid measures of these constructs that can be feasibly adopted in clinical practice
- Exploring the neurobiological, medical, psychological, behavioral (e.g., self-regulation), environmental, social, spiritual, and other quality-of-life mechanisms that influence and enhance recovery
- Evaluating the efficacy and effectiveness of continuing care models and recovery-oriented systems of care in the treatment of and recovery from AUD
- Leveraging digital health technologies to facilitate recovery and monitor long-term changes in outcomes
- Investigating the role of understudied mutual support groups and of spirituality and religion in recovery from AUD
- Investigating the value of AI approaches to developing algorithms for recovery

• Exploring how an individual's engagement in the community (e.g., religious, civic, and occupational activities) supports recovery from alcohol and other substances, and how and when health care practitioners should support community engagement among individuals in recovery

## **Objective 4: Reduce Barriers to Effective Treatment**

Bridging the gap between individuals who need alcohol treatment and individuals who seek and receive treatment represents a persistent public health challenge. Although evidence-based alcohol treatments exist, there are barriers to effective treatment. These barriers include stigma, reduced access to care, fear of punishment or criminalization, lack of health care coverage/payment options, employment, lack of child care, and lack of awareness of a need for care or of the availability of evidence-based care options, along with the misconception that treatment does not work. Populations such as individuals who are in the criminal justice system, are incarcerated, are unhoused, or have



disabilities, face unique and intersecting barriers to treatment. Furthermore, evidence-based treatments are often not disseminated or implemented in real-world settings.

Health care providers are in a prime position to prevent and address alcohol-related health problems, yet many are unfamiliar with the full range of available evidence-based alcohol prevention strategies, diagnostic tools, or treatment interventions or may be uncomfortable using them because of stigma or lack of training. In addition, as alcohol misuse contributes to and exacerbates other mental and physical health issues, addressing alcohol in the context of routine health care provides the opportunity to reach more individuals, prevent alcohol-specific and alcohol-related health problems before they develop, and identify, diagnose, and address alcohol problems before they become severe.

NIAAA supports efforts to improve care for alcohol-related health issues in a broad range of settings and for use by the full range of professionals involved in treatment. For example, NIAAA developed the <u>Healthcare Professional's Core Resource on Alcohol (HPCR)</u> to provide the basics of what every health care professional needs to know about alcohol, including the many ways that alcohol can impact a patient's health, and strategies for prevention and treatment. In the future, NIAAA aims to increase the dissemination of the HPCR to medical and other health care professional schools, health plans, and a broad range of health care professionals in practice.

NIAAA encourages research and other activities to increase the integration of evidence-based interventions for alcohol-related problems in a broad range of health care settings and that improve access to alcohol-related health care services for all—for example:

 Evaluating strategies at various levels (e.g., individual, societal) to increase education about the need for alcohol care and to reduce the stigma of alcohol-associated health problems, with the ultimate goal of encouraging appropriate, evidence-based care

- Enhancing the dissemination, implementation, adoption, adaptation, and sustainment of evidencebased alcohol screening and treatment strategies and longer-term support in real-world treatment settings, including nontraditional settings (e.g., faith-based organizations, shelters for the unstably housed and victims of domestic violence, and agencies for child and family services)
- Identifying and reducing barriers that keep underserved and other populations from seeking and receiving appropriate alcohol-related health care, including challenges with access and affordability
- Understanding the cost and cost-effectiveness of treatment interventions and exploring ways to make treatment more affordable
- Exploring health care models that promote collaboration between primary care and specialty care providers to improve implementation of evidence-based approaches and provide ongoing follow-up services
- Exploring and promoting mechanisms to integrate diagnosis and management of AUD with cooccurring mental health disorders and other health conditions
- Expanding affordable and accessible screening, diagnosis, and treatment options in populations, especially among people at risk for alcohol misuse and AUD such as individuals in the criminal justice system, in the child and family services system, in college, and in certain high stress workplaces

## **Supporting the Mission**

While funding innovative research is essential to achieving the NIAAA mission, NIAAA recognizes the importance of building a robust research capacity and serving as a responsible steward of public resources. This section is integral to the success of the <u>Research Goals</u>, <u>Cross-Cutting Research</u> <u>Themes</u>, and <u>Cross-Cutting Research Programs</u> sections of this strategic plan.

## **Goal 1: Building a Robust Research Capacity**

NIAAA's ability to pursue its research priorities is supported by the commitment to building and sustaining a robust research capacity. At the core of NIAAA's efforts to build research capacity are cultivating a talented and diverse scientific and administrative workforce to advance research to the next frontier and maximizing NIAAA research resources and infrastructure to promote discovery.

## Objective 1: Enhancing and Sustaining the Alcohol Research Workforce

The workforce of the alcohol research enterprise is its greatest asset and the key to its success. Cultivating and sustaining a robust, highly skilled, and diverse scientific and administrative workforce is a major NIAAA priority. A thriving workforce enables NIAAA and the alcohol research enterprise to effectively adapt to change, tackle complex challenges, and make use of emergent opportunities in a rapidly evolving research landscape. Additionally, supporting a diverse workforce that includes historically underrepresented populations enables the research to be informed by a wide range of perspectives and to capitalize on the full range of talent in the nation. Research suggests that diversity promotes creativity and fosters scientific innovation.

Sustained scientific progress requires investment in the next generation of researchers. NIAAA will continue to prioritize <u>research training and career development programs</u> that foster a talented biomedical workforce for today and for the future. To strengthen its training programs, NIAAA will focus on:

- Expanding outreach about NIAAA and NIH research training programs and opportunities to diverse communities and early-stage investigators
- Collaborating with NIH partners on training funding opportunities that advance the alcohol research workforce
- Developing and implementing best practices for NIAAA's research training programs
- Identifying strategies to assess training outcomes

NIAAA's <u>intramural research training program</u> will also continue to provide robust training opportunities to emerging scientists from all backgrounds.

Internally, NIAAA will continue to maintain a strong leadership team, enhance efforts to effectively leverage the strengths of NIAAA staff, provide training and career development opportunities to develop their skills and talents, and cultivate a positive and collaborative environment that embraces change and upholds the principles of diversity, equity, inclusion, and accessibility.

## Objective 2: Supporting Research Resources and Infrastructure

The scientific workforce's ability to advance biomedical and behavioral research depends on access to state-of-the-art resources and infrastructure that maximize their research potential.

NIAAA supports <u>Alcohol Research Centers</u> across the United States that serve as regional or national research resources and as incubators for collaborative studies that contribute to the development of new research methods, technologies, and approaches that sustain innovative goal-directed research. These centers have historically served as seeds for the development of researchers in the alcohol research field in diverse geographical regions that have limited ongoing alcohol research. NIAAA also supports research consortia, which conduct collaborative, interdisciplinary research among widely distributed research institutions. NIAAA-supported research centers and consortia serve as models for optimizing research resources and infrastructure, and as resources for data, biospecimens, tools, expertise, and training in the alcohol research field more broadly. NIAAA's <u>Alcohol Research Resource (R24 and R28)</u> <u>Awards</u> program supports investigator-initiated projects that develop research resources for the broader alcohol research community and represent NIAAA efforts to accelerate alcohol-related research in a cost-effective manner.

NIAAA's Intramural Research Program (IRP) provides a unique environment for stimulating cutting-edge, innovative basic, translational, and clinical research on AUD and other alcohol-related problems. This includes a clinical research facility on the NIH main campus that hosts an outpatient clinic and an inpatient unit for treatment and research. The NIAAA IRP's ability to generate groundbreaking technologies and advances to be shared for use by the alcohol research field is a particular strength of the program.

To promote data sharing and accelerate the pace of discovery, NIAAA established the <u>NIAAA Data</u> <u>Archive</u>, which houses and shares de-identified data from human participants in NIAAA-funded research. The NIAAA Data Archive is maintained within the larger <u>NIMH Data Archive</u>, which comprises a harmonization and sharing infrastructure that facilitates transparency, rigor, and reproducibility of scientific research.

## Goal 2: Serving as a Responsible Steward of the Public's Investment

As a federal agency, NIAAA works continually to uphold the values of responsible stewardship, research integrity, and public trust. These values are reinforced by NIAAA's commitment to optimal management and accountability, strategic collaboration, and communication of research results.

## **Objective 1: Ensuring Optimal Management and Accountability**

NIAAA strives to continually optimize operations across its administrative and scientific functions through sound, data-driven business practices. NIAAA also engages in risk management to proactively identify and mitigate risks to the institute's research objectives, including risks to patient safety. For example, NIAAA recently developed a <u>serious adverse event (SAE) reporting tool</u> to capture SAEs that occur in NIAAA-funded clinical trials. This tool will allow NIAAA to mitigate future risks in studies with similar parameters, interventions, or study populations.

NIAAA develops research programs and initiatives based on scientific needs and opportunities as well as budget considerations. Concepts for initiatives are presented publicly to the <u>National Advisory Council on</u> <u>Alcohol Abuse and Alcoholism</u> for feedback on the merit of the initiative as well as clearance to move forward. Proceedings of National Advisory Council meetings and concept descriptions are available to the public online. This process not only enhances transparency in NIAAA's operations but also provides the research community and NIAAA's constituents additional insight into the institute's research directions and priorities. Such transparency encourages participation of NIAAA's constituents in shaping the directions and goals of NIAAA's mission.

NIAAA demonstrates effective stewardship by funding research proposals that are deemed highly meritorious through scientific peer review. NIAAA uses a rigorous, two-level scientific peer review process that emphasizes fairness and accountability in funding decisions and prioritizes scientific ideas with the greatest potential to advance the NIAAA mission. The outcomes of peer review inform NIAAA's funding decisions, which also consider portfolio balance, scientific opportunity, public health needs, budget, and other priorities. To promote optimal stewardship in this domain, NIAAA will continue to

identify and recruit a diverse pool of scientific peer reviewers based on career stage, geographic region, and demographic characteristics. NIAAA will also continually assess and improve its <u>funding procedures</u> to ensure efficient, seamless awards management.

In support of NIH's focus on improving rigor and reproducibility of research, NIAAA emphasizes the importance of robust and unbiased experimental design, methodology, analysis, interpretation, and reporting of results in NIAAA-supported research. This includes standardization of animal models across NIAAA's Alcohol Research Centers and Consortia, transparency in reporting experimental details so that others can reproduce and extend the findings, and adequate inclusion of females into appropriately powered research designs for both animal and human studies. NIAAA will be focusing on key challenges in data management and sharing, such as developing common data elements for preclinical and clinical research, participating with data repositories and knowledge bases, and facilitating data science tools for analyses and predictions. NIAAA will continue to work with NIH and its partners to identify and implement best practices to enhance rigor and reproducibility in the research it supports.

## Objective 2: Collaborating Across the National Institutes of Health and Beyond to Address Common Challenges

Alcohol misuse affects virtually every tissue and organ in the body and is associated with more than 200 diseases and injury-related conditions. For this reason, coordination of efforts related to shared research interests across NIH and other federal agencies is a key strategy for efficiently responding to complex alcohol-related problems and maximizing research resources. NIAAA coordinates on various research areas, including the following examples.

Adverse effects of alcohol on health. NIAAA collaborates with NIH institutes, centers, and offices on a wide range of topics, such as cancer, liver cirrhosis, Alzheimer's disease and related dementias, sex differences and women's health research, maternal health, health disparities research, wearable biosensors, and data sharing and management. In the IRP, NIAAA jointly supports the <u>Center on</u> <u>Compulsive Behaviors</u> and will jointly launch the National Taste and Smell Center.

**Fetal alcohol spectrum disorder.** NIAAA sponsors and chairs the <u>Interagency Coordinating Committee</u> <u>on Fetal Alcohol Spectrum Disorders</u>, which coordinates communication and collaboration on issues related to prenatal alcohol exposure across NIH ICs (i.e., Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institute on Drug Abuse [NIDA]), and NIMH and HHS agencies.

**Prevention and treatment of substance misuse.** NIAAA partners with NIDA and the National Cancer Institute through the <u>Collaborative Research on Addiction at NIH (CRAN)</u>, which integrates resources and expertise to advance research on substance use and related consequences. A major CRAN-led initiative is the <u>Adolescent Brain Cognitive Development<sup>SM</sup> Study</u>, the largest long-term study of brain development and child health in the United States. NIAAA also participates in advancing the <u>HEALthy</u> <u>Brain and Child Development Study</u>, which aims to better understand brain development during childhood. NIAAA also participates in the <u>Interagency Coordinating Committee on the Prevention of</u> <u>Underage Drinking</u>, led by the Substance Abuse and Mental Health Services Administration, which coordinates federal activities related to the prevention of underage drinking.

**Neuroscience research.** NIAAA participates in the <u>NIH Blueprint for Neuroscience Research</u>, a collaborative framework that confronts neuroscience challenges that are too large for any single NIH institute, center, or office. As part of the <u>Brain Research Through Advancing Innovative</u> <u>Neurotechnologies<sup>®</sup> Initiative</u>, NIAAA provides support with other NIH ICs to develop cutting-edge tools that will contribute to an enhanced understanding of brain disorders.

**Pain research.** Understanding the relationship between alcohol and pain is an important area of research that may have implications for numerous health conditions. NIAAA participates in the <u>Helping to</u> <u>End Addiction Long-term<sup>®</sup> Initiative</u>, an NIH-wide effort to speed scientific research to address the opioid crisis by better addressing pain, opioid misuse, AUD, and other substance use disorders. NIAAA also participates in the <u>NIH Pain Consortium</u>.

**External partnerships.** In addition to research collaborations, NIAAA leverages partnerships with professional, patient, advocacy, and community organizations, as well as with the research community, to advance its strategic goals and priorities.

## **Objective 3: Communicating Research Results and Evidence-Based Information to the Public**

To promote responsible stewardship, NIAAA communicates research findings to the public and translates scientific findings into resources that the public can use. These efforts are vital to the NIAAA mission because they raise awareness of <u>alcohol's adverse effects on health</u> and empower individuals, <u>professionals, and communities</u> with evidence-based resources to address alcohol-related challenges. Together, these steps can help to reduce the stigma that often prevents people impacted by alcohol misuse from seeking help and support. Importantly, the communication of research results demonstrates progress in advancing research.

The goals of NIAAA's communications and outreach programs are to develop and evaluate content and activities that disseminate unbiased science information and position NIAAA as an authoritative source of credible health messaging. This work encompasses news media, social media, strategic partnerships, and the creation of educational and information resources for varied audiences. These resources include websites such as the <u>Alcohol Treatment Navigator</u>, which helps individuals identify and find quality AUD treatment for themselves or a loved one, and <u>Rethinking Drinking</u>, which assists people in evaluating their relationship with alcohol. NIAAA also developed the <u>HPCR</u> to assist health care professionals with preventing, identifying, and treating alcohol-related problems, as well as various <u>school-based resources</u> to facilitate the prevention of underage drinking.

NIAAA also prioritizes communicating research results and providing data to stimulate new research. Examples include <u>Alcohol Research: Current Reviews</u>, an open-access, peer-reviewed scientific journal, and the <u>Alcohol Policy Information System</u>, a database of alcohol-related policies at the state and federal levels and policies on the recreational use of cannabis. Going forward, NIAAA will continue to create and promote educational materials for addressing alcohol misuse and AUD in various settings. NIAAA will also pursue innovative ways to connect with the public so that they have access to research findings to make informed choices about alcohol use. NIAAA will continue to translate its products into multiple languages to increase equity and access to evidence-based information and to engage in strategic partnerships that extend the reach of NIAAA-supported research findings and information resources.

<sup>6</sup> Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality. 2022 National Survey on Drug Use and Health. Table 5.9A—Alcohol use disorder in past year: among people aged 12 or older; by age group and demographic characteristics, numbers in thousands, 2021 and 2022. [cited 2023 Dec 8]. Available from: <a href="https://www.samhsa.gov/data/sites/default/files/reports/rpt42728/NSDUHDetailedTabs2022/

<sup>7</sup> SAMHSA, Center for Behavioral Health Statistics and Quality. 2022 National Survey on Drug Use and Health. Table 5.32B— Received substance use treatment in past year: among people aged 12 or older; by age group and past year drug use disorder, past year alcohol use disorder, past year drug and alcohol use disorder, and past year substance use disorder, percentages, 2021 and 2022. [cited 2023 Dec 13]. Available from:

https://samhsa.gov/data/sites/default/files/reports/rpt42728/NSDUHDetailedTabs2022/NSDUHDetailedTabs2022/NSDUHDetTa bsSect5pe2022.htm?s=5.32&#tab5.32b

<sup>8</sup> White AM, Slater ME, Ng G, Hingson R, Breslow R. Trends in alcohol-related emergency department visits in the United States: results from the Nationwide Emergency Department Sample, 2006 to 2014. Alcohol Clin Exp Res. 2018 Feb;42(2):352-9. doi: 10.1111/acer.13559. Epub 2018 Jan 2. PubMed PMID: 29293274

<sup>9</sup> Case A, Deaton A. Rising morbidity and mortality in midlife among white non-Hispanic Americans in the 21st century. Proc Natl Acad Sci U S A. 2015 Dec 8;112(49):15078-83. doi: 10.1073/pnas.1518393112. Epub 2015 Nov 2. PubMed PMID: 26575631

<sup>&</sup>lt;sup>1</sup> Centers for Disease Control and Prevention (CDC). Alcohol and Public Health: Alcohol-Related Disease Impact. [Table], Annual average for United States 2020–2021 alcohol-attributable deaths due to excessive alcohol use, all ages. [cited 2024 Mar 15]. Available from: <u>https://nccd.cdc.gov/DPH\_ARDI/Default/Report.aspx?T=AAM&P=F1F85724-AEC5-4421-BC88-</u> 3E8899866842&R=EACE3036-77C9-4893-9F93-17A5E1FEBE01&M=7F40785C-D481-440A-970F-50EFBD21B35B&F=&D=

<sup>&</sup>lt;sup>2</sup> National Center for Health Statistics Mortality Data on CDC WONDER. Current final multiple cause of death data, 2018–2021. [Internet]. U.S. Department of Health and Human Services; 2023 Sept [cited 2023 Feb 9]. Available from: <u>https://wonder.cdc.gov/mcd.html</u>

<sup>&</sup>lt;sup>3</sup> National Center for Statistics and Analysis, National Highway Traffic Safety Administration. Overview of motor vehicle crashes in 2021 [Internet]. Washington: U.S. Department of Transportation; 2023 Apr [cited 2023 Apr 12]. 50 p. Available from: https://crashstats.nhtsa.dot.gov/Api/Public/ViewPublication/813435

<sup>&</sup>lt;sup>4</sup> Estimated liver disease deaths include deaths with underlying causes coded as alcoholic liver disease (K70); liver cirrhosis, unspecified (K74.0–K74.2, K74.6, K76.0, K76.7, and K76.9); chronic hepatitis (K73); portal hypertension (K76.6); liver cancer (C22); or other liver diseases (K71, K72, K74.3–K74.5, K75, K76.1–K76.5, and K76.8). Number of deaths from Multiple Causes of Deaths Public-Use Data File, 2022 (https://wonder.cdc.gov/mcd.html). Alcohol-attributable fractions (AAFs) from CDC Alcohol-Related Disease Impact (http://nccd.cdc.gov/DPH\_ARDI/Default/Default.aspx), accessed March 13, 2024. Prevalence of alcohol consumption from the National Survey on Drug Use and Health, 2022, for estimating indirect AAFs for chronic hepatitis and liver cancer.

<sup>&</sup>lt;sup>5</sup> Islami F, Sauer AG, Miller KD, Siegel RL, Fedewa SA, Jacobs EJ, McCullough ML, Patel AV, Ma J, Soerjomataram I, Flanders WD, Brawley OW, Gapstur SM, Jemal A. Proportion and number of cancer cases and deaths attributable to potentially modifiable risk factors in the United States. CA Cancer J Clin. 2018 Jan;68(1):31-54. doi:10.3322/caac.21440. Epub 2017 Nov 21. PubMed PMID: 29160902