EXECUTIVE SUMMARY

1. PURPOSE

This Action Plan for Liver Disease Research was developed by a broad consortium of basic and clinical research investigators, physicians, health care providers, and concerned lay persons for the purpose of advancing research on liver and biliary diseases, with the ultimate aim of decreasing the burden of liver and biliary diseases in the United States. The focus of the Action Plan was to identify areas of scientific opportunity to serve as a stimulus to progress and to help direct research resources at the National Institutes of Health (NIH) toward practical but important goals in the prevention, diagnosis, and management of liver and biliary diseases. Because these scientific research opportunities touch upon areas of importance to multiple NIH Institutes and Centers, this Action Plan was designed to ensure coordination of liver and biliary research efforts across the NIH.

2. CURRENT BURDEN OF LIVER AND BILIARY DISEASES IN THE UNITED STATES

The liver is the largest organ in the body and performs multiple interrelated functions that are essential for life. The importance of the liver, and the interrelated structures of the gallbladder and biliary tract, is illustrated by the severe conditions that result when normal functioning of these structures is compromised.

Liver and biliary diseases affect Americans of all ages and walks of life. At present, an estimated 5.5 million Americans have chronic liver disease or cirrhosis, and more than 20 million have gallbladder disease. Economic costs per year total approximately $1.6 billion for chronic liver disease and cirrhosis, $1.3 billion for liver cancer, and $6 billion for gallbladder disease. Chronic liver disease and cirrhosis is currently the 12th leading cause of death, accounting for approximately 27,000 deaths annually, in the United States. Both hepatocellular carcinoma (the most common form of primary liver cancer) and cholangiocarcinoma (the most common form of cancer of the biliary tract) are increasing in incidence in the United States, at a time when the frequencies of most other forms of cancer are decreasing.

Liver and biliary diseases can result from a variety of causes, including infectious agents, inherited defects, metabolic disturbances, alcohol, and toxins found in the environment, diet, or medicine cabinet. Common forms of liver and biliary diseases include viral hepatitis, alcoholic liver disease, nonalcoholic fatty liver disease, autoimmune liver disease, metabolic liver disease, drug-induced liver injury, and gallstones. The most important consequences of chronic liver disease are the development of portal hypertension, which puts the patient at increased risk of developing a host of complicating conditions, and cirrhosis, which leads to liver failure requiring liver transplantation. At present, in the United States, more than 5,000 liver transplants are performed in adults and more than 500 in

children each year; however, more than 17,000 patients still await a liver transplant.

While liver and biliary diseases can strike across age and racial/ethnic groups, genders, and socioeconomic classes, certain groups bear a heavier burden from these diseases. For example, liver disease affects many Americans in the most productive years of life as the 4th leading cause of death in the United States in adults between the ages of 45 and 54 years. Childhood liver diseases such as biliary atresia, Alagille syndrome, progressive familial intrahepatic cholestasis, and alpha-1-antitrypsin deficiency, though rare, tend to be severe and persist for life. Mortality from liver disease is higher in men than women, but certain conditions are more common in women, such as primary biliary cirrhosis, drug-induced liver injury, and gallstones. Members of certain racial or ethnic groups in the United States are at increased risk of diseases such as hemochromatosis or gallstones; of resistance to current therapy for hepatitis C; or of death from chronic liver disease and cirrhosis. Certain liver and biliary diseases are also more common in people who are overweight, including nonalcoholic steatohepatitis and gallstones. Liver disease is an increasingly common cause of morbidity and mortality in persons infected with the human immunodeficiency virus (HIV).

Liver and biliary diseases also have an impact on the personal lives of patients, affecting their abilities to work and engage in social activities, their physical and emotional well-being, and their overall quality of life. Common symptoms of liver disease include fatigue, muscle weakness, nausea, poor appetite and weight loss, fluid retention, predisposition to bleeding and infection, depression, anxiety, and inability to work.

Thus, the impact of liver and biliary diseases on the U.S. population is considerable, whether viewed in terms of the number of individuals affected; the severity of the disease and its frequency of fatality; the economic costs to the U.S. health care system; as well as those disease outcomes that are less readily quantifiable, but are important on a personal scale, such as disability and quality of life. The current burden of liver and biliary diseases in the United States warrants improved efforts in their prevention and control, which depend largely on advances in understanding of these diseases through research.

3. NIH SUPPORT FOR LIVER AND BILIARY DISEASE RESEARCH

Important advances in the understanding and management of liver and biliary diseases have occurred in recent decades as a result of public funding through the NIH and other Federal agencies, as well as from private funding through research foundations and industry. These advances include the development of vaccines against hepatitis A and B, elimination of post-transfusion hepatitis C, prevention of acetaminophen-induced liver failure, as well as the identification of the causes of Wilson disease, hemochromatosis, Alagille syndrome, and alpha-1-antitrypsin deficiency.

Within the NIH, 18 Institutes, Centers, and Offices currently support and collaborate on liver and biliary disease research, and the research investment made by the agency in this area has increased 3-fold within the past decade. Liver disease-related research supported by the NIH includes studies of the liver and biliary system, under normal and disease conditions, and in basic and clinical research settings. NIH support for liver and biliary research is provided in the form of grants, awards, contracts, and fellowships furnished to extramural researchers and institutions for research and training, as well as through the support of intramural research and investigator-initiated research projects. The NIH also plays an important

role in bringing together the external experts in clinical liver disease to conduct critical reviews of recent developments in liver and biliary disease management through conferences and workshops.

Building on this past progress, opportunities now exist to further advance research on liver and biliary diseases through NIH support and to translate findings on disease pathways into new means of treating liver and biliary diseases and alleviating patient suffering.

4. COORDINATION OF LIVER AND BILIARY DISEASE RESEARCH EFFORTS

To enable NIH-supported research activities to continue to yield breakthroughs toward reducing the burden of liver and biliary diseases, essential elements include effective coordination among NIH components, Federal agencies, and other organizations; a careful assessment of research opportunities; and planning for the optimal use of future investments. This coordination is made possible through the mechanism of the existing statutory Digestive Diseases Interagency Coordinating Committee (DDICC), which coordinates research efforts among NIH components and other Federal health agencies committed to combating digestive disease. The recently established Liver Disease Subcommittee of the DDICC, in particular, helps to coordinate efforts related to liver and biliary diseases. The Subcommittee includes representatives from 17 NIH Institutes and Centers that support liver and biliary research. In addition, the Liver Disease Research Branch within the Division of Digestive Diseases and Nutrition of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) serves as an important focus for the coordination of NIH-supported liver and biliary research efforts.

5. TRANS-NIH ACTION PLAN FOR LIVER DISEASE RESEARCH

5.1 Purpose and Guiding Principles

The purpose of the Action Plan for Liver Disease Research is to advance research on liver and biliary diseases, with the ultimate aim of decreasing the burden of these diseases in the United States. Guiding principles in the development of the Action Plan for Liver Disease Research include the following:

- **Stress basic research:** Important, fundamental advances in management and prevention of liver disease will come primarily from fundamental advances in knowledge of liver function and liver diseases.

- **Strive to rapidly translate findings from *basic* research into practical means of diagnosis, prevention, treatment, and cure of liver diseases:** Findings from basic research should be applied to clinical issues (bench-to-bedside research) in a timely, reasoned, efficient, and effective manner. The great increase in knowledge in biology and medicine triggered by advances in cell and molecular biology, genetics, genomics, and the Human Genome Project needs to be applied to diagnosis, prevention, treatment, and cure of human diseases. Translation is a major component of the NIH Roadmap *(http://nihroadmap.nih.gov)* and is also a central focus of this Action Plan.

- **Strive to rapidly translate findings from *clinical* research into important directions for basic research:** Translational research is bidirectional. For example, findings in clinical investigation and clinical trials often provide new insights that need to be further pursued by basic, laboratory research. Thus, it is important to provide means of interaction between clinical and basic researchers to focus

and refocus research efforts on important issues of liver disease prevention and management. The success of bidirectional translational research would be aided by the formulation of multidisciplinary research teams and productive communication, involvement, and interactions between clinical and basic researchers.

- **Strive to use the full potential of recent breakthroughs in research:** For example, research should capitalize on the wealth of molecular biologic information and tools stemming from such endeavors as the Human Genome Project and the Human Proteome Project and the advances in biotechnology and methodology in biomedical research.

5.2 Planning Process

The Action Plan was developed through an open and inclusive planning process with oversight by the Liver Disease Subcommittee, DDICC, and leadership by the NIDDK Liver Disease Research Branch. It represents the contributions of a diverse and talented group of individuals who are committed to advancing liver disease research, including participants from the NIH and other Federal agencies, intramural and extramural researchers, physicians, and representatives of professional and patient advocacy groups.

The Action Plan for Liver Disease Research originated with plans to build on the robust NIH liver disease research portfolio through various means to bring greater focus and coordination to liver disease research supported by the NIH. The Action Plan was initiated with the establishment of a Liver Disease Research Branch within the Division of Digestive Diseases and Nutrition in the NIDDK, and the creation of a Liver Disease Subcommittee within the existing statutory Digestive Diseases Interagency Coordinating Committee, which oversaw its development. The Subcommittee held several meetings to discuss the Action Plan, including an open meeting attended by intramural and extramural researchers, clinicians, and representatives of professional and patient advocacy organizations. Working Groups, involving a total of approximately 120 individuals, were composed mostly of liver disease researchers, physicians, and lay advocates from outside the NIH. These groups provided input and comments, which the NIDDK Liver Disease Research Branch staff used to develop each of the chapters. An additional group of 80 external experts reviewed the chapters and provided comments.

5.3 Public Input and the Action Plan for Liver Disease Research Website

A website on the Action Plan for Liver Disease Research was created to inform the research community and public of this effort. This website can be accessed using the following URL: *http://liverplan.niddk.nih.gov.* Information on public meetings held on the Action Plan is available on the website. Drafts of the chapters of the Action Plan were also posted to this website for a month-long period of public comment prior to its publication. Comments were received during this time from members of the general public, government, academic institutions, professional societies, advocacy organizations, and industry.

5.4 Content of the Action Plan Chapters

To structure the Action Plan, liver and biliary research was divided into 16 topic areas, which are the subjects of the 16 chapters as follows:

1. Cell and Molecular Biology of the Liver
2. Liver Injury, Inflammation, Repair, and Fibrosis
3. Developmental Biology and Regeneration
4. Bile, Bilirubin, and Cholestasis

5. Viral Hepatitis
6. HIV and Liver Disease
7. Fatty Liver Disease
8. Drug- and Toxicant-Induced Liver Disease
9. Autoimmune Liver Disease
10. Pediatric Liver Disease
11. Genetic Liver Disease
12. Liver Transplantation
13. Complications of Liver Disease
14. Liver Cancer
15. Gallbladder and Biliary Disease
16. Liver Imaging and Biotechnology

Each chapter includes sections on current understanding of a topic, recent research advances, research goals, and steps to achieve those research goals. The major focus of the Action Plan chapters is on the research goals, which represent areas of scientific opportunity that would be beneficial to pursue over the next decade within available resources of NIH support in order to advance knowledge and care of liver and biliary diseases. Research goals are categorized in terms of the degree of difficulty and time required to reach them within a "matrix" included at the end of each chapter.

Often, the research goals of these topic areas overlap with each other in a synergistic manner. For example, increased knowledge of liver development and regeneration will also improve understanding of the mechanisms underlying developmental defects, acute and chronic liver diseases, liver carcinogenesis, healing after liver injury, and recovery of the organ in both donors and recipients of living donor liver transplants.

The specific research goals build toward addressing the larger aims within each of the 16 topic areas, as follows:

- To gain a more thorough understanding of the processes, pathways, and molecules that underlie normal liver cell functioning, which can then be applied to understanding cellular and molecular disease processes.
- To understand the cellular mechanisms mediating liver injury, inflammation, repair, and fibrosis, and to develop effective means for monitoring and treating the diseases caused by these processes.
- To fully define the molecular and cellular mechanisms underlying liver development and regeneration in health and disease, and to apply these findings to developing improved therapies for liver disease.
- To fully delineate the normal pathways of uptake, metabolism, and secretion of bile salts, bilirubin, and other biliary lipids and solutes; to characterize the alterations in these pathways that participate in the pathogenesis of liver diseases; and to develop means of diagnosis, treatment, and prevention of cholestatic liver disease and disorders of bilirubin metabolism.
- To develop practical, safe, and effective means of prevention, treatment, and control of the five forms of viral hepatitis.
- To define the causes of liver disease associated with HIV and to develop means to prevent and treat liver disease in HIV-infected persons.
- To understand the basic mechanisms of injury and to develop means of prevention and treatment of nonalcoholic and alcoholic fatty liver disease.
- To establish means of predicting the likelihood of hepatotoxicity due to drugs, herbal medications, and environmental toxicants; to improve diagnostic ability; to elucidate the mechanisms of hepatotoxicity; and to develop means of preventing and treating liver cell injury.
- To understand the etiology and pathogenesis of autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis and to develop effective means of treatment and prevention.
- To elucidate the causes of various types of pediatric liver disease and to develop practical means of their diagnosis, treatment, and prevention.
- To develop practical and reliable means of screen-

ing for and diagnosing genetic liver diseases such as hemochromatosis, Wilson disease, porphyria, cystic fibrosis, and congenital hepatic fibrosis, as well as to provide a means of control and prevention of their disease manifestations.
- To optimize the availability and long-term success of liver transplantation as a treatment of acute and chronic liver failure and to provide means to reliably diagnose, manage, treat, or prevent its major complications.
- To identify ways to prevent or ameliorate the complications of portal hypertension, including variceal hemorrhage, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, and hepatorenal and hepatopulmonary syndromes.
- To understand the cellular and molecular mechanisms of hepatocarcinogenesis and to develop means for early detection, treatment, and prevention of hepatocellular carcinoma.
- To develop means to prevent and treat gallstones and other diseases of the biliary tract.
- To develop ways to improve the detection and characterization of liver and biliary diseases and to aid in targeting therapies to these sites.

A summary of major cross-cutting and representative research goals identified during the planning process is presented at the end of the Action Plan. These goals cover the following areas:

- Therapy of chronic hepatitis C,
- Diagnosis and treatment of nonalcoholic and alcoholic liver disease,
- Therapy of chronic hepatitis B,
- Detection of hepatic fibrosis,
- Early detection of hepatocellular carcinoma,
- Prevention of gallstones,
- Defining etiology of biliary atresia,
- Improving safety and outcome of living donor liver transplantation,
- Standardization of liver disease nomenclature and grading systems, and
- Reducing overall mortality from chronic liver disease and cirrhosis.

These goals will be used as benchmarks to gauge the overall success of this Action Plan, in terms of objective progress in liver and biliary disease research over the next ten years.

5.5 Implementation and Assessment

The Action Plan is not a static product, but is rather an ongoing process with specific goals and benchmarks. Its implementation and an assessment of its progress toward reaching research goals over the next decade will be overseen by the Liver Disease Subcommittee of the Digestive Diseases Interagency Coordinating Committee through communications and periodic meetings, including open meetings at the 5-year and 10-year marks to assess progress and remaining opportunities with input from the external research and advocacy community. The 214 research goals in liver and biliary research and ten representative benchmarks identified in the Action Plan will be used as guideposts by which to gauge progress toward meeting the overall aims of the Action Plan. Steps to reach these research goals could include such efforts as the organization of workshops, databases, and tissue banks; development of useful animal and cell culture models, program announcements and requests for applications; and the establishment or expansion of networks of investigators. Collaborations between basic and clinical researchers, researchers from different disciplines, and Federal, private, and industry partners will also be essential to the success of the Action Plan.

Efforts on behalf of the NIH, as well as all Federal, academic, professional, and advocacy partners committed to liver and biliary disease research, are needed to fulfill the goals of the Action Plan.