DR. SUMEET K ASRANI (Orcid ID : 0000-0001-9174-5670)
DR. JESSICA L MELLINGER (Orcid ID : 0000-0001-7364-5035)
DR. JUAN PABLO ARAB (Orcid ID : 0000-0002-8561-396X)
PROF. VIJAY H. SHAH (Orcid ID : 0000-0001-7620-573X)

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Corresponding Author Email ID: Sumeet.Asrani@BSWHealth.org

Reducing the Global Burden of Alcohol-Associated Liver Disease: A Blueprint for Action

Sumeet K Asrani MD MSc[1*^]
Jessica Mellinger MD MSc[2*]
Juan P Arab MD[3*]
Vijay H Shah MD[4]

[1]Baylor University Medical Center, Dallas, TX, United States

[2]Division of Gastroenterology and Hepatology, University of Michigan, Ann Arbor, MI

[3]Depto. Gastroenterología y Hepatología, Escuela de Medicina, Pontificia Universidad Católica de Chile, Chile.

[4]Division of Gastroenterology and Hepatology, Mayo Clinic, Rochester, MN

*all contributed equally

^Corresponding Author and reprint requests

Sumeet K Asrani MD MSc

Baylor University Medical Center

Dallas Texas

2148208500

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Abstract

Alcohol-associated liver disease (ALD) is a major driver of global liver related morbidity and mortality. There are 2.4 billion drinkers (950 million heavy drinkers) and the lifetime prevalence of any alcohol use disorder (AUD) is 5.1%-8.6%. In 2017, global prevalence of alcohol-associated compensated and decompensated cirrhosis was 23.6 million and 2.5 million, respectively. Combined, alcohol-associated cirrhosis and liver cancer account for 1% of all deaths worldwide with this burden expected to increase. Solutions for this growing epidemic must be multi-faceted and focused on both population and patient-level interventions. Reductions in ALD-related morbidity and mortality require solutions that focus on early identification and intervention, reducing alcohol consumption at the population level (taxation, reduced availability and restricted promotion), and solutions tailored to local socioeconomic realities (unrecorded alcohol consumption, focused youth education). Simple screening tools and algorithms can be applied at the population level to identify alcohol misuse, diagnose ALD using non-invasive serum and imaging markers, and risk-stratify higher-risk ALD/AUD patients. Novel methods of healthcare delivery and platforms are needed (telehealth, outreach, use of non-healthcare providers, partnerships between primary and specialty care/tertiary hospitals) to proactively mitigate the global burden of ALD. An integrated approach that combines medical and AUD treatment is needed at the individual level to have the highest impact. Future needs include (1) improving quality of ALD data and standardizing care, (2) supporting innovative healthcare delivery platforms that can treat both ALD and AUD, (3) stronger and concerted advocacy by professional hepatology organizations, and (4) advancing implementation of digital interventions.

Introduction

Alcohol-associated liver disease (ALD) is a major driver of global liver-related morbidity and mortality. Around the world, in 2016, alcohol use was associated with 3 million

deaths (5.3% of all deaths) surpassing hypertension and diabetes combined.(1, 2) The purpose of our review is three-fold. First, we briefly review the global burden of ALD and place it in context of relevant changes anticipated to drive future trends. Second, we discuss population level screening for ALD and AUD for early recognition and management. Finally, we discuss strategies for mitigating the impact of ALD at the global level and offer focused solutions for delivering healthcare services at the regional and individual level.

A. Current and future burden of ALD

Alcohol use and misuse: In 2016, 2.4 billion people consumed alcohol (1.5 billion male and 0.9 billion female) and approximately 39.5% of these were heavy episodic drinkers (1, 2). Globally, per capita alcohol use rose from 5.7 L to 6.4 L over a 16-year period (2000-2016) (1, 3). Though the overall prevalence of heavy episodic drinking decreased, it rose in established drinkers, indicating that those who drink already are drinking heavily than ever before (1). Drinking among youth remains high (26.5% age 15-19 years) with persistently high rates of heavy episodic drinking over the last 16 years (49.3% in 2000, 47.5% in 2010 and 45.7% in 2016). The prevalence of current drinkers is lower among women than men across most regions except for South-East Asia and Western Pacific region. However, the absolute number of currently drinking women and amount of alcohol consumption has increased globally (1, 2).

The most severe form of alcohol misuse, alcohol use disorder (AUD), is characterized by the accumulation of multiple symptoms of alcohol use: increasing use of alcohol despite negative consequences and persistent, unsuccessful attempts to stop (4). The lifetime prevalence of any AUD was 8.6% overall, ranging from a low of 0.7% (Iraq) to 22.7% (Australia) (5). AUD symptoms persisted in 21-37% of those who reported a history of AUD in the past (5). Importantly, comorbid mental health disorders were frequently present alongside AUDs and often preceded the onset of alcohol use (6). The adjusted odds ratio (OR) for lifetime presence of any mood disorder was 1.5 (OR 1.8 for severe AUD), any drug use disorder, OR 4.1 (OR 6.4 for sever AUD) and borderline personality disorder, OR 1.5 (OR 2.5 for severe AUD) respectively.

Alcohol-associated liver disease (Figure 1)

Recently commissioned works describe country and region-specific burden of liver disease in Europe (Hepahealth) as well as in Asia and Pacific regions (7-9).

Prevalence of alcohol associated cirrhosis and hepatocellular carcinoma (HCC)

Alcohol is responsible for about 21% of prevalent compensated cirrhosis cases. The global prevalence of alcohol associated compensated cirrhosis remained stable, 13.5 million (290/100,000 in 1990) to 23.6 million (288/100,000 in 2017) but decompensated cirrhosis increased from 1.1 million (25/100,000 in 1990) to 2.5 million (30 per 100,000 in 2017) (3). Regionally, the highest proportions are seen in Western Europe (42-43%) and Central Europe (43-46%). Alcohol was responsible for approximately 30% of HCC cases (10).

Mortality: Cirrhosis due to alcohol use is responsible for 25% of all cirrhosis deaths (308K, 0.5% of total deaths worldwide) and ALD-cancer related deaths account for 30% of all liver cancer deaths (250K, 0.4% of deaths worldwide). Combined, alcohol related cirrhosis and liver cancer account for 1% of all deaths worldwide, but may be underestimated. Alcohol as a diagnosis may be under reported as a cause of liver disease due to social stigma (11). In addition, alcohol is a cofactor in deaths attributed to other causes of liver disease (12). As expected, the highest proportions were seen in central Europe (44.0%), Western Europe (41.7%) and Andean Latin America (38.1%). However, by absolute numbers 45% of all ALD-related deaths occurred in 5 countries (India, US, Mexico, China and Russia) and 21.6% of all ALD deaths worldwide occurred in India (1, 3). Liver related deaths in the Asia-Pacific region accounted for under half of global ALD-related deaths (7).

The burden of ALD is expected to increase (13). There are several measured and unmeasured factors driving this change, specifically, changes in drinking patterns, socioeconomic factors as well as relevant comorbidities such as obesity that may impact the future burden of ALD.

B. Screening and early diagnosis at the population level: A Blueprint for Early Action

Screening at the population level requires a practical approach (**Figure 2**) as well as efficient care delivery methods to appropriately triage of ALD and AUD patients (**Figure 3**). An example that may be applicable to healthcare systems in the United States is shown in **Supplemental Figure 1**. There are several guiding principles. **First, early detection and screening for AUD and ALD may be key for mitigating future burden.** ALD is often detected at a late stage when patients are more likely to present with decompensated cirrhosis (14). Consequently, there is an unmet need for effective and economically reasonable pathways to screen for AUD and ALD-fibrosis *before* patients develop end-stage liver disease. Screening for presence of fibrosis using noninvasive imaging based markers in patients with ALD may be cost effective across different populations.(15) **Second, easy to use tools for ALD and AUD screening and linkage to treatment are needed.** Alcohol misuse needs to be widely screened for and linked directly to effective referrals to alcohol treatment personnel or pathways. Unfortunately, AUD treatment is limited by a shortage of providers, poor reimbursement, as well as patient attitudinal barriers that must be overcome. **Third, technology should be leveraged to effectively screen at the population level.** Currently most alcohol screening is linked to healthcare environments, potentially leaving those who don't interact with their health-care system undiagnosed. Novel "screening extenders" (smartphone apps and other mobile health innovations) may be one approach to achieve greater population-level screening. Smartphone apps to assess alcohol use are abundant, but evidence for their efficacy in the general population is varied and few, if any, have been tested in an ALD population (16). In resource rich areas, the use of electronic medical records (EMR) may be able to assist in screening, risk-stratifying and triaging patients to a care pathway through the creation of automated early warning systems for liver disease (17). **Fourth, novel settings for screening need to be considered.** Though screening may be easily accomplished if related to a healthcare visit (e.g. "for cause" consultation for elevated liver enzymes), unrelated screening opportunities need to be explored. For example, offering screening for alcohol misuse to

all medical admissions to hospital with automatic referral to treatment services for those at the highest risk of dependency and risk for alcohol associated liver disease is feasible (17). Novel settings for alcohol use and ALD screening outside healthcare facilities should be pursued. Screening for hypertension at local barbershops frequented by African-American men was an effective screening approach and may be an example of a non-traditional healthcare setting for initial ALD and AUD screening or clinical interventions (18). Other novel settings for screening may include pharmacies, integration into annual wellness checks or annual employee vaccination drives or at time of renewal of driver's licenses. **Finally, screening approaches need to be tailored to different regions of the world, especially in underserved areas.** Smartphone technology is not simply an urban phenomenon; its penetration in rural areas is high and may be a potential medium for screening and intervention. Acceptance of smartphone and telehealth technology by cirrhosis patients is high, leaving a potential untapped area for intervention (19). Screening approaches that leverage risk of liver disease and participants concern for their liver health may have more success than generic screening approaches (20). Barriers to screening include social stigma, access to care, access to cost-effective screening tools, and attitudinal barriers (denial of alcohol use problems, lack of perceived need to alcohol use treatment).

C. Diagnosing AUD: Building on the Screening Blueprint

The diagnosis of AUD is best made with an individual interview. Though adapting this at a population level is difficult, screening tests may identify the high-risk patient who would benefit from more in-depth questioning. A combination of consumption patterns, validated questionnaires for screening, and alcohol biomarkers may help providers know when to refer to an alcohol treatment professional for a more thorough diagnosis of a potential AUD and any underlying mental health disorder or comorbid substance use disorder. The *Alcohol Use Disorders Identification Test* (AUDIT) can differentiate between more severe alcohol dependence (mod/severe AUD) and less risky drinking. (21). A shorter version, AUDIT-C has 73% sensitivity and 91% specificity for AUD and

85% sensitivity and 89% specificity for detecting alcohol dependence (22). In addition, it has been adapted in regional languages and validated in several patient populations (23). Biomarkers may increase sensitivity for detection of alcohol use beyond self-report methods (24). Direct markers of alcohol metabolism, such as ethyl glucuronide (EtG), ethyl sulfate (EtS) and phosphatidylethanol (PEth), have the benefit of higher specificity. Urine markers may be detectable in urine up to 90 hours after alcohol ingestion (reported sensitivity of 62-89% and specificity of 93-99%). Serum markers (e.g. PEth) may detect use for 28 days (reported sensitivity of 90-99% and specificity of 100%). Though not diagnostic of an alcohol use disorder on their own, alcohol biomarkers should be used, particularly when a patient has more concerning alcohol misuse as these may aid identification of slips or relapses and facilitate engagement with alcohol use treatment where needed.(24, 25)

D. Diagnosis of liver disease: Expanding the Blueprint

Population level screening with a combination of non-invasive markers may help identify patients at highest risk. Patented and non-patented serum markers for non-invasive liver disease assessment (NILDA) may play a role in early diagnosis. As an example, the Enhanced Liver Fibrosis (ELF) score is predictive of clinical outcomes including liver-related mortality and may be useful as a screening test within primary care (26, 27). Fibrosis-4 index (FIB-4), a widely used non patented index (age, aminotransferases and platelet count) may have a lower accuracy than patented markers but could have broad applications for screening at population level across different socio-demographic index (SDI) regions (15, 28).Other markers such as Fibrotest, AST to Platelet Ratio index (APRI) and Hepamet may also play a role (28).

Besides serum biomarkers, liver stiffness measurement (LSM) by transient elastography has good diagnostic performance to exclude significant fibrosis or cirrhosis in patients first assessed for ALD across Asian and European populations (15). Cutoffs values for presence of cirrhosis in ALD may be higher compared to other diseases. LSM closely correlates with the degree of fibrosis and has good diagnostic performance to

exclude ≥F3 fibrosis or cirrhosis in patients first assessed for ALD with sensitivity of 91% (81-97%), specificity of 95% (91-98%), area under the receiver operating characteristic curve (AUROC) of 0.90-0.97 (28). These tools may be more helpful at the population level to rule out liver disease (higher negative predictive value). Due to availability, imaging-based screening may be second-line for those at intermediate or high risk for ALD. Noninvasive screening for advanced alcohol-related fibrosis is a cost-effective intervention when a positive screening tool triggers the appropriate referral to more specialized care (MR elastography, hepatologists, transplant centers), and tailored to the prevalence of advanced fibrosis (27).

E. Delivering targeted interventions: Broadening the Blueprint to Policy and Populations

Though treatment needs to be focused on the individual, a combination of global and regional interventions is needed to decrease the number of potential people at risk (29) **(Figure 4).** Three broad goals are 1) society wide alcohol reduction (global solutions), 2) early identification of AUD and ALD (regional and local level), and 3) personalized treatment for AUD and ALD (individual level).

***Global solutions*:**

The World Health Organization (WHO) has led a number of initiatives at a global level to decrease the impact of alcohol (30). Of these, three are highlighted as “best buys” and include taxation, reduced availability, and restricted promotion to reduce per capital alcohol consumption.

1. Pricing strategies: The price of alcohol purchase is the single strongest driver of alcohol consumption at a per capita population level. Strategies include a national alcohol policy, price regulation (minimum unit pricing of alcohol or a set price below which alcohol beverages cannot be sold), and taxation of alcohol beverages. Though most countries have alcohol excise taxes, less than half use alternate strategies such as adjusting taxes to keep up with inflation and income levels, imposing minimum pricing policies, volumetric taxes or banning below-cost selling or volume discounts (30). When pricing rises, alcohol consumption and alcohol related liver disease burden

decreases and these gains are often felt most in those with the highest amount of alcohol use and in the lower socioeconomic status groups (31-33). Impact of pricing policies may however be variable, especially for low income moderate drinkers compared with high income heavy drinkers who can absorb pricing changes. Conversely, when prices are dropped through reduced taxation and other mechanisms, alcohol consumption and alcohol-related death rates increase (7-9). Blunting the impact of unrecorded alcohol use is another concern. In lower SDI countries, alcohol products may be homebrewed in an unregulated manner, leaving a large percentage of alcohol use unmeasured and "unseen". This results in an inability to regulate by government measures and adds another dimension of health toxicity from products used in home-brewing that may have adverse health consequences (34). This translates into lower SDI regions having higher mortality for alcohol-attributable causes, despite reporting lower levels of recorded consumption (35). In Central America, for example, where homemade alcohol consumption is high, pricing-policies may not have the desired effect.

2. Reduction in availability of alcohol: In addition to direct taxation, regulation of days and hours of alcohol sales, and control over the sale of liquor licenses and constraints on alcohol sales outlets may help (36-38). There is benefit in establishing a minimum legal purchasing age, but age restrictions vary globally and policy impact likewise varies (39). The impact of establishing a minimum legal drinking age on alcohol-related chronic disease mortality may be more pronounced in those that do not attend college (40). Although educational initiatives have been viewed as less effective in influencing per capita alcohol consumption at a national level compared to policies that regulate price of sale, there are some notable exceptions: Iceland was able to reduce its alcohol and drug use in younger individuals from 42% to 5% over a period of two decades with the implementation of several policy principles. This included (a) bringing in a curfew beyond which youth needed to be off public streets, (b) parents signing a pledge that they will not allow their teens to drink alcohol, (c) a purposeful increase in family time at night, (d) increasing after school activities including voucher programs to incentivize, (e) survey-based measurements and research aim to lower teen alcohol and illicit substance consumption, and (f) engaging politicians to assist in

policy development and implementation to support these initiatives (41). The Icelandic experience shows that effective alcohol policy at a population level will likely need to be targeted to specific populations (in this case, youth) and involve a multi-faceted approach to achieve success.

3. **Restricted promotion:** A focus on protecting children from alcohol marketing as well as targeting clinicians is advised (42). Government policies should regulate marketing promotions at the level of sports, standardize alcohol warning label messaging, and limit advertising targeting vulnerable populations, especially young individuals and, more recently, women (43, 44). Controls need to be placed on content and volume of marketing, decrease connections with youth related activities, limit use of digital media and increase oversight by public health at the country level (45, 46). Challenges to these government interventions exist including lobbying initiatives from contrarian groups (47).

Regional and local solutions: Changing the Healthcare Delivery Blueprint Through Digital Solutions

Innovative models of health care delivery that leverage novel telehealth initiatives (provider to patient and provider to provider) are needed in order expand the reach for screening and interventions at the state or health system level.

1. **Identifying high risk populations:** Based on resource availability, infrastructure needs to be in place for implementing screening and linkage to treatment for AUD and ALD (**Figure 3)**. Such models will need to be adapted to local circumstances and may include use of regional data to identify areas of highest risk within a system's reach (e.g. use of hospitalization data for referral patterns or alcohol sales pattern in resource poor countries), and electronic medical records in resource rich countries for implementing screening. There has been some success at identifying cirrhosis patients in an electronic medical record for population health management using natural language processing or algorithm based identification of target population (48).

2. Linkage to treatment: Critical to improving care for ALD patients is "knowledge extension". Expanding the expertise of providers without having more providers will require digital solutions. Appropriate referral pathways tailored to regional and local characteristics are important for efficient and appropriate use of existing provider networks (49). For large health care systems, this may include development of networks of outreach clinics, with some areas able to implement integrated multidisciplinary ALD clinics incorporating both mental health and hepatology providers in caring for more advanced ALD patients (50). The establishment of acute liver services in district general hospitals linked with regional specialist centers for more complex investigations and treatment has been implemented successfully in the United Kingdom (51). Moreover, even advanced care (such as upper GI endoscopy, elastography or imaging) can be brought to the high-risk regions by coordinated outreach activities. For example, in India, the Rural Health Care Project, a network of modified buses with self-sufficient water and electric supply serve as mobile hospitals with diagnostic capabilities (in-person visits, testing, and procedures) and telemedicine capacities to provide free local healthcare to underserved populations (52). Other options are the implementation of provider-to-provider teleconsultation models, which allow access to specialist evaluation or co-management with other trained providers in the community. The Extension for Community Healthcare Outcomes (ECHO) model has been successfully used for substance use treatment as well as liver disease care (53, 54). Use of non-specialist informal health worker extenders in the community has also met with success (55).

3**. Innovative clinics:** At the clinic level, cross training gastroenterology and hepatology to provide substance abuse care, primary care to assist with risk stratification of ALD and AUD, combined with telemedicine to deliver care across a wide geographic area and interface with networks of multidisciplinary providers may help extend the reach of ALD care through efficient use of existing resources (56). Dedicated multidisciplinary clinics may help to treat ALD and AUD given that integrated therapy with cognitive behavioral therapy and medical care increases abstinence (57). In the future, digital interventions via smartphone for reducing hazardous and harmful alcohol consumption, alcohol-related problems, or both, for people living in the community may be helpful

(58). Slips and relapses to alcohol use occur outside of clinic and, as such, the time for intervention prior to these events frequently goes unnoticed. Mobile health interventions, particularly if they have a component of "just-in-time" access to alcohol use interventions during times of crisis, may be well-suited to this population. Though not developed specifically for ALD patients, there are many proprietary web and smartphone applications that assist in alcohol use treatment and recovery and have an evidence base to support their effectiveness which could be applied to ALD patients with AUD (59).

Deliver targeted interventions: A Blueprint for Individualized Patient-level Care

Treatment of ALD: Recent guidelines (35, 60, 61) provide further recommendations for clinical management and will not be reviewed here.

***Treatment of AUD*:** Access to robust mental health care remains low for substance use disorders (11%) and AUD treatment (10%), with only 0.4% receiving any Food and Drug Administration (FDA) approved relapse prevention medication (62, 63). Barriers vary from attitudinal barriers (not feeling like they need treatment), to logistical barriers (lack of insurance coverage, distance from available AUD treatment) to concerns about anonymity and dislike of available AUD treatment modalities (64). AUD treatment is effective and reduces the risk of hepatic decompensation by 15% (63). Where possible, hepatologists should liaise with their local mental health and substance use providers to develop multidisciplinary clinics to treat advanced ALD patients, many of whom have moderate to severe AUD and comorbid mental health and substance use disorders. Integrated care, with mental health providers in the clinic, produced improved rates of alcohol abstinence, with cognitive behavior therapy and motivational enhancement therapy modalities providing benefit (57). Motivational interviewing is an evidence-based approach to assist ambivalent patients in moving towards changing unhealthy habits (65). Targeted, liver-focused feedback, where alcohol use and cessation is linked directly to changes in liver function and risk of developing worsening liver disease can help patients decrease alcohol use in a primary care setting (20). Though Alcoholics Anonymous is a popular, free, and easily accessible means of support for alcohol cessation, many ALD patients dislike this modality (64). Clinic assessments of alcohol

treatment preference, such as for group therapies versus one-on-one treatment, longer or shorter duration of treatment, or involvement of family members, may help give patients more agency in their choice of alcohol treatment and improve the likelihood of attendance. Treatment locators, such as the NIAAA Treatment navigator (https://alcoholtreatment.niaaa.nih.gov) and the SAMHSA Treatment Locator (www.findtreatment.samhsa.gov), can help patients and clinicians educate themselves about treatment options and find nearby substance use treatment resources. Likewise, regional resources need to be identified and highlighted in a synchronized manner. The use of relapse prevention medications is recommended by society guidelines (61, 66).

Conclusion and future directions

Future needs include the following:

1. **Improving quality of ALD data and standardizing care:** Certain countries may have low rates of reporting potentially related to social stigma, low availability and quality of data, and poorly standardized definitions and diagnostic criteria. Standard drink sizes and recommendations differ worldwide from 8 grams of alcohol (United Kingdom), to 14 grams (United States), to 20 grams (Japan). A concerted effort is needed across regions to standardize definitions of alcohol use and alcohol content to facilitate generalizability of interventions and ease international research in alcohol use and ALD. As an example, consensus on a certain amount that constitutes a standard drink (e.g.10 grams) as well as labeling of beverages with the number of standard drinks may be helpful.
2. **Standardizing nomenclature as well as definitions:** Uniform nomenclature should be utilized by professional societies for alcohol associated liver disease and alcohol use disorder. Definitions proposed by NIAAA and DSM V may be potential starting points.
3. **Supporting innovative healthcare delivery platforms that can treat both ALD and AUD.** At the present time, much of the focus is on *boots on the ground* interventions from impassioned mission-oriented physicians and other health care providers who decide to participate and contribute to care in these regions. There needs to be concerted effort to cross train local providers and non-medical

extenders. In the future, populations lacking access to care may benefit from interventions which incorporate digital technologies that allow biomonitoring and connected care.

4. **Advancing Implementation of digital Interventions**: Workforce limitations exist for both liver and substance use providers, and these limitations in numbers are unlikely to change rapidly. Implementing digital interventions to increase screening in healthcare systems, linkage to alcohol use and hepatology care (through e-consultations, ECHO-like models, remote monitoring), collating community resources for mental health and addiction services and digital interventions to decrease alcohol use are critical to improving care for ALD patients.
5. **Stronger advocacy by liver societies:** There remains a disparity between burden of liver disease attributed to alcohol and the relative research attention focused on ALD.(67) Engagement and a stronger position taken by hepatology professional societies to eradicate infectious liver diseases such as Hepatitis C and Hepatitis B, including vaccination strategies, screening for infection and treatment has led to several benefits. It will be critical to begin to adapt some of the infrastructures used for these initiatives towards global alcohol consumption, although the tactics will vary given the distinctively different nature of alcohol as a precipitant of liver disease compared to viral etiologies. In this regard, the World Health Organization, non-governmental organizations and societies have provided varying levels of engagement for the global problem. Endorsement of the WHO global “best buys” for effective interventions may foster further collaboration (30). In addition, a joint curriculum endorsed by liver, psychiatry and addiction medicine professional societies would be helpful. . In addition, comparative research on cost effectiveness of various screening methods in diverse populations is needed.

Given the increasing burden of ALD and AUD worldwide, strategies to screen and provide care must be implemented at multiple levels and will require robust communication and coordination at all levels. With efficient, smart targeting of tailored

local solutions and broader adoption of society-level solutions through improved alcohol policies, the tide of ALD and AUD may begin to turn.

FIGURES

Figure 1: Global burden of alcohol associated liver disease.

Figure 2: Screening and risk stratification for alcohol associated liver disease

*Daily and weekly doses within recommended standards of the National Institute of Alcohol Abuse and Alcoholism [NIAAA]: ≤4 drinks per day for men; ≤3 drinks per day for women; and ≤14 drinks per week for men; and ≤7 drinks per week for women.

§AUDIT-c (a shorter version of AUDIT) is considered positive screening with a result ≥3 for women and ≥4 for men.

∂High risk clinical features: aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio >2, elevated GGT, thrombocytopenia, jaundice, stigmas of advanced liver disease.

Figure 3: Treatment paradigm for alcohol associated liver disease and alcohol use disorder

Figure 4: Suggested strategies to mitigate impact of alcohol associated liver disease at the global, local/regional and individual level

Supplemental Figure 1: Representative figure for screening and stratification for alcohol associated liver disease in the United States

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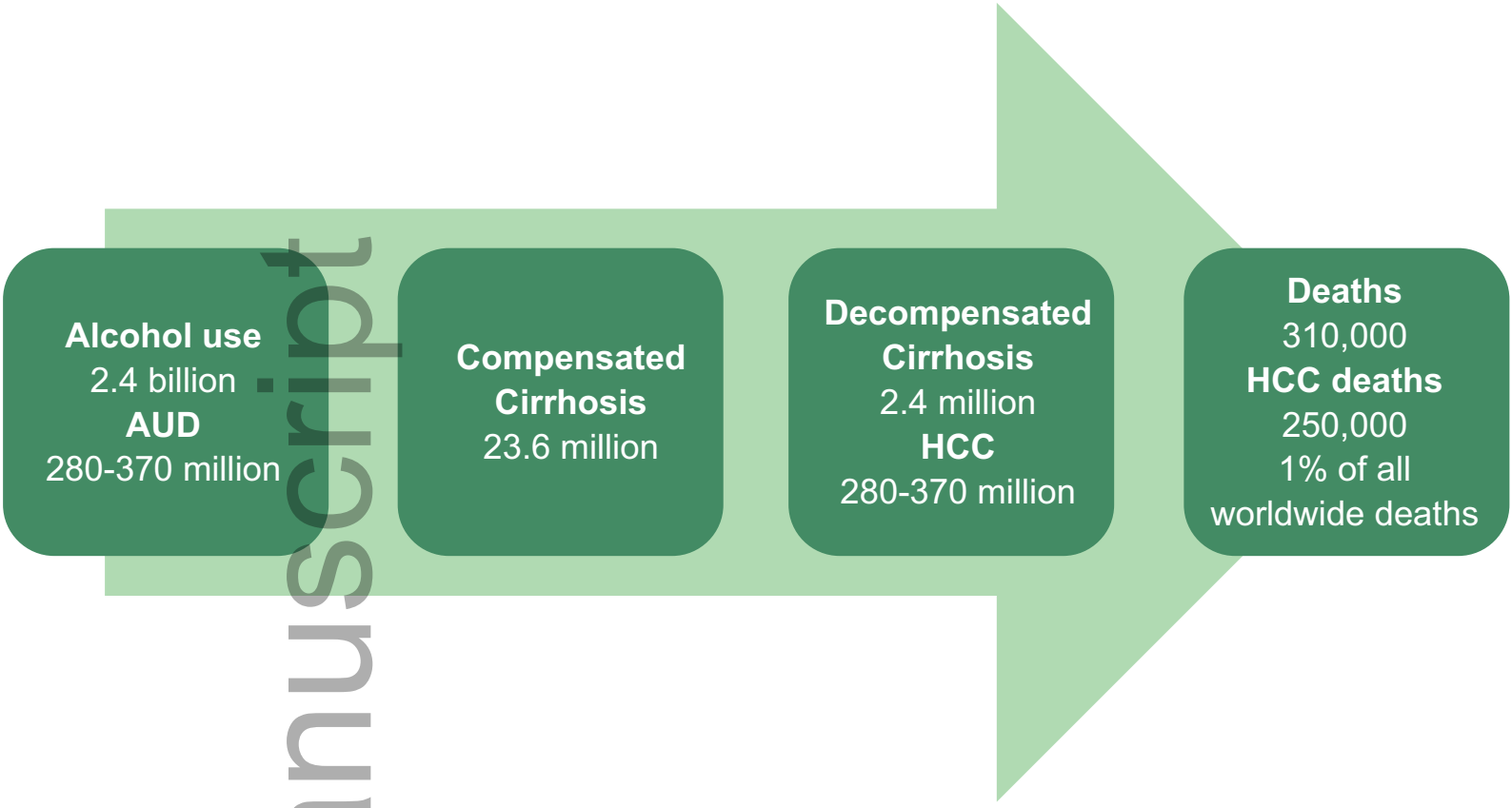

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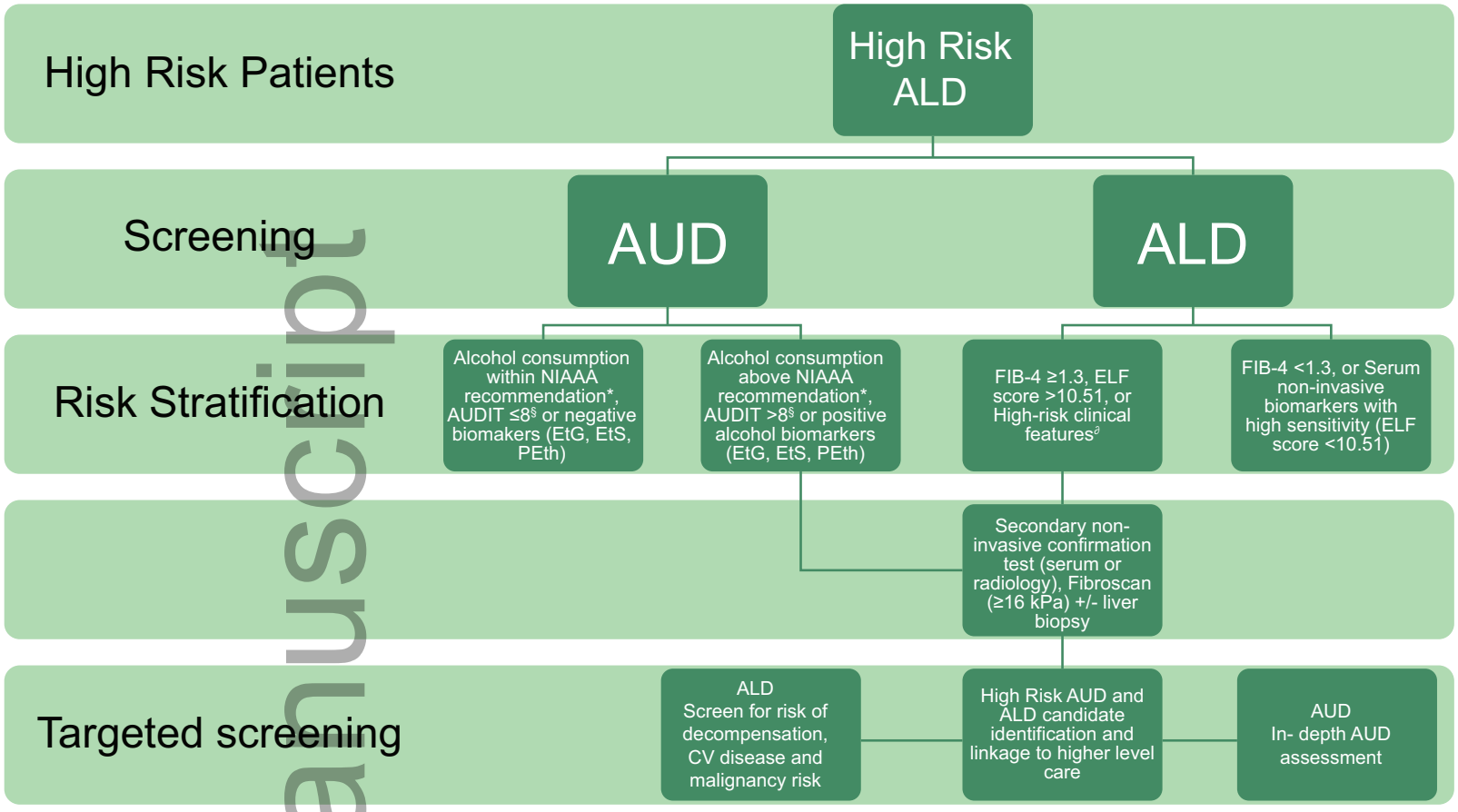

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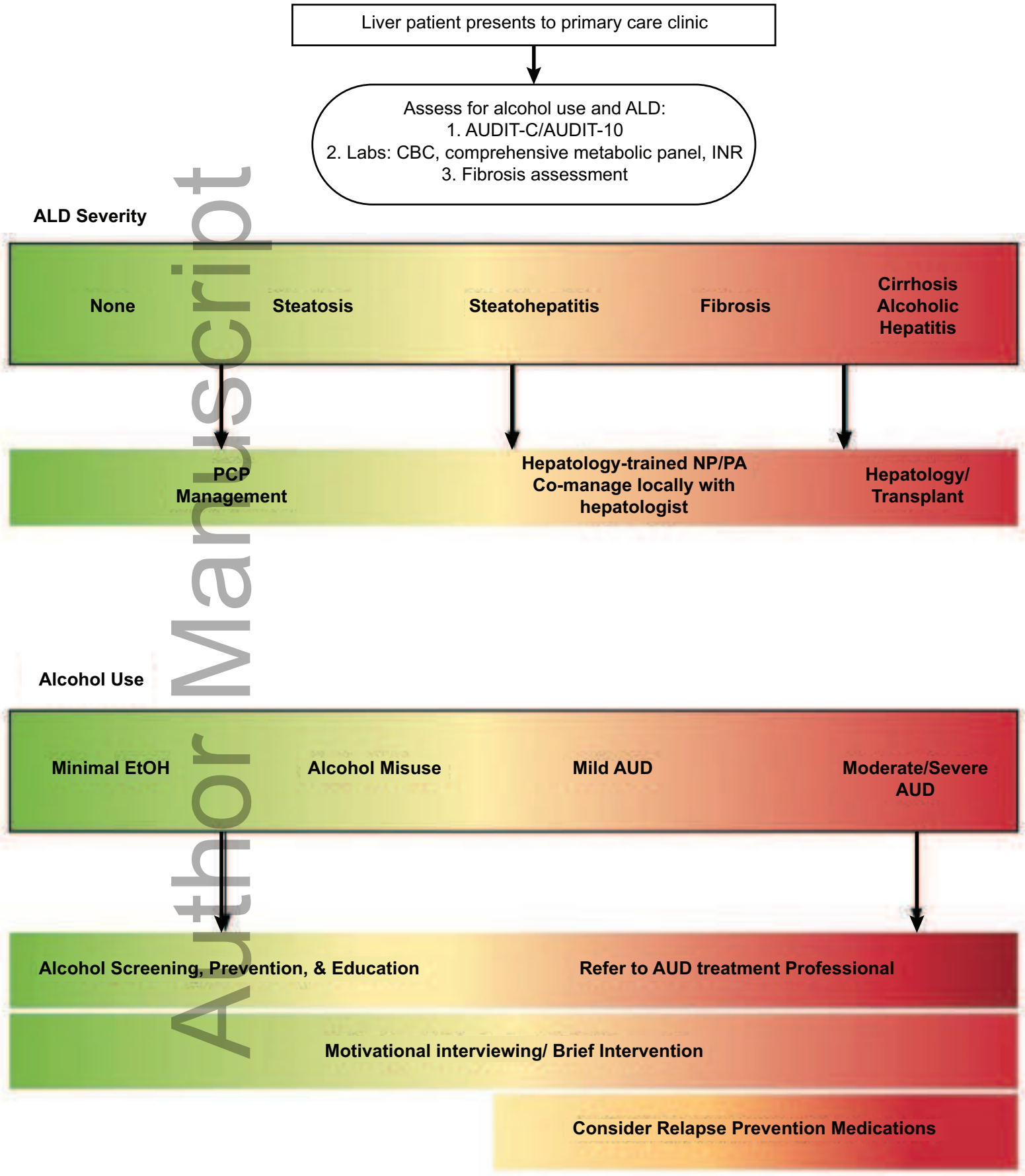

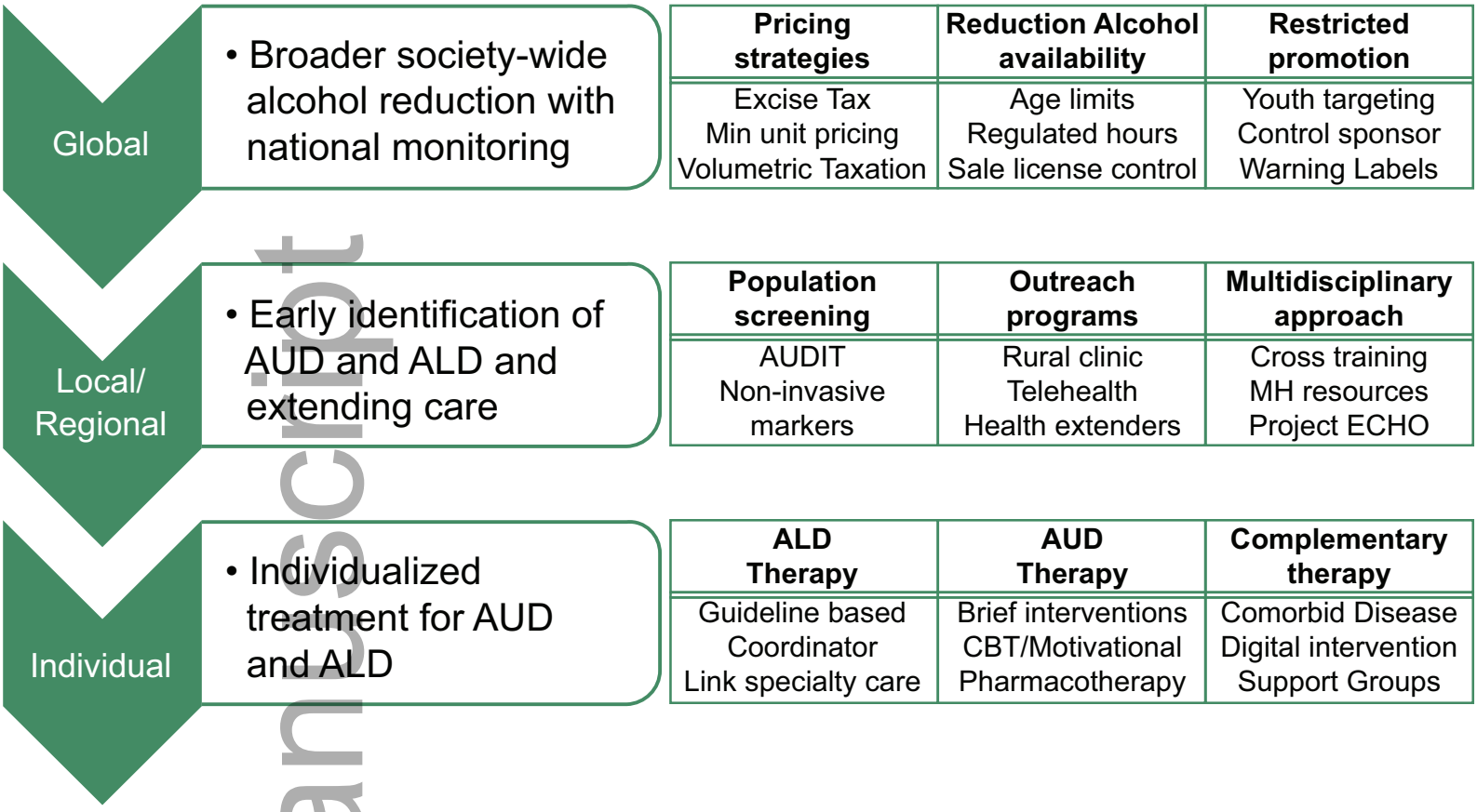

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