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Psychosocial and Ethical Considerations in Patient Selection for Liver Transplantation

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Psychosocial and ethical considerations are common in liver transplantation (LT) and typically involve matters of psychiatric disease, substance use disorders, and social support. These are pertinent matters before, around, and after surgery given their impact on organ allocation decision-making and patient outcomes. Psychosocial issues are accompanied by substantial uncertainty, controversy, and stigma. Despite their importance and ambiguity, there is little consensus to guide practice, magnifying the importance of existing primary literature and the need for future research.

INTERPROFESSIONAL TEAMWORK

Multidisciplinary collaboration in LT is foundational to understanding the various topics below and applying them to clinical work. Such collaboration appears in numerous consensus guidelines(1-5) which requires interprofessional teamwork, an underemphasized and already-challenging matter in LT given its large teams comprised of numerous specialties and training backgrounds. Psychosocial specialties within LT include psychiatry, social work, psychology, addiction medicine, and ethicists who may be embedded into or otherwise affiliated with LT teams. Their roles can be unique (i.e. psychopharmacology recommendations from physicians in psychiatry and/or addiction medicine) as well as redundant (i.e. impressions of a patient's transplant understanding and readiness evaluated by all specialties).

Like hand hygiene's impact on bedside care, teamwork quality greatly facilitates or obstructs LT psychosocial evaluations and follow-up. Barriers to adequate LT teamwork include clinician stress, weak relationships and poor trust, disparate professional cultures and tribalism, traditional medical hierarchies, bias and strong emotion, and the subjectivity of psychosocial data(6). General practices which promote LT teamwork include optimizing clinician wellness, relationship building initiatives, conflict resolution, workspace orientation adjustment, role definition and division of labor, team communication optimization, and psychosocial data management strategies(6).

DECISION-MAKING PROCEDURES & CLINICIAN RATING SCALES

LT selection committee proceedings vary in structure despite their preserved primary function of building informal consensus on treatment recommendations via orderly patient case review and discussion(7). Psychosocial factors are prominent in LT selection conferences in terms of time spent reviewing them (i.e. over several meetings) and discussions' emotional tone and intensity. Psychosocial issues are among the most difficult topics addressed by selection committees(7) and policies regarding the matters discussed below vary widely across centers(8). Psychosocial clinicians who collaboratively collate data, vet cases, and polish their recommendations outside of selection conferences may better facilitate a LT team's ensuing decision-making and transparent policy-making around such challenging and sensitive matters(6).

Transplant clinician rating scales like the Stanford Integrated Psychosocial Assessment for Transplant(9) can be useful tools to standardize psychosocial evaluations which must address a wide and diverse array of parameters (see below), ensure evaluations include adequate breadth and depth in relevant domains, and condense overall patient psychosocial risk profiles into a score. Additional assessment using validated psychometric questionnaires querying depression, anxiety, sleep, and substance use, for example, may further expedite clinicians' understanding of patients' mental health. Validated scales, however, may offer false security that numerical scores are "more objective" than narrative summaries. Psychosocial evaluations remain highly subjective however they are carried out and reported. Subjectivity obliges teams to iteratively optimize team workflows, communication, and collaboration.

ETHICAL CONSIDERATIONS

Key ethical principles applicable elsewhere in LT (consent, justice, non-maleficence, utility, autonomy, beneficence) also pertain to psychosocial topics. Patient consent and decision-making capacity should be assessed according to established principles(10) and does not necessarily require psychiatric consultation. Individual patient beneficence in LT must always be balanced with justice to society and other listed patients. Justice demands that organs be allocated 1) to the sickest patients, 2) to those whose post-LT outcomes are acceptable, and 3) equitably regardless of diagnosis or disease(11). Teams must guard against psychosocial matters or certain behaviors being unfairly scrutinized (i.e. alcohol consumption judged more harshly than poor diet choices)(11). Simultaneously, teams are obligated to rule-out patients whose psychology, behaviors, or social condition will worsen treatment adherence and transplant outcomes. In living liver donation (LLD; see below), the autonomy of both donor and recipient must be carefully and independently assessed. Teams must assure preserved donor non-maleficence and recipient beneficence. Assigning separate advocates for donor and recipient facilitate these analyses.

PATIENT READINESS AND ILLNESS MANAGEMENT

A patient's history of and capacity for medical adherence are main components of LT psychosocial evaluations (Figure 1). Numerous risk factors, warning signs, and measurement strategies exist for detecting immunosuppressive regimen nonadherence (Figure 2). Several possible interventions are recommended including counseling and psychotherapy (inpatient training, adherence reminders, medication schedules, family involvement, support groups, behavioral change strategies); educational and cognitive (printed instructions, individual teaching, literacy level appropriate information, monitored mental status); and medical (simplified regimens, long-acting preparations, pill boxes, contingency planning) approaches(12). Nonadherence should be a regular part of each clinical encounter and open, neutral, and respectful communication should be used

with patients and families(12). Reassessment of progress should occur regularly using a flexible approach to plan adjustment as needed(12).

SOCIAL SUPPORT

Assessment of social support is a main component of the psychosocial evaluation (Figure 1). Poor social support is deemed a risk factor for patient nonadherence(12). Sober support persons are recommended for early LT in acute alcohol-associated hepatitis (AAH) and are an intrinsic aspect of AUD treatment; their absence may be a relapse risk factor(1, 11).

PSYCHOLOGICAL STABILITY AND PSYCHOPATHOLOGY

This concise review does not permit broad exploration of the spectrum of psychiatric pathology relevant to LT. Specific consensus guidelines and data are absent or sparse for most disorders apart from allusions to their general importance(1). Clinicians should prioritize screening, referral, and treatment of psychiatric disorders pre- and post-LT(1) given the potential negative impact of general psychiatric conditions on outcomes (i.e. increasing or persisting depression doubles post-LT all-cause mortality)(13).

Various psychotherapeutic paradigms should be considered in affected liver patients though few have been rigorously tested(14). Medications for psychiatric and addictive disorders can be safely used in liver disease and LT though many require dosing adjustments for hepatic and renal insufficiency; careful risk-benefit analyses are best done in multidisciplinary fashion. For patients with active and/or risky psychiatric disorders, teams may require treatment engagement and some level of clinical improvement before moving forward with LT listing.

SUBSTANCE USE

Alcohol

Alcohol-related cirrhosis mortality has increased alarmingly including in young people aged 25-34 years(15). Alcohol is the leading indication for LT in the United States(16) and alcohol use disorder (AUD), a chronic and relapsing condition comorbid with ALD, should be treated and carefully monitored during pre- and post-LT care(11). Destigmatizing ALD and its terminology is a priority, which has resulted in a shift to the use of “alcohol-related liver disease” or “alcohol-associated liver disease” over the more outdated term “alcoholic liver disease”(1, 11). Alcohol abstinence is the ultimate treatment goal in ALD(1, 2) given the substantial mortality and decompensation risks of ongoing drinking(17).

Alcohol screening, referral for treatment, and follow-up interventions across the care continuum, including formation of dedicated and/or embedded multidisciplinary alcohol care teams, are recommended(1, 2). Several AUD screening methods can be employed: validated questionnaires (i.e. Alcohol Use Disorders Inventory Test), Timeline Follow-back methodology, and electronic apps(1, 2) though fewer programs regularly use them(8). In addition to use of AUD screening questionnaires, alcohol exposure should be queried at intervals before and after LT using biomarkers (Table 1) which have varying detection windows, advantages, and disadvantages(1, 2, 11). Pharmacological treatment (i.e. acamprosate, baclofen) should be considered as part of AUD treatment(1, 2) alongside various psychotherapy paradigms(14).

Inflexible periods of abstinence (i.e. "6-month rules") are not recommended to determine LT eligibility(1, 2, 11). Instead, eligibility decisions require careful patient and collateral interviewing across multiple psychosocial domains (Table 2). The subjective nature, nuance, and high variability of psychosocial data means that benchmarks, protocols, and/or numerical scores are insufficient alone to determine LT eligibility and must be accompanied by robust team collaboration, rigorous and nuanced case discussion, and multidisciplinary decision-making(1, 2).

Cannabinoids

Social, legal, and medical landscapes of cannabinoid use are rapidly evolving in the United States and LT policies are similarly heterogenous(8). Cannabinoid use is increasing in LT patients(18, 19) and there is no expert consensus regarding cannabinoid use in LT despite the numerous medical and psychosocial considerations of which clinicians must be aware including possible drug interactions with immunosuppressants(20). A minority of LT programs allow active marijuana use in their candidates(8). While cannabinoids have not been shown to consistently adversely affect LT outcomes(21), their use often coexists with substantial patient psychosocial complexity and risks.

Nicotine

Tobacco use is common in the LT population and should be routinely addressed in LT evaluations(1, 12). Tobacco users have elevated 5-year post-LT mortality rates when compared to never users(21) and yet LT programs have variable nicotine policies: some allow it, touting the need to improve LT access, while others prohibit it, citing adverse health outcomes. There is little consensus regarding tobacco use in LT and even less about electronic cigarette use.

Other Controlled Substances & Polysubstance Use

Many recreational substances are illicit and risky; their active use is often rightfully deemed an absolute contraindication to LT. Accordingly, there is comparatively much less data on any direct impact in LT by other drugs such as hallucinogens, cocaine and other stimulants, heroin, and synthetic designer drugs despite the prevalence of historical polysubstance use in liver patients. Use of other substances can associate with AUD relapses(22).

Prescribed controlled substances, however, opioids and benzodiazepines are representative examples, are common in liver patients and there is no consensus about their use. For instance, few programs maintain written opioid policies(23). A survey of LT programs found that less than half allow methadone use(8) despite high opioid use disorder (OUD) relapse risks without medication assisted treatment (MAT). Another survey found that few LT programs regard opioids as an absolute contraindication and many programs deemed chronic opioid regimens and MAT as relative contraindications (64% and 38%, respectively)(23). LT clinicians must scrutinize their patients' opioid use but MAT for OUD, methadone or buprenorphine, should be continued throughout the LT course; its empiric discontinuation, without adequate clinical or literature justification, is evidence of stigma and could provoke relapse to active OUD symptoms(24). While LT clinicians should assertively use benzodiazepines to treat severe alcohol withdrawal, they should be otherwise cautious about their use given risks of hepatic encephalopathy, physiological dependence, and misuse and addiction(1).

LIVING DONATION

Main objectives in the multidisciplinary evaluation of a living donor are assessment of decision-making capacity, motivation, social support, and psychological status, preferably completed by a donor advocate with transplant experience(3-5). Active psychosis or severe substance use disorders may represent firm psychological barriers while financial hardship or marital problems could be social obstacles(3). Donor psychosocial evaluations and interventions enhance LLD rather than restrict it, bringing the opportunity to more individuals including those with psychosocial challenges(3).

Mortality and adverse outcomes after LLD are rare and most donors fully return to their previous levels of physical and psychological function. Regular monitoring for 2 years post-donation is recommended and prompt referral to mental health specialists should occur when indicated(4, 5). Extra care should be taken in donors donating to patients in urgent need of LT, such as AAH(4, 11). In such cases, there may be unique donor psychological risks peri-operatively (coercion) or post-operatively (recipient alcohol relapse and/or graft loss)(11). Post-operative donor risks may be pronounced and undetected particularly if they occur after long-term donor follow-up concludes(11).

ACUTE PATIENT PRESENTATIONS

Psychosocial evaluations are particularly crucial during certain emergent LT evaluations such as suicide attempts via overdose (acetaminophen toxicity and other drug-induced liver injuries) and AAH. In such patients, much of the pathophysiology underlying the liver presentation is psychiatric and/or substance related. Teams may wish to prioritize psychosocial evaluations ahead of other medical and surgical LT workup to maximize quality and length of patient interviews given mental status changes in liver failure(11).

LT should be considered in carefully selected AAH patients(2). A seminal prospective study showed that highly selected AAH patients have similar outcomes as non-alcohol patients(25). Other largely retrospective studies show that AAH patients' survival rates in early LT are comparable to those performed for other indications(26). LT in AAH has increased in recent years and during COVID-19(27) driven by trends of increasing societal alcohol consumption.

Post-LT drinking rates in AAH patients are 25% at 1 year and 34% at 3 years for any alcohol use and 10% at 1 year and 17% at 3 years for sustained drinking; sustained drinking was defined as use for more than 100 days and was associated with increased mortality(26). The field continues to discover and debate how best to evaluate and follow-up on AAH patients pre- and post-LT (guidelines appear in Figure 3) but psychosocial expertise remains crucial in all phases of care(11). Transplant psychosocial assessments in AUD patients, particularly those with short sobriety periods, require unique attention to nuance across multiple clinical domains (Table 2) to make appropriate decisions about organ allocation.

KEY POINTS

1. AUD is highly prevalent in LT candidates and must be routinely screened for, evaluated and treated in multidisciplinary fashion, and monitored prospectively with toxicology.
2. Early LT should be considered in certain AAH patients who have low psychosocial risks as evaluated by multidisciplinary colleagues; AUD treatment and monitoring, including the use of alcohol biomarkers, should remain part of long-term post-LT management.
3. Substance use is common in LT patients and clinicians must understand and regularly screen for cannabinoids, tobacco and other nicotine products, and illicit drugs as part of routine care.
4. Psychiatric disorders are commonly encountered in LT patients and may negatively affect patient adherence and outcomes; multidisciplinary screening, evaluation, and treatment are optimal.
5. LT teams are ethically obligated to balance the beneficence of individual patients against societal justice and the beneficence of other listed patients; psychosocial matters should not be judged differently than other medical and surgical aspects of LT.

QUESTIONS

1. Which of the following medications should be considered as part of alcohol use disorder management in liver transplant patients?

A. Sertraline
B. Valproic acid
C. Acamprosate
D. Lorazepam
E. Risperidone

2. A 31-year-old patient with acute alcohol-associated hepatitis with a MELD score of 40 is transferred from an outside hospital for liver transplantation evaluation. The physician who accepted the transfer reports patient may have a history of major depression, suicide attempts, and marijuana use. What is the most appropriate next step?

A. Start escitalopram for major depression
B. Consult the ethics committee
C. Immediately decline the patient for transplant given the obvious contraindications
D. Prioritize bedside psychosocial interview ahead of possible mental status changes
E. Prescribe naltrexone for alcohol use disorder

3. A hepatologist is concerned that her 52-year-old patient with alcohol-related cirrhosis has relapsed to drinking based on missing appointments and changes in liver function tests. Which biomarker would give her the widest detection window to check for alcohol exposure?

A. Serum ethanol
B. Urinary ethyl sulfate
C. Urinary ethyl glucuronide
D. Serum phosphatidylethanol
E. Urinary cotinine

4. A hepatologist is concerned about recurrent bleeding in a 68-year-old patient listed for liver transplant who has a history of multiple suicide attempts, serial psychiatric hospitalizations, and severe major depressive disorder treated with sertraline. What is the most appropriate next step?

A. Carefully weigh the medical and psychiatric risks and benefits of antidepressant cessation and consider psychiatric consultation
B. Stop sertraline
C. Add mirtazapine to the antidepressant regimen
D. De-list the patient
E. Refer patient for cognitive behavioral therapy

5. A 47-year-old patient with alcohol use disorder and alcohol-related liver disease is listed for liver transplant and informs the hepatologist during a liver clinic visit that she is getting a divorce. What is the most appropriate next step?

A. Place the patient on hold
B. Refer patient for interpersonal psychotherapy
C. Facilitate a prompt visit with a psychosocial specialist
D. No immediate action is required
E. Send patient to lab for urine toxicology screening

Table 1 – Alcohol biomarkers for monitoring exposure(14)

Ethanol	Serum	12-24 hours	Easily obtained, testing widely available	Detects only very recent use
	Urine	12-24 hours	Easily obtained, testing widely available, slightly higher concentration than serum, bladder storage time may widen detection window	Detects only very recent use
	Breath	12-24 hours	Point-of-care, immediate results, approximates blood alcohol concentration	Detects only very recent use and requires a breathalyzer which clinics may not have
	Sweat	New technologies enable continuous monitoring	Some devices provide continuous estimates of blood alcohol concentrations	Newer technology for research and law enforcement which is less practical for clinical use
Ethyl glucuronide and ethyl sulfate	Urine	3-4 days	Wider detection window than ethanol, testing widely available	Incidental exposures can cause false positives
	Hair	90 days	Very wide detection window, assay can also detect presence of drugs	Poor detector of binge drinking, better for regular and chronic use; costly; requires specialty lab; requires large hair sample patients may wish to avoid
Phosphatidylethanol	Serum	Up to 4 weeks	Wide detection window, results not influenced by liver disease	Very low lab cutoff required to detect low level drinkers

*detection depends on amount consumed, time interval over which consumption occurred, and length of time between last use and assay performed

Table 2 - Key domains for liver transplant psychosocial evaluations in acute alcohol-associated hepatitis and other short-sobriety presentations of alcohol-related liver disease(11)

Alcohol use history	• Age of first use, duration and context of use, consumption patterns, periods of abstinence • AUD diagnostic criteria (DSM-5) • Cravings and urges to drink • Past sobriety attempts (voluntary, mandated) • Past AUD treatment (modality, results, experiences, preferences) • Alcohol-related insight: acceptance of the problem, commitment to treatment and sobriety • Changes in alcohol use in response to life stressors and assessment of modifiable behaviors and situations	• Younger age at drinking onset • >10 drinks per day at time of evaluation • Multiple unsuccessful rehabilitation attempts • History of alcohol-related legal problems • Shorter periods of pre-LT abstinence • Lack of alcohol insight • Denial of alcohol as a health problem • Deceptive behavior and/or lack of candor • Severe AUD per DSM-5
Other substance use history	• Age of first use, duration and context of use, consumption patterns, periods of abstinence • SUD diagnostic criteria (DSM-5) • Cravings and urges to use • Treatment history and insight (as above)	• Active, untreated polysubstance use • Comorbid tobacco/nicotine use
Mental health history	• History of psychiatric diagnoses • Past suicide attempts • History of any mental health treatment including hospitalizations • Response to mental health treatment	• Active, untreated mental health diagnoses • Recent suicide attempt
Treatment adherence history	• Past and current adherence to medical and mental health treatment • Ability to understand and adhere to transplant treatment plan	• History of extensive nonadherence to medical and/or mental health treatment
Social factors	• Sober support system	• Lack of sober support network • Only 1 sober support person

	• Number of support persons, relationship to patient, ability to dedicate time/resources to medical and mental health care	
Optimal assessment criteria	• Awake, alert patient (not comatose, altered, intubated), able to be directly interviewed • Psychosocial team to assess patient 1st to obtain unbiased evaluation of above factors • Consistent history and commitments verbalized by patient • Multiple assessments over time • Active involvement and sober support by family/caregivers • Corroboration of elicited history from patient collaterals	
AUD – alcohol use disorder; DSM – Diagnostic and Statistical Manual; SUD – substance use disorder		

Figure 1 – General domains and components of psychosocial assessment in liver transplantation(9)

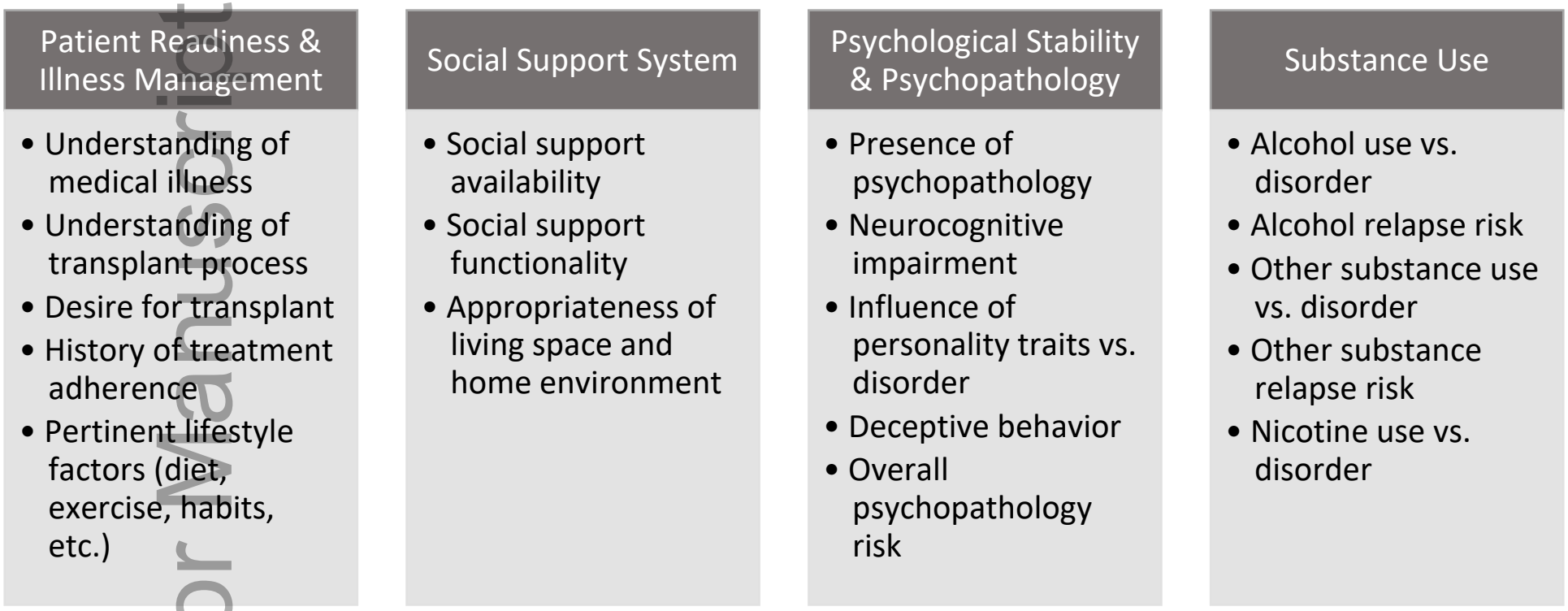


Figure 2 – Multilevel risk factors, warning signs, and measurement strategies for immunosuppressant regimen nonadherence(12)

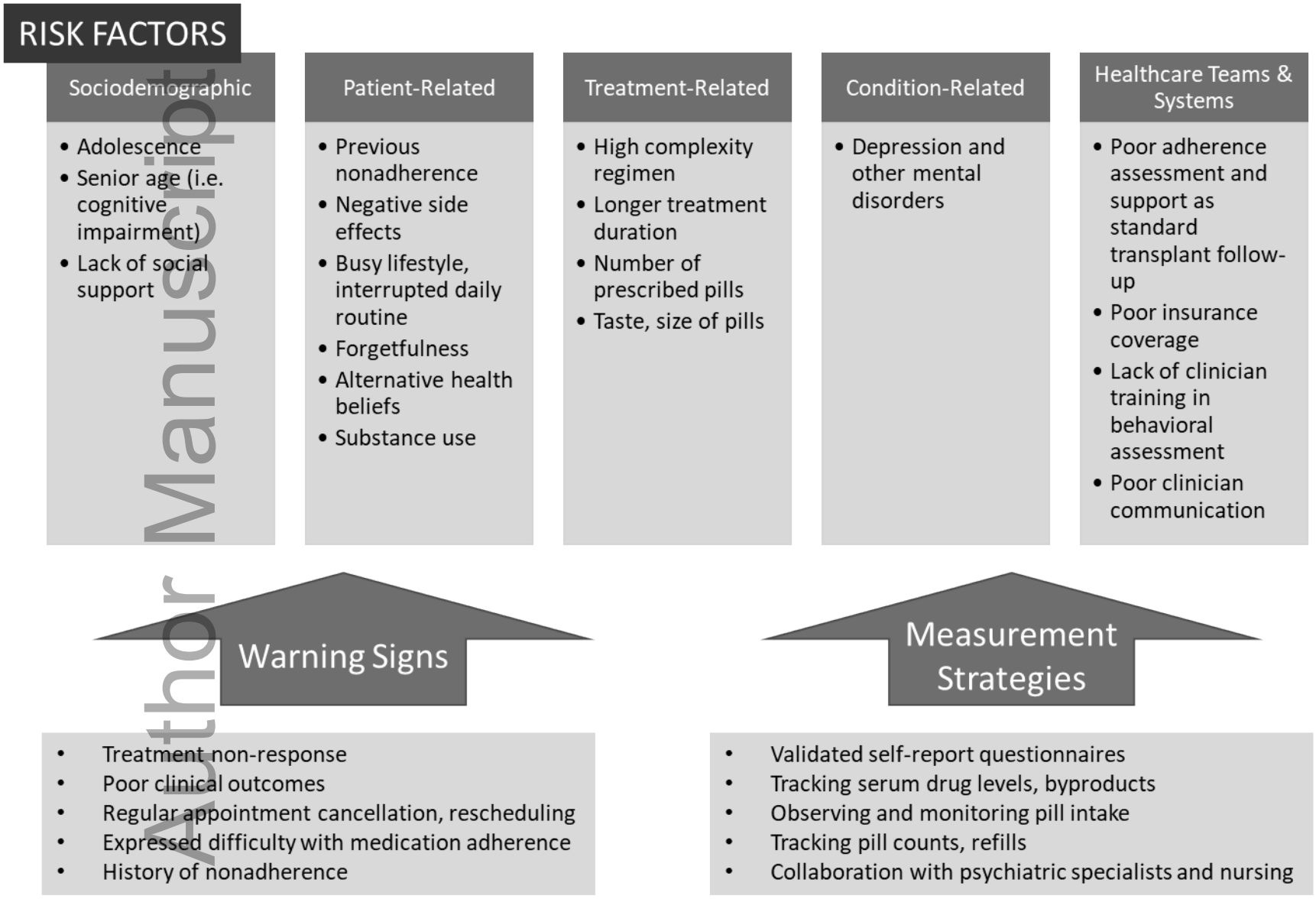
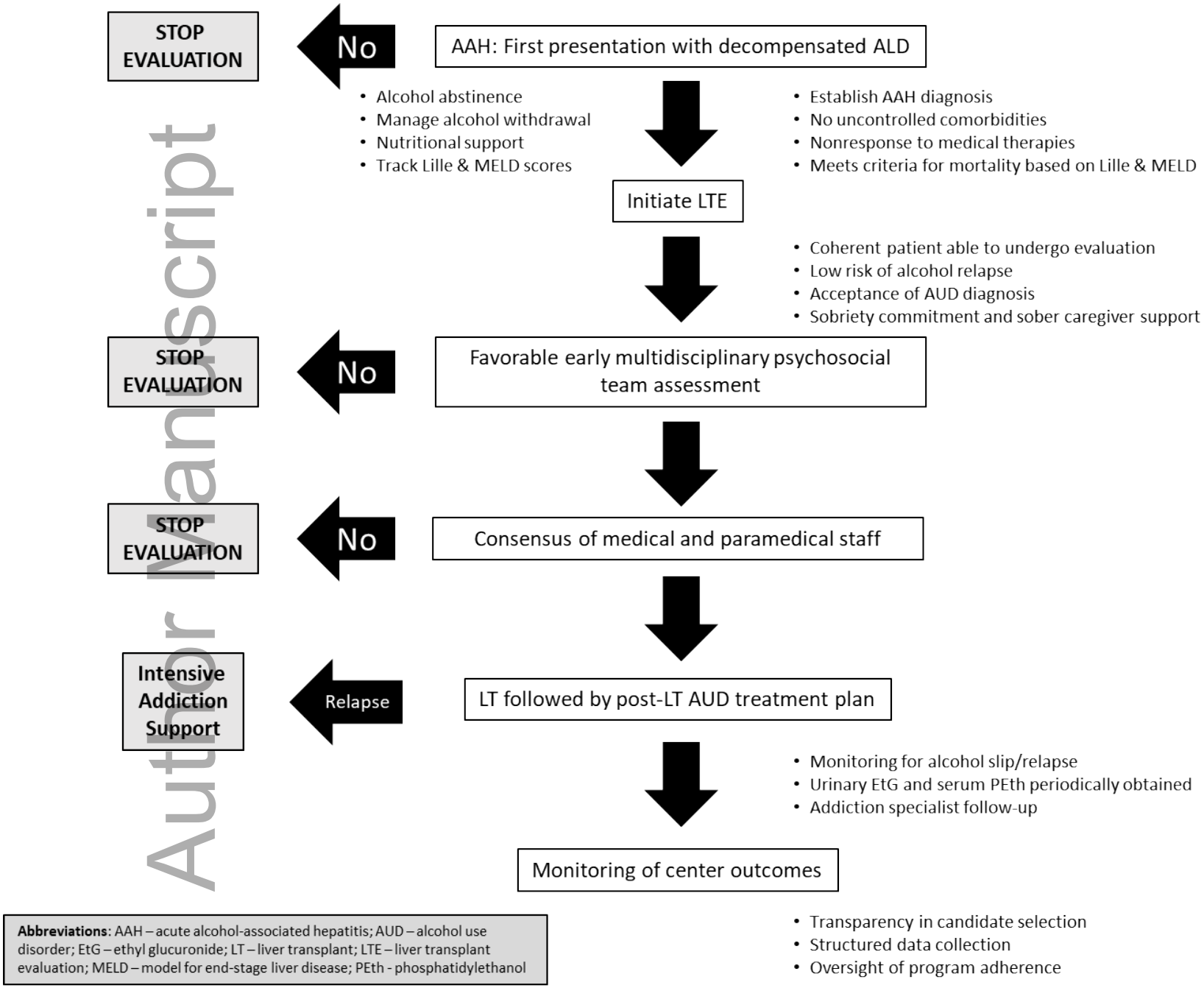


Figure 3 - Listing criteria and program processes and components for liver transplantation in acute alcohol-associated hepatitis(11)



Abbreviations: AAH – acute alcohol-associated hepatitis; AUD – alcohol use disorder; EtG – ethyl glucuronide; LT – liver transplant; LTE – liver transplant evaluation; MELD – model for end-stage liver disease; PEth - phosphatidylethanol

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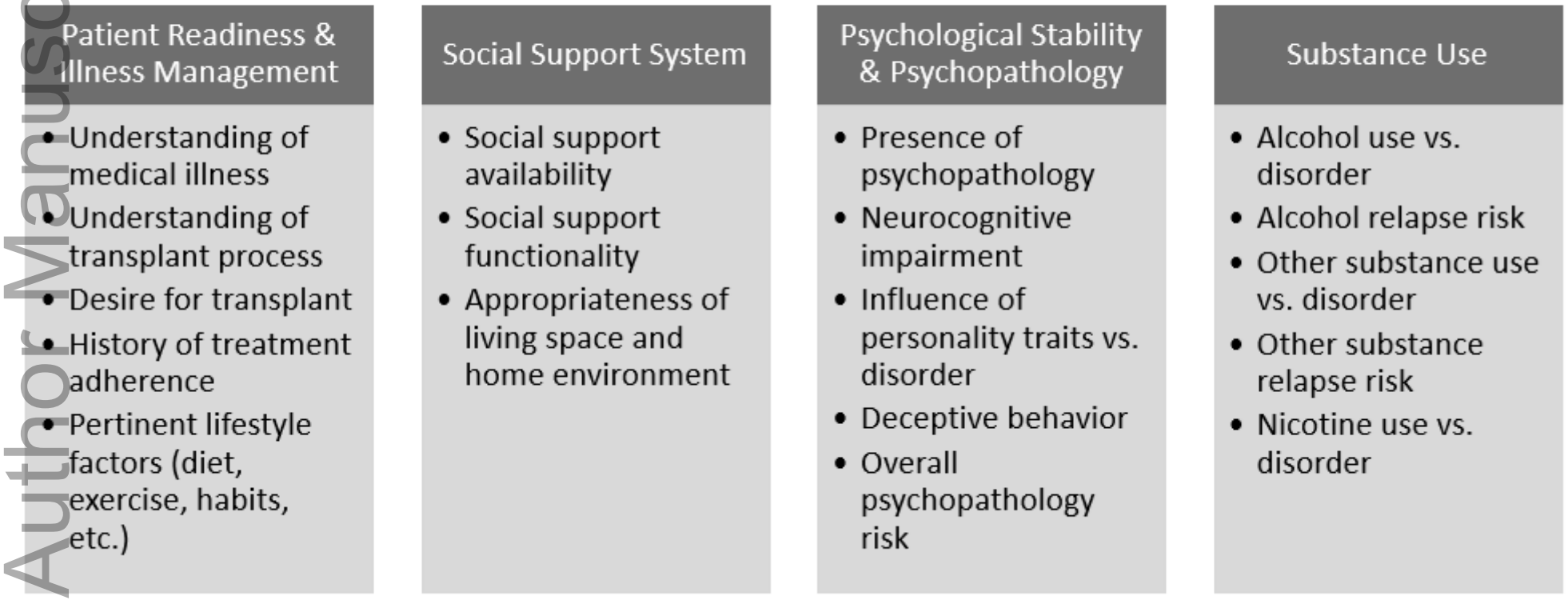
Figure 1 – General domains and components of psychosocial assessment in liver transplantation(9)



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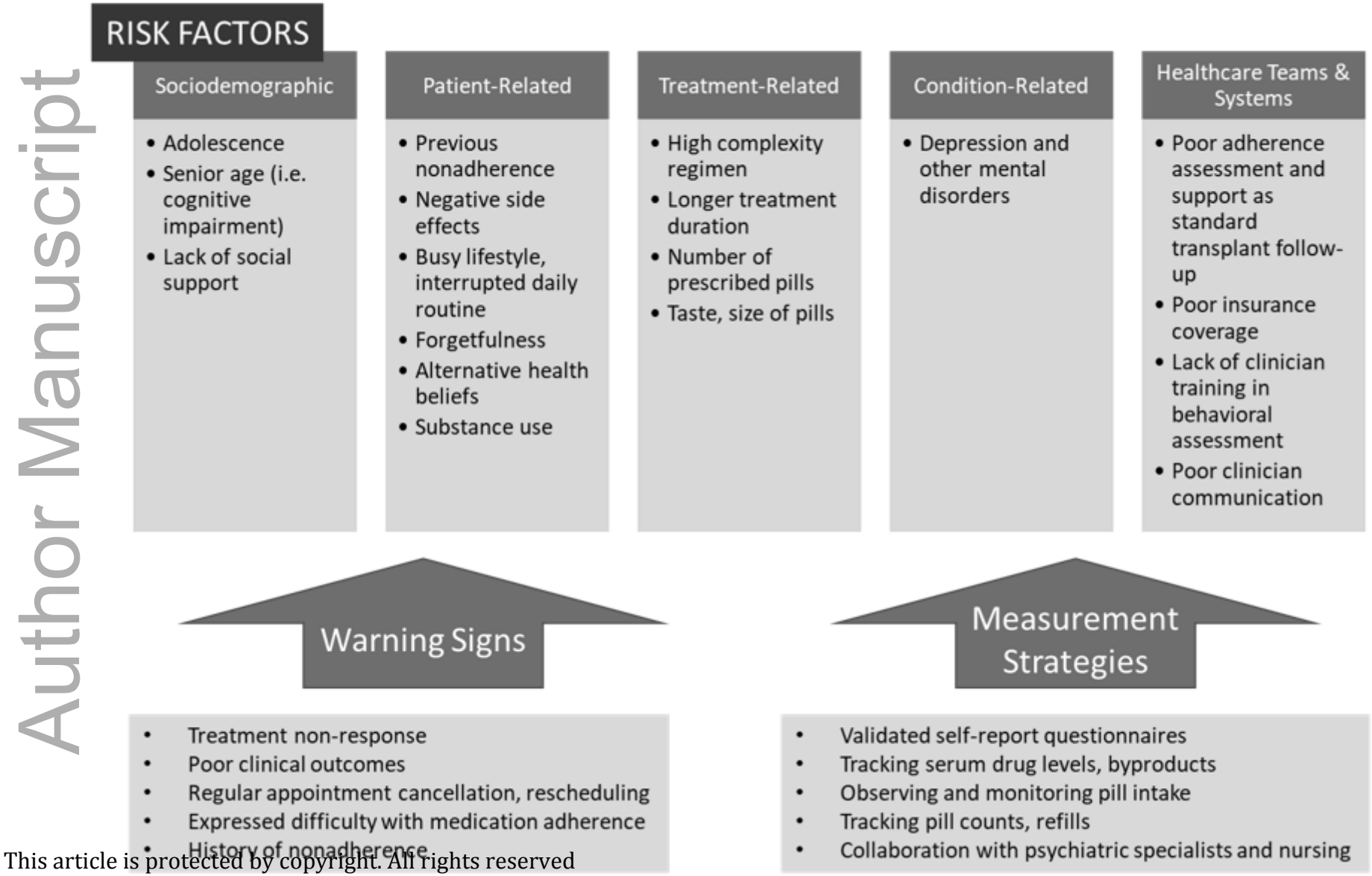

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Figure 3 - Listing criteria and program processes and components for liver transplantation in acute alcohol-associated hepatitis(11)