Journal of Hepatocellular Carcinoma

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Systemic Treatment for Unresectable Hepatocellular Carcinoma: A Surgeon's Perspective

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Abstract: In recent years, the standard treatment for hepatocellular carcinoma (HCC) has changed dramatically due to the emergence of potent systemic treatment options. These advanced therapies have led to increased survival benefits for patients with advanced or intermediate-stage HCC. Advancements in HCC treatments also offer the possibility of conversion therapy for initially unresectable HCC. However, the treatment of HCC is becoming increasingly complex, due to the expanding availability of systemic therapies, their use in combination with locoregional therapies, and their perioperative applications. Patient characteristics such as liver function, esophageal and gastric variceal status, and treatment goal (downstaging resection or long-term maintenance treatment), are the most critical factors when selecting a systemic treatment strategy. Consequently, the necessity to tailor a personalized and comprehensive treatment strategy for individual patients is growing. This review briefly summarizes the current systemic treatment regimens for HCC from a surgeon's perspective. It is based on results from clinical studies as well as personal experience and introduces the concept of a patient-centered, treatment goals-driven, individualized systemic treatment strategy for managing HCC.
Keywords: hepatocellular carcinoma, systemic therapy, targeted therapy, immune-checkpoint inhibitor, conversion therapy, patient-centered

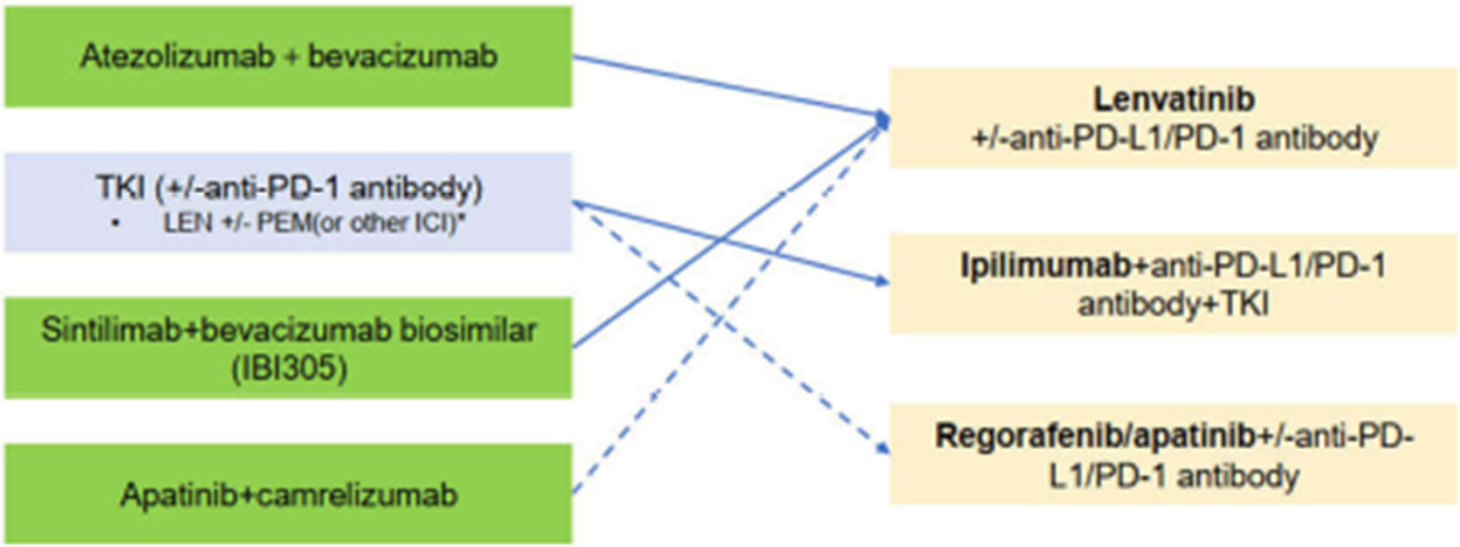

Figure 1 Algorithm for patient-centered, individualized systemic treatment strategy for patients with potentially resectable HCC in China.

Notes: The flow chart diagram is for discussion only and is not for a medication recommendation. *The combination is not approved as a first-line systemic treatment for hepatocellular carcinoma in China. Lenvatinib monotherapy and lenvatinib-based combination treatments have relatively high ORRs and DCRs, and comparatively low PD rates. As a result, lenvatinib monotherapy or used in combination with other drugs is a widely used treatment option for patients in clinical practice in China. Solid lines represent second-line treatment recommendations with greater certainty; dotted lines represent those with less certainty.

Abbreviations: ICI, immune checkpoint inhibitors; TKI, tyrosine kinase inhibitor; PD-1, programmed death-1; PD-L1, Programmed cell death ligand 1; LEN, lenvatinib; PEM, pembrolizumab. ORR, objective response rate; DCR, disease control rate; PD, progressive disease.

Discussion And Conclusions

In this perspective, we propose the incorporation of a novel concept into HCC treatment, that is, the theory of a patient-centered, treatment goals-driven, individualized systemic treatment strategy, illustrated by the treatment algorithms in Figure 1. The selection of an appropriate second-line treatment regimen following the failure of targeted therapy in combination with immunotherapy is a subject that requires further investigation. Unfortunately, the wide range of first-line treatment options complicates the exploration and decision-making process for subsequent second-line treatments. Furthermore, it remains unclear whether persisting with immunotherapy following the failure of combined treatment involving targeted therapy and immunotherapy is advantageous.

Finally, sub-classifying HCC according to its molecular and histological subtype may also facilitate the individualized management of patients with advanced HCC.[6,10] Additionally, research on emerging treatment targets such as T cell

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REVIEW OPEN ACCESS

Advancements in Diagnostics and Therapeutics for Cancer of Unknown Primary in the Era of Precision Medicine

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ABSTRACT

Cancer of unknown primary (CUP), a set of histologically confirmed metastases that cannot be identified or traced back to its primary despite comprehensive investigations, accounts for 2–5% of all malignancies. CUP is the fourth leading cause of cancer-related deaths worldwide, with a median overall survival (OS) of 3–16 months. CUP has long been challenging to diagnose principally due to the occult properties of primary site. In the current era of molecular diagnostics, advancements in methodologies based on cytology, histology, gene expression profiling (GEP), and genomic and epigenomic analysis have greatly improved the diagnostic accuracy of CUP, surpassing 90%. Our center conducted the world's first phase III trial and demonstrated improved progression-free survival and favorable OS by GEP-guided site-specific treatment of CUP, setting the foundation of site-specific treatment in first-line management for CUP. In this review, we detailed the epidemiology, etiology, pathogenesis, as well as the histologic, genetic, and clinical characteristics of CUP. We also provided an overview of the advancements in the diagnostics and therapeutics of CUP over the past 50 years. Moving forward, we propose optimizing diagnostic modalities and exploring further-line treatment regimens as two focus areas for future studies on CUP.

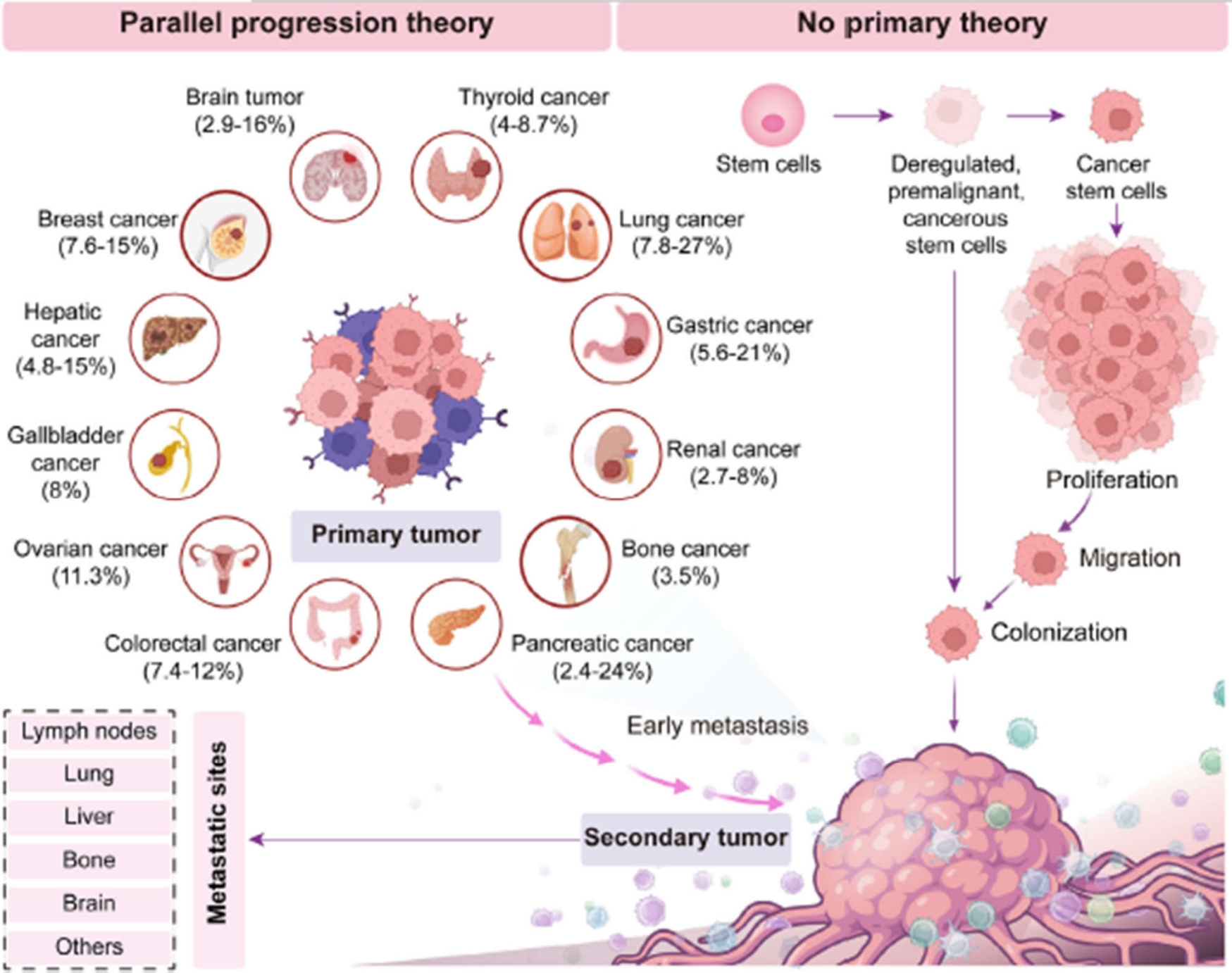

FIGURE 1 | The underlying mechanisms involved in the carcinogenesis and progression of CUP. In the first scenario, the "no primary theory"

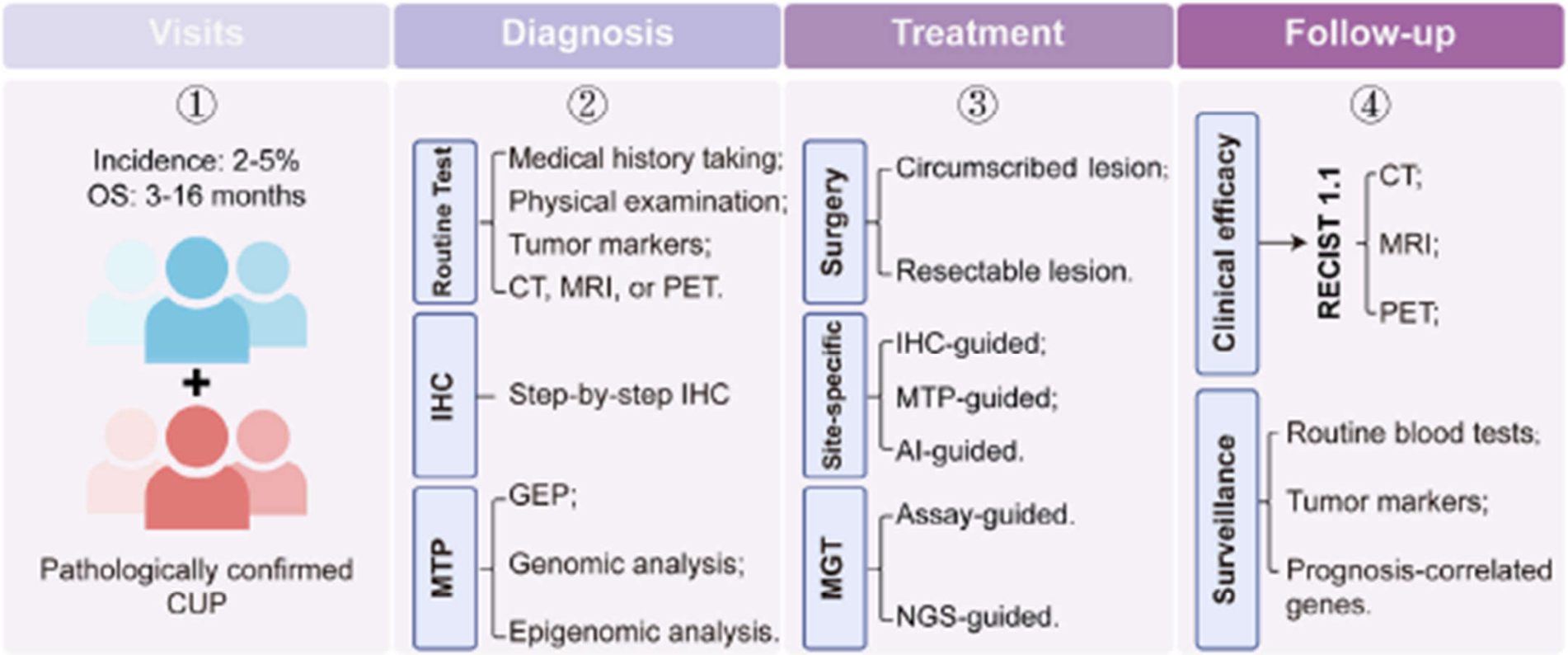

FIGURE 4 | Proposed workflow for the diagnosis and management of CUP. Patients present to the clinic for symptoms and signs of metastatic tumors. A precise diagnosis starts with a comprehensive approach, including routine tests like medical history, physical examination, blood tests, tumor marker detection, imaging examinations, and a step-by-step manner immunohistochemistry (IHC) staining. In certain cases, when deemed necessary, molecular tumor profiling (MTP) is recommended. After diagnosis, patients received surgery, site-specific treatment or MGT according to the clinical

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expected to provide strong evidence for second-line therapy in CUP.

In summary, we encounter both significant opportunities and challenges in the diagnosis and further-line treatment of CUP in the current era of precision medicine, and there is still much progress to be made in this field.

Incidental findings evident in 70% of lung screening exams, but few reported

The results of a new prospective study that included data from nearly 4,500 patients who underwent lung cancer screening suggest incidental findings have become increasingly common. Despite this, consensus is lacking on whether radiologists should be required to report on findings that are not relevant to the cancer screening itself.

In the United States, there is no official mandate for readers to report incidental findings in patients' radiology reports, though the American College of Radiology highly recommends it. Australia, however, will soon require rads to report several incidentals—pleural effusions, abdominal lesions, coronary artery calcifications and reduced bone density—under the country's new National Lung Cancer Screening Program set to begin in less than two months.

Under the mandate, radiologists will follow a structured template designed for LDCT exams, which will include a section where readers can notate the presence of the aforementioned findings. A driving factor behind the new

months.

Under the mandate, radiologists will follow a structured template designed for LDCT exams, which will include a section where readers can notate the presence of the aforementioned findings. A driving factor behind the new reporting requirement is the mounting evidence supporting the use of cancer screenings as opportunistic exams for identifying adverse health conditions.

“Incidental findings are a major consideration for lung cancer screening using LDCT. Unlike other cancer screening techniques, it can detect tissue changes other than lung cancer and pulmonary nodules,” Asha Bonney, with Royal Melbourne Hospital, and colleagues explained. “Some incidental findings could facilitate earlier detection of clinically significant changes, such as coronary artery calcification and cardiovascular disease, and vertebral fractures and osteoporosis.”

The authors pointed to previous work from the United States that suggested up

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Incidental findings during lung low-dose computed tomography cancer screening in Australia and

ARRS: Cancer status should be considered for axillary breast ultrasound

Amerigo Allegretto

Breast cancer status and exam indication should be factored into axillary ultrasound interpretation, according to research presented May 1 at the American Roentgen Ray Society (ARRS) annual meeting in San Diego, CA.

In his talk, Howard Yan, MD, from Stanford Health Care in California, discussed his team's findings, showing that about three out of every five axillary ultrasound exams are performed on women without breast cancer, with a low rate of lymph node metastases. The group also reported that clinical concern was the most common indication, while treatment planning was the least common one.

"The one-size-fits-all approach that's currently used in our setting, and I'm sure used in many other institutions, should really be called into

Recent reports suggest that breast cancer incidence rates are rising among women who are younger than the age ranges recommended for annual screening by medical societies. Younger women tend to be diagnosed at later stages with more aggressive cancers and are more likely to carry genetic mutations.

For women under 40 years of age, breast cancer screening is not considered or available. The American College of Radiology (ACR) does not recommend breast cancer screening for average-risk women under 40 years. But for high-risk women, it does recommend annual MRI surveillance starting from ages 25 to 30 and annual screening mammography for women ages 25 to 40 years depending on risk type.

JCI The Journal of Clinical Investigation

Glucagon-like peptide-1 receptor agonists, but not dipeptidyl peptidase-4 inhibitors, reduce alcohol intake

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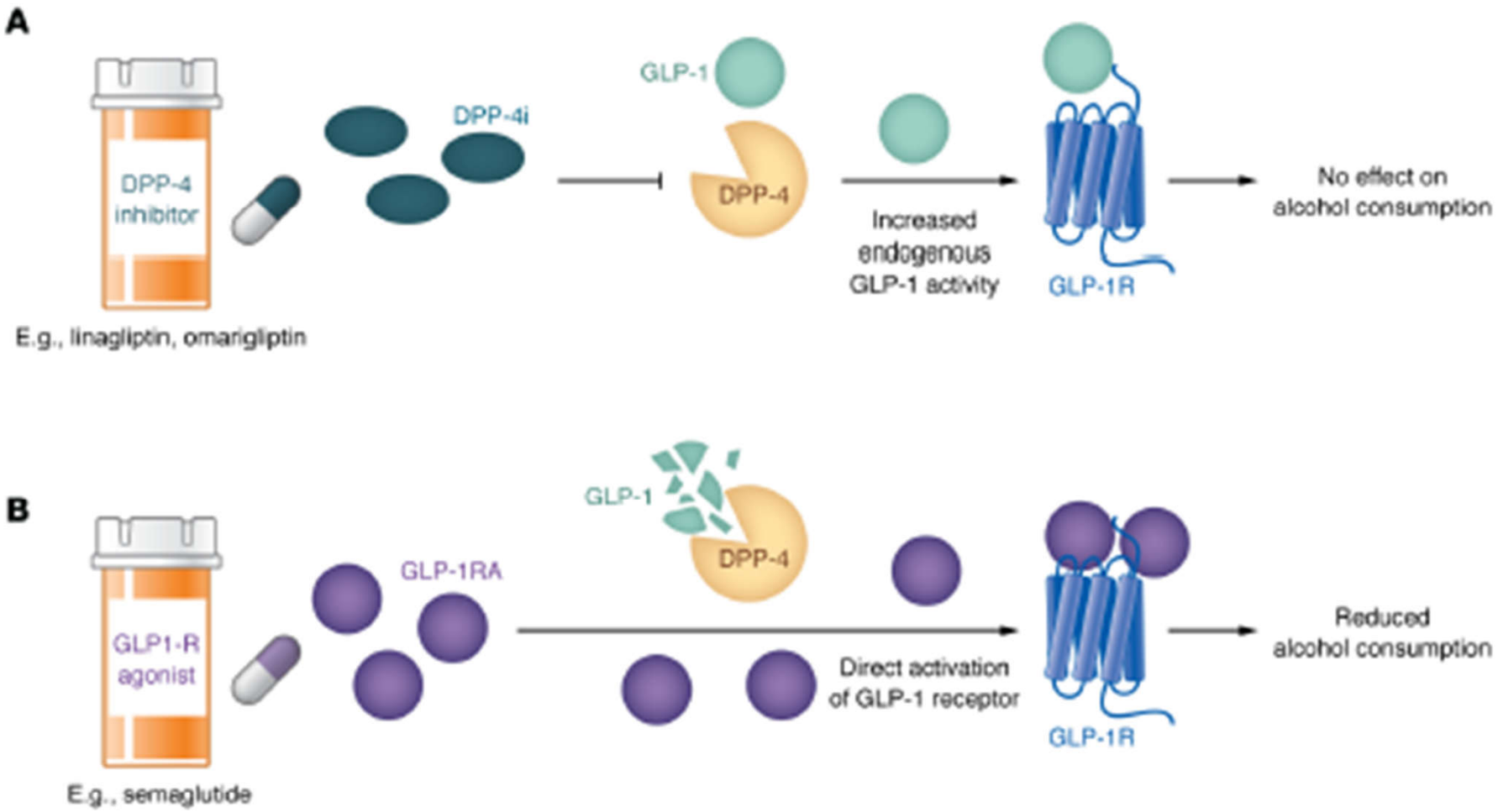
Clinical Research and Public Health | Endocrinology | Neuroscience

Glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as semaglutide, are widely used in the treatment of metabolic disorders, including type 2 diabetes (T2D) and obesity. These medications primarily function by enhancing insulin secretion; however, emerging evidence suggests that the effects extend beyond metabolic regulation. In this issue of the *JCI*, Farokhnia et al. evaluated the effects of GLP-1RAs alongside another T2D treatment, dipeptidyl peptidase-4 inhibitors (DPP-4Is), on alcohol consumption in humans and preclinical models. In humans, GLP1-RAs, but not DPP-4Is, were associated with reductions in alcohol consumption. Similarly, DPP-4 inhibition had no effect on alcohol intake in rodents. These findings invite further exploration of the mechanisms by which GLP-1RAs reduce alcohol consumption and redefine our pharmacotherapy approach to alcohol use disorder (AUD) by opening the possibility for application as an early harm-reduction tool.



gure 1. Distinct mechanisms underlie the differential effects of DPP-4Is and GLP-1RAs on alcohol consumption. DPP-4Is (**A**) have no effects on alcohol nsumption, while GLP-1RAs (**B**) reduce it. Both drug classes increase activity at the GLP-1 receptor, but through different mechanisms. DPP-4Is, such linagliptin and omarigliptin, target activity of the DDP-4 enzyme, which normally functions to inactivate GLP-1 and thus prevents it from binding to e GLP-1 receptor. However, inhibition of DDP-4 via an DDP-4I boosts the endogenous GLP-1 signal. Critically, this effect is constrained by the capacity produce endogenous GLP-1. In contrast, GLP1-RAs, such as semaglutide, are analogs to the GLP-1 peptide that have longer half lives as well as greater tency at, and affinity for, the GLP-1 receptor. The precise mechanisms underpinning the ability of GLP1-RAs to reduce alcohol consumption are, as of yet, known, but may relate to these differences in how DPP-4Is and GLP1-RAs affect the GLP-1 system.

tion tool for individuals with severe AUD? Could they be used as an early intervention strategy for those at risk of developing severe AUD? And how do we navigate the ethical and clinical implications of prescribing a medication that reduces alcohol use without requiring behavioral change? While these questions remain unanswered, one thing is clear: GLP-1RAs challenge the conventional approach to AUD treatment, offering an avenue that aligns more closely with real-world drinking behaviors and patient needs.

If we are willing to step beyond traditional abstinence-based paradigms, GLP-1RAs may pave the way for a more inclusive, effective, and pragmatic approach to reducing alcohol-related harm.

THE END