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From pilot programs to nationwide implementation: Reform of China's long-term care insurance in an aging society

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SUMMARY: China is experiencing rapid population aging and a growing burden of disability, creating urgent demand for sustainable long-term care systems. In response, China has progressively developed a long-term care insurance system since the launch of national pilot programs in 2016. China's long-term care insurance has evolved through three major stages: Pilot launch phase (2016–2019), Expansion phase (2020–2025), and Comprehensive implementation phase (2026–present). The system has significantly expanded coverage, improved access to long-term care for severely disabled older adults, reduced the family caregiving burden, and promoted the transformation of elder care from a family-based responsibility to a shared social responsibility. However, substantial structural challenges remain. These include heavy dependence on medical insurance funds, lack of a sustainable financing mechanism, regional disparities in disability assessment standards, a dearth of professional caregivers, fragmented governance structures, and inadequate digital supervision systems. Looking forward, China's long-term care insurance is expected to transition from a supplementary medical insurance arrangement toward an integrated social care security system. Future reforms should focus on establishing diversified financing mechanisms, unified disability assessment standards, delivery of community-centered care, integrated health and social care governance, and digitalized regulatory systems. China's experience may provide an important policy reference for other rapidly aging middle-income countries facing growing long-term care demands.

Keywords: long-term care insurance, aging society, disability, integrated care, China

1. Introduction

As the population continues to age, China is gradually transitioning from a "long-life society" to a stage characterized by disability and the need for long-term care. By the end of 2024, the population of people aged 65 and older accounted for 15.6% of China's total population. By the end of 2022, there were approximately 44 million old adults with full or partial disability, with the proportion of those aged 80 and older with full or partial disability reaching about 40% (*1,2*). In addition, the number of old adults with dementia has exceeded 15 million (*3*). The conventional healthcare system, which focuses primarily on treatment of disease, struggles to meet the care-related needs of old adults with disabilities or dementia in terms of daily living assistance, functional maintenance, and continuous care. To address this, China launched pilot programs for long-term care insurance in 2016. Data from 2020 to 2024 show that the number of long-term care insurance enrollees in 49 pilot cities increased from 108.353 million to 187.8634 million, while the number of beneficiaries increased from 835,000 to 1.4625 million (Figure 1). Despite the institutional evolution from local exploration to expanded pilot programs and ultimately nationwide implementation, China's current long-term care insurance system still faces core challenges, including insufficient sustainability of its financing mechanism, a lack of fully standardized disability assessment criteria, and shortages in both the supply of care and professional nursing personnel (*4*). If these challenges are not effectively addressed, they will directly undermine the sustainability of care and the equity of benefits under the long-term care insurance system. To that end, this paper systematically reviews the institutional significance and current progress of China's long-term care insurance, it conducts an in-depth analysis of the structural challenges the system currently faces and their potential consequences, and, on this basis, explores future development trends to provide a reference for the development of long-term care insurance systems from an international perspective.

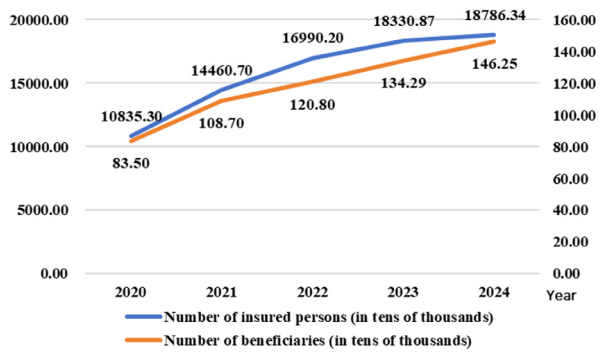

Figure 1. Enrollment in and receipt of benefits from China's long-term care insurance, 2020–2024.

2. The strategic value of establishing a long-term care insurance system in China

2.1. Promoting high-quality population development

A massive population is a defining feature of Chinese modernization. To promote high-quality population development, a support and care system that covers the entire population across the entire life cycle needs to be established. For old adults with disabilities, long-term care insurance is not merely about general cost reimbursement; rather, it shifts the provision of long-term professional care from "depending on whether families can afford it" to "basic support that the system should provide" (*5*). Establishing a unified national long-term care insurance system would systematically mitigate care risks among aging populations and provide a solid institutional foundation for high-quality population development.

2.2. Improving the social security system

Long-term care insurance marks a key expansion of China's social security system. The existing "five social insurance schemes" primarily address social risks such as illness, elderly care, unemployment, work-related injuries, and maternity, whereas long-term care insurance incorporates "care risks" into the institutional framework for the first time, expanding the system from "treatment of disease" to "long-term care" (*6,7*). This shift not only fills a gap in the long-term protection of people with disabilities but also reflects the social security system's proactive adaptation to demographic changes.

2.3. Promoting the shared social responsibility of care

In the traditional family-centered model of care for older adults, the responsibility for caring for older adults with disabilities has relied heavily on family members such as spouses and children. However, with further aging of the population and the ongoing trend toward families of smaller sizes, the traditional family care model faces multiple practical constraints, including a shortage of caregivers and heavy physical and financial burdens. Long-term care insurance, through institutionalized funding and benefit mechanisms, systematically shares the costs of long-term care and promotes a shift in caregiving responsibilities toward a "shared social responsibility" model characterized by diverse collaboration (*8*), thereby freeing up family caregiving to some extent.

2.4. Optimizing the healthcare system

Long-term care insurance is also systematically driving a functional reallocation of roles between medical care and nursing care. Previously, a lack of stable avenues of professional care resulted in many older adults with disabilities being forced to meet their daily care needs through long-term hospitalization, creating a phenomenon known as "social hospitalization" and exacerbating the misallocation of medical resources. By providing institutionalized support to expand and improve the quality of professional care, long-term care insurance systematically transfers non-medical care needs, which were previously concentrated within the medical system, to the long-term care system, thereby effectively optimizing the allocation of medical resources (*9*).

2.5. Enriching national long-term care insurance practices

As the pioneer of long-term care insurance systems, Germany has adhered to the core framework of statutory social insurance, emphasizing the stability, sustainability, and universal coverage of the system, with a social security framework that clearly defines rights and responsibilities. Japan, in contrast, has established a community-centered integrated care system that is focusing on improving the accessibility and quality of care. China, because of its specific conditions, has adopted a gradual approach of "pilot programs first and gradual expansion." Its system is highly flexible and adaptable to China's national conditions, representing a "Chinese approach" to the creation of long-term care insurance systems worldwide.

3. The exploration and development of long-term care insurance in China

3.1. Pilot launch phase (2016–2019)

To address the challenges of providing long-term care for people with disabilities resulting from an aging population, China has successively issued a series of policy documents. In June 2016, the General Office of the Ministry of Human Resources and Social Security issued the Guiding Opinions on Launching

the Pilot Program of the Long-Term Care Insurance System. This officially designated 15 cities, including Chengde and Changchun, as well as the provinces of Jilin and Shandong, as the first batch of national-level pilot regions for long-term care insurance, marking the start of a standardized pilot program phase for China's long-term care insurance system (*10*). In March 2018, the establishment of the National Healthcare Security Administration led to further reforms of the long-term care insurance system. The core task of this phase was to explore key aspects of the long-term care insurance system, including its institutional model, financing mechanisms, standards for receiving benefits, and assessment systems, while defining the primary population to be covered as participants in the employee medical insurance scheme and prioritizing the care needs of individuals with severe disabilities (*11*) (Table 1).

3.2. Expansion phase (2020–2025)

After 2020, the long-term care insurance program entered a phase of expanded pilot programs, which were launched in multiple cities across the country, and a comprehensive set of supporting policies introduced by the central government (Table 2). In September 2020, the National Healthcare Security Administration officially issued the Guiding Opinions on Expanding the Pilot Program for the Long-Term Care Insurance System (*12*), adding 14 new pilot regions, including the Shijingshan District in Beijing. This initiative gradually extended coverage to urban and rural residents and, for the first time, clearly defined LTCI as an independent insurance arrangement, establishing a diversified financing mechanism primarily based on employer and individual contributions, supplemented by government subsidies. Subsequently, a series of supporting documents were issued at the national level, gradually forming a comprehensive institutional framework that included assessment, administration, delivery of care, and supervision (*13*). The core tasks of this phase were to expand the scope of coverage, improve the financing mechanism, unify the standard system, and standardize the assessment process (*14*).

3.3. Comprehensive implementation phase (2026–present)

Since 2026, following nearly a decade of pilot programs and exploration, China' s long-term care insurance system has established a nationwide policy framework and a system of implementation rules (Table 3), marking a new phase of nationwide implementation and comprehensive advancement. In March 2026, the General Office of the Central Committee of the Communist Party of China and the General Office of the State Council issued the Opinions on Accelerating the Establishment of the Long-Term Care Insurance System (*15*), explicitly proposing to establish, within approximately three years, a long-term care insurance system that is adapted to China's basic national conditions, that covers the entire population, that integrates urban and rural areas, that is fair and unified, that is safe and standardized, and that is sustainable. This marked the formal transition of the long-term care insurance system from the pilot program phase to the comprehensive implementation phase. The core tasks of this phase are to implement a nationally unified institutional framework, to provide comprehensive coverage, universal accessibility, and standardized operation of the system, and to promote the full maturation and consolidation of the long-term care insurance system.

Overall, China's long-term care insurance system

Table 1. Overview of policies for the long-term care insurance system during the pilot launch phase (2016–2019)

Release date	Policy document	Key points
June 2016	Guiding Opinions of the General Office of the Ministry of Human Resources and Social Security on Piloting the Long-Term Care Insurance System	Identified 15 pilot cities and two key partner provinces—Jilin and Shandong; specified that the system would cover individuals with long-term disabilities, with a focus on addressing basic daily care needs and medical care costs closely related to daily living for those with severe disabilities; explored the establishment of a social insurance system funded through social mutual aid and solidarity.
June 2017	Opinions of the General Office of the State Council on Formulating and Implementing Elderly Care Service Projects	Proposed establishing a subsidy system for older adults of advanced age or with disabilities facing financial hardship, and ensuring seamless integration with the long-term care insurance system; required the active implementation of long-term care insurance pilot programs to explore the establishment of a long-term care insurance system.
March 2019	Report on the Work of the Government (2019)	Formally proposed "expanding pilot programs for the long-term care insurance system".
April 2019	Opinions of the General Office of the State Council on Promoting the Development of Elderly Care Services	First proposed "establishing and improving a long-term care system"; called for accelerating the implementation of pilot programs for the long-term care insurance system; encouraged the development of commercial long-term care insurance products.

Table 2. Overview of policies for the long-term care insurance system during the expansion phase (2020–2025)

Release date	Policy document	Key points
September 2020	Guiding Opinions of the National Healthcare Security Administration and the Ministry of Finance on Expanding the Pilot Program of the Long-term Care Insurance System	The pilot program was expanded to 49 cities; the system was defined as a standalone insurance product, and a diversified financing mechanism was established, primarily based on contributions from employers and individuals.
July 2021	Long-term Care Disability Level Assessment Standard (Trial)	Established the first nationwide unified disability assessment standards, standardizing assessment indicators and classification levels.
September 2021	14th Five-Year Plan for National Healthcare Security	Stated that during the period of the 14th Five-Year Plan, the long-term care insurance system would be steadily established, and a policy framework would be constructed; national unified standards for disability assessment would be formulated, the administrative system would be improved, and the development of commercial long-term care insurance would be encouraged.
November 2021	Opinions of the CPC Central Committee and the State Council on Advancing Efforts to Address Population Ageing in the New Era	Proposed to steadily advance pilot programs for the long-term care insurance system, intensify exploratory efforts, and improve existing pilot programs.
February 2022	14th Five-Year Plan for the Development of National Undertakings for the Aged and the Elderly Care Service System	Systematically planned the enrollment, service, and financing mechanisms for long-term care insurance, and promoted pilot programs.
December 2023	Measures for the Administration of Disability Level Assessment for Long-Term Care Insurance (Trial)	Standardizes the management of designated assessment institutions, the qualifications of assessors, and the assessment process.
February 2024	National Occupational Standards for Health Caregivers (Long-term Caregivers) (2024 Edition)	Clarifies the occupational standards for long-term care workers and promotes the professional development of care personnel.
April 2024	Measures for the Administration of Designated Disability Level Assessment Institutions for Long-Term Care Insurance (Trial)	Clarifies the application criteria, designation procedures, operational management, and supervision requirements for designated assessment institutions.
September 2024	Operational Procedures for Long-Term Care Insurance (Trial)	Guides local authorities in managing assessments, services, and third-party institutions for long-term care insurance, and clarifies the disability assessment process.
September 2024	Model Service Agreement for Designated Disability Level Assessment Institutions for Long-Term Care Insurance (Trial)	Provides a standardized model service agreement for assessment institutions to regulate the management of designated assessment institutions.
October 2024	Measures for the Administration of Designated Nursing Service Institutions for Long-Term Care Insurance (Trial)	Clarifies the entry criteria, management requirements, and exit mechanisms for long-term care providers.
November 2024	Implementation Opinions on Promoting Vocational Skill Level Certification for Long-term Caregivers	Provides institutional safeguards for the vocational qualification assessment of long-term care workers and promotes the standardization of the nursing workforce development.
March 2025	Report on the Work of the Government (2025)	Explicitly proposes to "accelerate the establishment of the long-term care insurance system", marking the fifth consecutive year this has been included in the Report on the Work of the Government and signaling accelerated nationwide implementation.

has undergone three key phases of development, from the launch of pilot programs to the expansion of those programs, and finally to full-scale implementation (Figure 2). It has evolved from localized pilot programs to nationwide rollout, from fragmented approaches to unified standards, and from single-source coverage to multi-stakeholder collaboration, and it is now accelerating toward a new phase of universal coverage and institutional consolidation.

4. International experiences with long-term care insurance systems

4.1. Japan's long-term care insurance system

Japan is one of the most rapidly aging countries in the world. In response to the ongoing aging of the population and the lessening of traditional family caregiving, Japan enacted the Long-Term Care Insurance Act in

Table 3. Overview of policies for the long-term care insurance system during the comprehensive implementation phase (2026–present)

Release date	Policy document	Key points
March 2026	Opinions of the General Office of the CPC Central Committee and the General Office of the State Council on Accelerating the Establishment of the Long-Term Care Insurance System	Marked the transition of long-term care insurance from localized pilot programs to nationwide implementation; proposed establishing a long-term care insurance system that aligns with China's basic national conditions within approximately three years.
March 2026	Implementation Plan for Accelerating the Establishment of the Long-Term Care Insurance System	Provides detailed provisions on funding, benefit coverage, and management services; establishes a benchmark premium rate system; supports differentiated benefits for institutional care, home care, and community care; and strengthens interdepartmental coordination and collaboration.
Feb 2026	Implementation Rules for the Regulations on the Supervision and Administration of the Use of Healthcare Security Funds	Provides detailed provisions on fund usage, supervision, and legal liabilities.

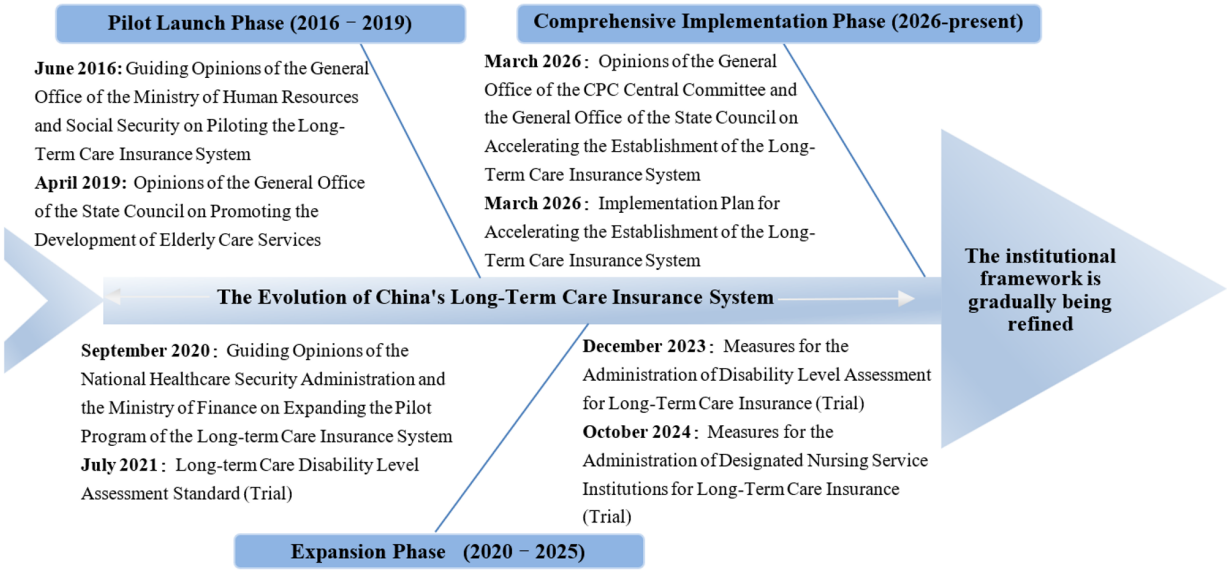

Figure 2. Diagram of the development stages of long-term care insurance in China (Representative documents).

1997, becoming the first country in Asia to establish a socialized long-term care insurance system. Its core objective is to shift the burden of caregiving from families to society and to build a comprehensive care system centered on the community. The program covers all citizens aged 40 and older, but benefits are provided only to old individuals with disabilities and those with disabilities resulting from specific illnesses. Funding is provided through a hybrid model in which taxes and premiums each account for 50% of the total. Fiscal subsidies are shared among the central government, prefectures, and municipalities, with premiums determined on a sliding scale based on income (*16*). Actuarial assessments are conducted every three years, and premium rates are dynamically adjusted accordingly. Benefits are primarily provided in the form of in-kind services, with no cash subsidies offered, and cover home-based care, day care, and institutional care (*17*). Accurate disability assessments are achieved through "home visits and secondary evaluations by expert committees," driving the professionalization and standardization of care.

4.2. Germany's long-term care insurance system

Germany is the birthplace of the modern social insurance system. Against the backdrop of diminishing family caregiving capacity and a growing demand for care, Germany enacted the Long-Term Care Insurance Act in 1994, becoming the first country in the world to establish a public long-term care insurance system through legislation. The system covers residents of all ages, and benefits are available to anyone who meets the criteria for disability. Funding is centered on payroll taxes, with employers and employees each contributing half. Childless individuals are subject to an additional

premium, and government subsidies account for only 2%, creating a sustainable funding system independent of health insurance (*18*). Payments are made through a dual system of cash subsidies and care subsidies. Cash subsidies are paid directly to family members providing home care to encourage family involvement in caregiving while alleviating pressure on fund expenditures. Care subsidies, meanwhile, cover the costs of professional care (*19*). The government will enhance the efficiency of fund management by adopting a market-oriented approach to the operation of the LTCI fund, while ensuring the stability of the system by clarifying the funding responsibilities and standards for receiving benefits of all parties through legislation.

4.3. South Korea's long-term care insurance system

Faced with the severe challenges of an accelerating aging population and the gradual breakdown of traditional family caregiving, South Korea enacted the Long-Term Care Insurance Act in 2007. Administered by the National Health Insurance Service, the program covers all health insurance enrollees and provides benefits to disabled seniors aged 65 and older, as well as individuals under the age of 65 with disabilities resulting from specific diseases. Funding is shared among individuals, employers, and the government (*20*). Benefits are provided in two forms: cash payments and services. Service offerings include home care (such as in-home nursing and day care), institutional care, short-term residential care, and specialized care for dementia. Cash payments are provided only under special circumstances, such as when a relative provides care and access to service facilities is unavailable, or when an old person living in a remote area cannot access in-person services. This approach is designed to mitigate the risk of uncontrolled service quality that could arise from cash payments (*17*). The system is designed to balance equity and sustainability, aligning with trends in population aging and changing family structures in South Korea.

4.4. A comparison of the core systems of long-term care insurance in China, Japan, Germany, and South Korea

Japan, Germany, and South Korea are all leading examples of social insurance models for long-term care, but each country has its own unique characteristics in terms of institutional development (Table 4). Compared to Germany and South Korea, Japan's long-term care insurance system has the highest proportion of government subsidies (approximately 50%) and the greatest extent of government involvement in its operation. However, the high level of benefits also poses greater challenges to the financial sustainability of the system. The most distinctive feature of the German system is the design of its benefits, which combine cash subsidies with home care, and its robust self-balancing

Table 4. Comparison of long-term care insurance systems in China, Japan, Germany, and South Korea

	Legal basis	System model	Population covered	Method of financing	Methods of delivering benefits
China	2016: Guiding Opinions of the General Office of the Ministry of Human Resources and Social Security on Piloting the Long-Term Care Insurance System	Social insurance-based model, with pilot programs being rolled out nationwide and gradually becoming a standalone insurance category.	Employee medical insurance serves as the starting point, gradually expanding to cover urban and rural residents, with a focus on providing coverage for severe disability.	Transfers from health insurance funds, individual and employer contributions, and government subsidies; high level of reliance on health insurance.	Service-oriented, with some regions piloting cash subsidies; the fund covers approximately 70% of costs.
Japan	1997: Long-Term Care Insurance Act	Social insurance-based, statutory and mandatory, community-oriented.	Coverage for those aged 40 and older; benefits available to those aged 65 and older and individuals with disabilities due to specific illnesses.	Funding is 50% government and 50% premiums; premiums are income-based and adjusted every three years.	Primarily in-kind services; individuals pay 10–30% out-of-pocket.
Germany	1994: Long-Term Care Insurance Act	Social insurance-based, legally mandatory, and market-driven.	Covers all residents of all ages; benefits are available upon the onset of disability.	Employers and employees each contribute half of the payroll tax; a surcharge applies to those without children, with a 2% government subsidy.	Beneficiaries may choose between cash benefits and in-kind services; reimbursement covers up to 75% of costs.
South Korea	2007: Long-Term Care Insurance Act	Social insurance-based system, integrated with health insurance, and legally mandatory.	All health insurance subscribers, individuals aged 65 and older, and those with disabilities due to specific illnesses are eligible for benefits.	Costs are shared by individuals, employers, and the government, with the government subsidizing approximately 30%.	Beneficiaries may choose between cash benefits and in-kind services; for institutional care, the out-of-pocket cost is 20%, and for home care, it is 15%.

mechanism. It has the lowest proportion of government subsidies (approximately 2%). The South Korean system was established most recently. Its key features include centralized management and operations, as well as a competitive mechanism that separates purchasers from providers. It has seen the fastest rise in contribution rates, reflecting the practical need for rapid systemic adjustments to address the pressures of an aging population. The experiences of these three countries provide useful institutional benchmarks for China's long-term care insurance system as it transitions from pilot programs to nationwide implementation, offering particularly valuable insights regarding the sustainability of funding, the standardization of assessment criteria, and the selection of models for delivery of benefits.

5. The practical challenges of China's long-term care insurance

5.1. The sustainability of the funding mechanism needs to be improved

First, current funding relies heavily on basic medical insurance funds; in more than 80% of pilot cities, funding primarily comes from transfers from basic medical insurance funds, with individual contributions generally accounting for less than 30%; some cities even waive individual fees entirely (*21*). Against the backdrop of an aging population and a steadily growing number of people with disabilities, the financial pressures on basic medical insurance funds are mounting. A model that relies excessively on basic medical insurance is not only unsustainable for the long-term operation of long-term care insurance but may also divert resources from basic medical insurance coverage. Second, the division of funding responsibilities is unclear, and there is a lack of a scientific mechanism for dynamic adjustment (*22*). Most pilot cities have not clearly defined the statutory responsibilities of individuals, employers, and the government. Funding standards are mostly fixed amounts that are not linked to changes in economic conditions, household income, care costs, or the risk of disability, hampering its ability to cope with the pressure of rising long-term expenditures.

5.2. The disability assessment system still needs improvement

First, the long-term care insurance system lacks uniform assessment standards for beneficiaries. A study analyzing 49 pilot cities found that while 47 of them had published disability grading assessment standards, only 38 adopted the provisional standards issued by the National Healthcare Security Administration (*23*), which to some extent undermines the fairness of benefits allocated under the long-term care insurance system. Second, there is a lack of uniform regulations governing the assessment process and personnel management. Currently, long-term care assessments in China's pilot cities are mostly conducted by third-party agencies, but there is no unified certification for these agencies, and assessment results lack rigorous review (*24*). Moreover, the information system supporting disability assessments is relatively underdeveloped; assessment results are primarily archived on paper forms, and a nationwide unified electronic database has yet to be established. When insured individuals move across provincial borders, they must resubmit their medical records and undergo repeated assessments, which increases the administrative costs of the system (*25*).

5.3. Inadequate supply and quality of care services

For old adults with disabilities in rural areas, most prefer home-based care over institutional care (*26*). However, the scattered nature of rural communities makes home-based services costly, which has, to some extent, limited the expansion of long-term care insurance in rural areas. Second, the supply structure does not align with the core needs of the population. Of the beds available through institutional care, those intended for people with disabilities account for less than 40%, and the home and community care networks are underdeveloped, hampering the system's ability to meet the core need of old adults with disabilities for "local and nearby care" (*27*). Third, China currently faces a shortage of over 5 million elderly care workers, and in pilot regions, certified personnel account for less than 30% of the workforce. Caregivers continue to face issues such as low wages, inadequate career development pathways, and an intense workload. This shortage of professional personnel constrains supply and the professionalism of care (*28*).

5.4. Urgent improvement needed for rule of law construction and institutional norms

Although China has begun the top-level design of its long-term care insurance system, unified legislation has not yet been enacted. Local implementation primarily relies on central government guidelines and provisional measures and detailed rules formulated by pilot cities themselves, with a "one city, one policy" approach becoming increasingly evident (*29*). Moreover, pilot cities differ in key areas such as the scope of coverage, funding standards, benefit entitlements, and payment rules; some cities cover only the employed population, while others have achieved full coverage of both urban and rural residents. Benefit payment rates, the scope of coverage, and payment methods also vary (*30*). In addition, the measures adopted by various regions to integrate long-term care insurance with medical insurance are interim solutions derived from practical experience. Facilitating the coordination of

benefits between long-term care insurance and basic medical insurance is a topic that still needs to be further explored (*31*).

5.5. Weak foundations in digitalization and regulation

First, there is a lack of a full-process regulatory mechanism. The regulatory framework for the long-term care insurance system is still in its exploratory or refinement stage. Specifically, a legal and regulatory foundation has not yet been systematically established, the delineation of responsibilities among regulatory bodies and the pathways for collaborative governance remain unclear, and there is a lack of channels for feedback on the quality of care (*32*). Second, the foundation for digital supervision is weak. Most pilot cities have not yet established a full-process digital supervision system for long-term care insurance, so there is no real-time tracking or intelligent auditing of services, their duration, their quality, or fund usage. The use of technologies such as the Internet of Things (IoT), big data, and artificial intelligence (AI) in the supervision of care remains insufficient, hampering the system's ability to effectively address regulatory challenges in dispersed settings such as home-based and community-based care, which results in a low level of efficiency and limited accuracy of supervision (*33*).

6. Trends in China's long-term care insurance

6.1. Establishing a diverse and sustainable financing mechanism

The 2026 "Opinions of the General Office of the CPC Central Committee and the General Office of the State Council on Accelerating the Establishment of the Long-Term Care Insurance System" emphasize the establishment of a diversified financing mechanism that is commensurate with the level of economic development, aligned with the financial capacity of all parties, and consistent with sustainability requirements (*34*). In contrast, Japan's long-term care insurance Act clearly defines an independent social insurance framework for long-term care insurance through legislation. Premiums are shared equally between insurance contributions and taxes, with premiums for insured individuals aged 65 and older deducted directly from their pensions, and a dynamic adjustment mechanism is in place (*35*). South Korea's long-term care insurance builds upon a social insurance model by incorporating elements of public assistance. Drawing on the experiences mentioned earlier, on the one hand, the funding responsibilities of individuals, employers, and the government will be further enhanced through legislation or regulatory documents. Individual contribution rates will be reasonably increased to gradually achieve universal coverage, while exploring contribution mechanisms linked to income. On the other hand, funding standards will shift from fixed amounts to dynamic adjustments, establishing a mechanism for the dynamic adjustment of contribution rates and benefits linked to changes in residents' income, care costs, and the degree of population aging, thereby ensuring the fund's revenue-expenditure balance.

6.2. Improving the disability assessment system

In recent years, China has actively promoted the cross-departmental sharing and mutual recognition of disability assessment results (*36*). The institutional experiences of leading countries worldwide have also provided a model for China's assessment system. Germany's long-term care insurance system relies on independent professional assessment agencies to conduct assessments of care needs on behalf of the long-term care insurance funds through the Medical Service of Health Insurance Funds (MDK) (*37*). Japan's long-term care insurance system employs a "two-stage assessment" model: an initial home survey is conducted by municipal staff or contracted agencies, followed by a comprehensive review by the Long-Term Care Certification Review Committee—consisting of personnel from the fields of healthcare, medical care, and social welfare—which incorporates the attending physician's opinion. Building upon the promotion of a unified national assessment standard, efforts should be made to further enhance professional training and certification for assessors, establish and improve a database of assessors and a dynamic management mechanism, standardize assessment procedures, and introduce multidisciplinary expertise into the assessment review process. This will comprehensively enhance the scientific rigor and fairness of disability level assessments (*38*).

6.3. Optimizing the provision of care services

From an international perspective, long-term care systems are gradually shifting from a health insurance model centered on treatment of disease to a care model focused on functional maintenance, assistance with daily living, and continuous care (*39*). Japan's regional integrated care system has established a small-scale, multifunctional home-based care model combining "day care, home-visit services, and short-term residential stays," effectively meeting the core need of old adults to age in place. In contrast, China's long-term care insurance system remains in the early stages of development, characterized by a supply model that prioritizes institutional care over home-based services (*40*). In the future, China's long-term care insurance should promote the decentralization of care provision from centralized institutions to community-based and home-based settings. It should focus on fostering integrated, multifunctional community care providers

that combine "day care, home-based services, and short-term residential care" and build a service network centered on the home, linked to the community, and supplemented by institutions, thereby achieving the close integration of care with the daily living conditions of old adults. At the same time, efforts should be made to improve dementia-friendly community care networks and to enhance the capacity for continuous care and family support for old adults with dementia who exhibit behavioral and psychological symptoms.

6.4. Advancing the coordination and integration of systems

Japan's Community-based Integrated Care System is built around the goal of enabling older adults to continue living in their familiar communities with dignity and independence. The system integrates five essential components: medical care, long-term care, preventive care, housing, and daily living support, thereby providing comprehensive support for ageing in place (*41*). This approach differs from the current single financial focus of China's long-term care insurance, which primarily covers costs for individuals with severe disabilities. This institutional design points the way forward for the evolution of China's long-term care insurance. In the future, China's long-term care insurance will gradually move beyond its current role as a "supplement to medical insurance." It will transition from a system focused solely on reimbursing care costs to a comprehensive, integrated social security system that includes preventive care, care for the disabled, coordination of medical care, assistance with daily living, and housing. The system will evolve from a financial design focused on "who pays" to a systematic design focused on "how to provide comprehensive support for the lives of old adults", ultimately becoming one of the core pillars of China's old adult care and health security.

6.5. Strengthening digital empowerment and regulation

The reliable operation of long-term care insurance in the future will rely heavily on technology-enabled regulation. On the one hand, laws and regulations should be improved to grant regulatory authorities clear enforcement powers and responsibilities, as well as

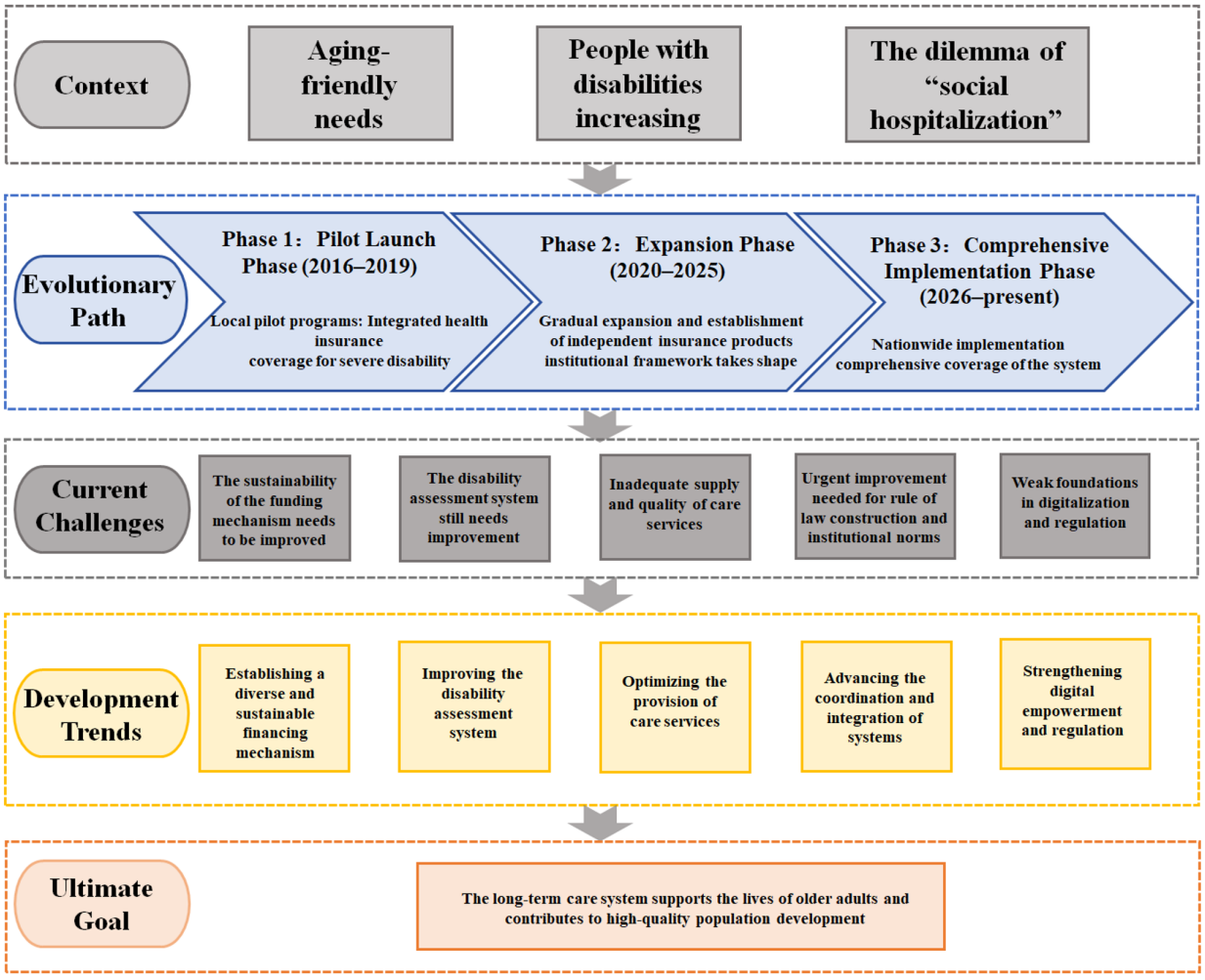

Figure 3. The path of development of long-term care insurance in China.

coordination mechanisms, while ensuring unimpeded avenues for public oversight and reporting of complaints. On the other hand, efforts should be accelerated to build a unified national information system for long-term care insurance, to standardize data formats, and to achieve data integration with departments such as medical insurance, civil affairs, and the Disabled Persons' Federation to break down data silos (*42*). The promotion of smart care devices and digital management tools should be prioritized to ensure full traceability throughout the care process. For example, mobile apps can be used to record the duration and details of care, facilitating verification by regulatory authorities. At the same time, administrative service processes should be optimized by implementing convenient services such as online applications, online assessments, and online payments. This will reduce the administrative burden on insured individuals, improve the efficiency of administrative services, and alleviate the pressure caused by a shortage of administrative staff (Figure 3).

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Editorial

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Brain-computer interfaces: A lifeline for paralysis or a Pandora's box for humanity?

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SUMMARY: Recent advances in computerized technologies, neuroscience, and materials and engineering have transformed brain-computer interfaces (BCIs) from conventional unidirectional signal recording systems (brain-to-device) to bidirectional closed-loop neuromodulation systems (brain-device-brain). BCI-based devices enable direct information exchange between the human central nervous system and external electronic devices, and they are widely used in scenarios such as rehabilitation of patients with dyskinesia or enhancement of the self-care ability of disabled individuals. This editorial discusses the rapidly evolving field of BCIs, highlighting both their transformative potential to restore neurological function and the emerging ethical concerns associated with neural data access, cognitive enhancement, and human autonomy. The academic consensus and future translational prospects are also discussed. This article attempts to provide insightful, balanced, and critical viewpoints to help BCI-related research. Indeed, the future of BCIs will depend not only on technological innovation but also on society's ability to establish robust ethical and regulatory frameworks. Whether BCIs become a lifeline for millions of patients or a source of new societal risks will be determined by the choices made today.

Keywords: brain-computer interface, neural decoding, rehabilitation, ethical problems, paralysis

1. Introduction

As computerized technologies are increasingly used in clinical practice, the topic of brain-computer interfaces (BCIs) has garnered attention. Advances in neuroscience (such as neural signal acquisition, surgical implantation technology, and neuromodulation technology), computerized technologies (such as decoding algorithms and artificial intelligence (AI)), and material and engineering (such as implantable system design, microsensors, and organically compatible materials) have facilitated the development of and research on devices based on BCIs. Earlier BCI-related research mainly focused on unidirectional brain-to-device control, whereas post-2024 studies highlight bidirectional brain-device-brain interactions and functional restoration for patients with severe neurological conditions or sequelae. This study attempts to, from critical viewpoints, briefly summarize insights and concerns regarding the clinical applications of BCI-based devices based on rapidly updated evidence. We hope to encourage readers to think about the actual value of BCIs.

2. Updating definitions and technical classification of BCI-based devices

The definition of a BCI is changing as technology advances. According to the Brain-Computer Interface Society (*1*) and a study by Jain *et al*. (*2*), there are several components of the newest definition of a BCI: *i*) A BCI is bidirectional, namely, brain-device-brain. The core upgrade of modern BCIs is closed-loop bidirectional interactions rather than conventional one-way signal acquisition. It is fundamentally different from neural prostheses that rely on direct peripheral nerve conduction, such as cochlear and retinal implants. It also differs from electromyography-based control devices that require voluntary muscle contractions. *ii*) The interactions are real-time or nearly real-time. *iii*) It is useful at improving neurological function and has translational value. We should bear in mind that the definitions are constantly updated as technology and applications advance. For example, interactions between the brain and external electronic devices are currently being studied. As devices are developed in response to clinical requirements, many third-party devices may achieve better modulation, neural activity, and neurological functions. Thus, "bidirectional" might be changed to "multidirectional", involving multiple devices, which may form a complex BCI-based system to improve clinical outcomes for patients.

Currently available BCIs can be roughly classified into three categories according to invasiveness and clinical practicability: *i*) An invasive BCI: Devices of this type require conventional surgical implantation of intracortical electrode arrays with high signal bandwidth and decoding precision. These invasive devices are primarily used for restoration of high-level motor function. *ii*) A semi-invasive BCI: Devices of this type require minimally invasive surgical technology, such as intravascular electrode sensors or robots. A semi-invasive BCI balances biosafety and signal quality and is the most popular type in terms of clinical translation. *iii*) A noninvasive BCI: Devices of this type use technologies such as electroencephalography (EEG) or electromyogram (EMG)-based wearable systems and do not require surgery. A typical device of this type is the postmarketing Hybrid Assistive Limb (HAL) system in Japan, which has a noticeable efficacy in improving walking function in patients with stroke (*3*) and spinal cord injury (*4*). One appeal of these systems is the absence of surgical risk. Moreover, some devices even achieve the so-called "idiodynamics" of simple body actions, such as leg lifting or leg extension, which can only be seen in science fiction, and significantly improve walking function. However, these devices have limitations. For HAL, the lack of evidence from large-scale, multicenter, and long-term randomized controlled trials might be a problem (*3*). The long-term efficacy of this treatment is unknown. In addition, the high cost may further restrict its application.

3. Applications of BCI-based devices

BCI-based devices have been widely used for the restoration of motor function and communication in patients with various neurological diseases, such as stroke and spinal cord injury, Alzheimer's disease (AD), Parkinson's disease (PD), and psychiatric disorders such as attention deficit hyperactivity disorder (*2*). Between 2024-2026, the numerous studies that directly implanted BCI-related devices is breath-taking. One noticeable aspect is their use to improve speech. Wairagkar *et al*. implanted 256 microelectrodes into the ventral precentral gyrus of a patient with amyotrophic lateral sclerosis-related dysarthria. This BCI-based device can synthesize a voice with closed-loop audio feedback by decoding neural activity; using this device, the patient was able to talk in real-time and sing a short song (*5*). Thus, BCI-based device can help to enable patients with dysarthria to regain the ability to speak. Qian *et al.* reported a BCI-based 256-channel-microelectrocorticographic speech decoding device for Mandarin Chinese. They made remarkable improvements in Mandarin Chinese-based tonally integrated direct syllable neural decoding, which might be useful for patients with aphasia (*6*). In addition to speech, Vargas-Irwin *et al*. observed the single-unit ensemble activity recorded in two patients with a cervical spinal cord injury in whom two 96-channel intracortical microelectrodes were implanted in the precentral gyrus. They found that single-unit ensemble activity recorded in a single precentral gyrus has the potential to generate more related signals, which might be used in BCI-based rehabilitation to produce gestures (*7*). Willsey *et al*. developed a finger-based BCI device that was able to control three independent fingers in two dimensions (*8*). This device made significant improvements in the finger functioning of patients with a severe spinal cord injury. Dexterous finger control can be achieved, allowing patients with tetraplegia to control devices such as robotic limbs and ultimately perform daily self-care (*8*). This device has great value in improving welfare, a sense of enablement, recreation and social connectedness, and quality of life (QOL) in patients with paralysis. Recent studies are clinical explorations with small sample sizes. Although they obtained primary evidence indicating that BCI-based devices have the potential to restore communication and motor control in individuals with severe paralysis, subsequent well-designed clinical studies are highly anticipated.

In this regard, BCIs seem to represent a lifeline for patients with diseases that are traditionally regarded as "incurable" diseases and "hopeless" dysfunctions and to light a candle to reignite their hope of performing self-care.

In addition to rehabilitation of patients, BCI-based devices are also useful in scientific research and even improve the daily lives of healthy participants. In terms of research, BCI can serve as a valuable tool for investigating the neural mechanisms underlying human cognition, decision-making, and language processing. Non-invasive EEG-based BCIs can be used in research on real-time attention quantification and attention/memory training in educational research. In terms of the daily lives of healthy users, non-invasive BCI-based devices may be used for sleep regulation and detection of mental fatigue. Thought-activated smart home operation, immersive VR/AR interaction, and wearable neural feedback systems based on BCI technology can be developed to improve the QOL of both patients and healthy users. Accordingly, BCI may be involved in many settings of daily life in the future.

4. Discussion of current BCIs and their advantages, technical bottlenecks and ethical risks

Advantages: To date, a BCI is the only technical approach that enables clinicians to bypass damaged somatic pathways and directly restore central neural output, significantly improving the QOL and social participation of disabled populations. Personalized and precise neuromodulation is superior to conventional pharmacology and physical therapy. Moreover, "thought activation" is achieved for some simple but important

motors, which means that paralyzed patients can fully or partially perform self-care using BCI-based robots, which have great economic and social value. The global BCI market reached USD 2 billion in 2024 and is projected to grow to USD 3.25 billion by 2029, showing strong translational and commercial potential.

Technical Bottlenecks: Currently, the known invasive BCI-related concerns include unavoidable surgical risks, immune rejection, limited electrode lifespan, and long-term signal instability. Non-invasive BCIs are commonly restricted by low signal-to-noise ratios, poor anti-interference performance, and marked individual differences in terms of decoding accuracy.

Ethical risks during clinical application: Because BCI technology is still emerging, many indispensable data for their clinical use are still insufficient, such as long-term safety and efficacy data on invasive implants. In the ethical domain, bidirectional BCIs may bring unprecedented challenges (*9*), such as neural privacy leakage risks, cognitive stratification caused by cognitive enhancement technologies, potential manipulation of human free will *via* targeted brain stimulation, and risks of misuse in military, criminal, and mandatory neural intervention scenarios. These risks should be fully considered in future BCI research. Moreover, the current heatedly discussed concerns, such as neuro-rights, cognitive liberty, mental integrity, psychological continuity, highlight the importance of ethical concerns in BCI research.

Regulatory challenges: Although governments worldwide have established relatively powerful regulatory systems for the development of medicine and medical devices, the regulatory system for BCI still faces challenges due to its emerging and fast-developing nature. Technological iteration usually occurs and areas of technical interest easily change; this is particularly true for AI-related computerized technologies. These contexts may cause difficulties in establishing a stable, balanced, and operable BCI-related regulatory system. This is an important issue that should be addressed by global health administration authorities worldwide.

The nature of consciousness is an unaddressed topic: To date, the precise decoding of abstract cognition and complex emotional signals has yet to be achieved (*10*). This issue cannot be resolved before the question of "what is the nature of consciousness" has an appropriate scientific answer. Metaphysical neuroscience research relies on elements that can be "observed", "captured", or "recorded", such as neurotransmitters and electroneurographic signals. One can easily understand the dilemmas in the development of consciousness-related BCIs, which also lie at the heart of the development of neuro-medications: PD-related medications (mainly for motor dysfunction) are sufficient and effective, whereas AD-related medications (mainly for cognitive impairment) are insufficient and have relatively poorer efficacy, which might be due to insufficient knowledge regarding the "nature of consciousness". Accordingly, BCIs have made progress in motor decoding and sensory restoration, but efforts such as decoding higher-order cognition, subjective experiences, and consciousness remain a major scientific challenge. Current neuroscientific frameworks have not yet provided a comprehensive understanding of consciousness, limiting the development of cognition-oriented BCI systems. Revolutionary breakthroughs need to be made in neuroscience, not only in observational approaches but also in research mindsets, so that the essence of consciousness can be further recognized. BCIs may play a role as a powerful tool for that research.

5. Current academic consensus and future prospects

In light of the latest available literature, we have summarized the current academic consensus on BCI research and applications based on the current technical level and related ethical concerns:

i) Current BCI-related research should prioritize meeting the stringent demands of disabled patients, such as functional restoration and medical rehabilitation, rather than development and research for non-essential demands, and especially applications for non-medical aims, such as enhancements in motor or cognitive functions in a healthy person (making a "superhuman"). Exaggerated "mind-reading" narratives should be rejected.

ii) Invasive high-precision systems and non-invasive safe, wearable systems should be developed in parallel. Semi-invasive BCIs, and minimally invasive ones in particular, are predicted to be the optimal clinical solution in the next 5–10 years.

iii) Advances in AI-driven decoding algorithms and flexible bioelectronic materials may lead to significant breakthroughs in BCI-related devices.

iv) The establishment of the aforementioned BCI-related ethical principles is an urgent task for researchers worldwide. Underlying topics should include, but not be limited to, repair priority, cautious enhancement, and strict supervision, restricting non-medical elective cognitive enhancement, and protecting neural autonomy and mental privacy. Standardized neural data privacy protection systems will be constructed synchronously.

6. Conclusions

Undoubtedly, BCIs have entered a new era of closed-loop neuromodulation and clinical translation, as they gradually begin to play a crucial role in scenarios such as rehabilitation of patients with dyskinesia or enhancement of the self-care ability of disabled individuals. BCIs are regarded as the most transformative neurotechnologies and they have great commercial value. Nevertheless, technical stability, long-term clinical safety and

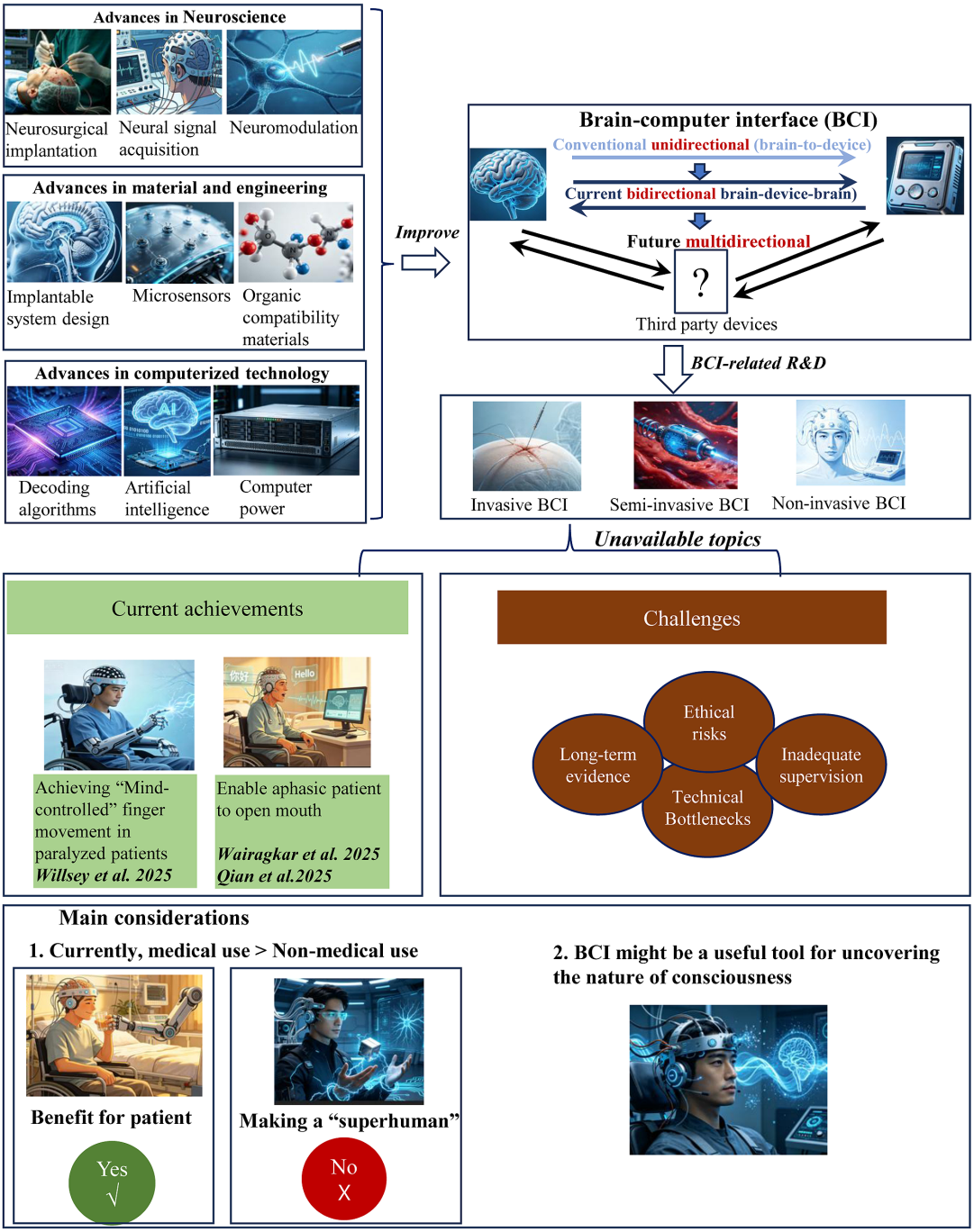

Figure 1. Brain-computer interfaces: A lifeline or a Pandora's box for humanity?

efficacy, and ethical risks are limiting the maturity of the field. The future of BCIs will depend not only on technological innovation but also on society's ability to establish robust ethical and regulatory frameworks. Whether BCIs become a lifeline for millions of patients or a source of new societal risks will be determined by the choices made today (Figure 1).

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Policy Forum

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Moving long-term care insurance upstream: A geriatric-syndrome-oriented framework for healthy aging in China

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SUMMARY: Long-term care insurance (LTCI) is commonly understood as a social insurance mechanism that compensates care-related costs after disability has occurred. This compensation function remains essential, but it is insufficient in the context of rapid population aging, multimorbidity, cognitive impairment, and long-term family caregiving burden. In older adults, disability often emerges from the cumulative interaction of geriatric syndromes, including frailty, recurrent falls, cognitive decline, malnutrition, depressive symptoms, pressure injuries, together with multimorbidity, environmental vulnerability, and caregiver burden. This article argues that the next stage of LTCI reform should not simply expand coverage or reimbursement, but should incorporate earlier identification of functional risk, comprehensive geriatric assessment, continuous care, caregiver support, and functional outcome evaluation. Existing quasi-experimental studies from China suggest that current LTCI pilots are associated with partial benefits in cognitive and psychological outcomes, changes in healthcare utilization including reduced hospitalization in some studies, modest improvements in health-related quality of life, and favorable frailty-related outcomes. However, these studies do not establish the effectiveness or added value of a geriatric-syndrome-oriented LTCI model. We therefore distinguish between the current evidence base and a proposed reform model, outline potential pathways linking LTCI to healthy aging, and propose operational priorities for future evaluation.

Keywords: intrinsic capacity, caregiver burden, frailty, cognitive impairment, dementia care, CHARLS

1. Why long-term care insurance (LTCI) should target geriatric syndromes

The primary rationale for LTCI is economic protection. Long-term disability generates persistent, unpredictable, and often catastrophic costs for families. Recent work based on the China Health and Retirement Longitudinal Study (CHARLS) has shown that conventional measures of catastrophic health expenditure may underestimate the real burden borne by older adults with cognitive or physical functional limitations when formal long-term care costs and informal caregiving costs are not included (*1*). This finding supports LTCI as a necessary social protection instrument.

However, a purely compensatory interpretation of LTCI is clinically incomplete. Disability in later life is rarely a sudden or static state. The World Health Organization has emphasized that complex health states in older age often arise from multiple interacting factors, including frailty, falls, delirium, urinary incontinence, and pressure injuries (*2*). If LTCI intervenes only after severe disability has occurred, it remains largely an ex post payment system. If it can identify declining functional capacity earlier and support care continuity, it may become part of the infrastructure for healthy aging. In this context, healthy aging should not be reduced to fewer hospitalizations or delayed disability alone. It also includes maintaining functional ability, autonomy, social participation, and the possibility of aging in place despite chronic disease and declining intrinsic capacity.

This question is timely in China, where LTCI is moving from local pilots toward broader institutionalization (*3*). The key policy issue is not whether LTCI should retain its compensation function; it must. The question is whether the system can add a second function: identifying modifiable geriatric risks before disability becomes irreversible. LTCI is not expected to replace medical care, rehabilitation, or public health services. Its distinctive role lies in its longitudinal relationship with functional dependency, daily care needs, and family caregiving. While medical services are often episodic and disease-oriented, LTCI is positioned around sustained functional support across home, community, and institutional settings. This makes LTCI a potentially suitable financing

and coordination platform for linking geriatric risk identification with long-term functional maintenance. International experience supports this broader view. Japan's community-based integrated care system links medical care, long-term care, preventive care, and daily living support within local community settings, illustrating that LTCI can be embedded in service organization rather than limited to reimbursement (*4*).

A useful clinical distinction is between disease-driven disability and syndrome-driven disability. Disease-driven disability refers to persistent functional limitation after a specific disease or injury, such as residual motor impairment after stroke, advanced Parkinsonian disability, or functional decline after hip fracture. These conditions require disease-specific treatment, rehabilitation, and secondary prevention. Syndrome-driven disability, in contrast, results from multifactorial states not attributable to a single disease. Frailty, recurrent falls, malnutrition, depressive symptoms, cognitive impairment, dysphagia, pain, and caregiver exhaustion may interact with multimorbidity, polypharmacy, unsafe environments, and weak social support to reduce functional reserve. In this article, a geriatric-syndrome-oriented LTCI model refers to an LTCI design that uses geriatric syndromes and intrinsic capacity decline as early indicators of functional vulnerability, and links risk assessment, care planning, service packages, caregiver support, and outcome evaluation around the goal of maintaining functional ability.

In real-world geriatrics, these two pathways overlap. A specific disease may trigger functional decline, but frailty, nutrition, cognition, and caregiver capacity often determine whether recovery is sustained. This is the clinical basis for moving LTCI upstream. Frailty assessment research in Japan highlights the importance of early identification for preventing disability and long-term care dependence (*5*). Japan's dementia strategy similarly emphasizes early screening, memory clinics, community-based integrated care, and coordination among medical care, long-term care, and family support (*6*). Intervention trials also suggest that multicomponent programs incorporating physical activity and nutritional counseling can reduce mobility disability among older adults with physical frailty and sarcopenia (*7*). These findings do not prove that LTCI-funded geriatric interventions are effective, but they support the plausibility of targeting a pre-disability intervention window.

2. What current evidence shows and what it does not show

Evidence from China is important but should be interpreted carefully. Existing studies mainly evaluate current LTCI pilots, which remain largely eligibility- and compensation-oriented. They therefore provide evidence on the effects of existing models, not direct evidence that a geriatric-syndrome-oriented model is superior.

Several quasi-experimental studies using CHARLS data suggest partial health-related benefits. Lin *et al.* found that LTCI implementation was associated with lower frailty levels among older adult beneficiaries and with spillover effects among spouses (*8*). Ye *et al.* reported improvements in self-rated health and cognitive function, especially among older adults with functional or cognitive impairment (*9*). Chen and Zhao found reductions in depressive symptoms and improvements in subjective well-being, as well as spillover effects on caregivers' physical health and social participation (*10*). The reported reduction in depressive symptoms should nevertheless be interpreted as modest in clinical terms, even when statistically significant.

Findings on healthcare utilization are directionally suggestive but not uniform. Yang *et al.* reported statistically significant but modest reductions in hospitalization frequency and inpatient expenditure, with no significant effect on outpatient utilization (*11*). Jiang *et al.* found reductions in outpatient visits and hospitalization, but also noted that disability status and rural residence weakened policy effects (*12*). These results may reflect competing mechanisms: formal care may reduce avoidable hospitalization, while reduced financial barriers may also release previously unmet medical needs.

Evidence on quality of life and equity further underscores the need for cautious interpretation. Lin *et al.* reported modest improvements in health-related quality of life after LTCI reform (*13*). Tian *et al.* found that LTCI improved average self-rated health, but its measured contribution to income-related health inequality was small and positive (*14*). This does not justify a strong claim that LTCI substantially widens inequity, but it does suggest that system expansion without equity safeguards may incrementally reinforce existing disparities.

The limitations of this evidence are substantial. CHARLS does not adequately capture LTCI service processes, service intensity, care quality, or whether an individual actually received specific services. Clinical geriatric outcomes such as gait speed, grip strength, fall events, pressure injuries, delirium, clinically diagnosed dementia, or caregiver burden are limited or absent. Pilot cities were not randomly selected, and local policy designs vary. Thus, current evidence supports a two-level argument: existing LTCI pilots may generate partial health-related benefits; a geriatric-syndrome-oriented model may plausibly amplify these benefits, but this remains a theoretical and policy inference requiring direct empirical testing.

3. A proposed conceptual framework

Figure 1 summarizes a proposed conceptual framework rather than an established causal mechanism. The framework distinguishes five potential pathways with different levels of evidentiary support.

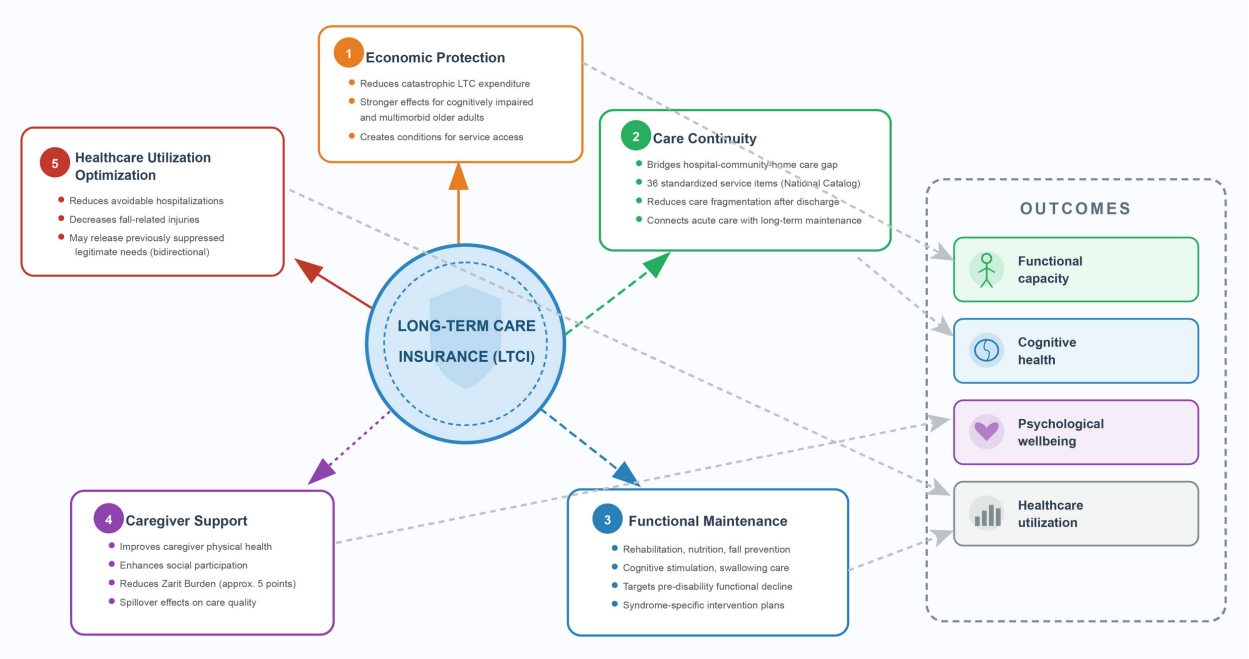

Figure 1. Proposed conceptual framework linking long-term care insurance to geriatric-syndrome-oriented reform and healthy aging outcomes. LTCI may influence healthy aging through five potential pathways: economic protection, care continuity, functional maintenance, caregiver support, and appropriate healthcare utilization. These pathways differ in evidentiary strength, ranging from quasi-experimental evidence to policy-based or theoretically plausible inference. Dashed arrows indicate hypothesized or variably supported relationships rather than established causal mechanisms.

First, economic protection is supported by quasi-experimental evidence. By reducing catastrophic health and care expenditure, LTCI may create conditions for obtaining formal care, maintaining rehabilitation, improving nutrition, and purchasing assistive devices (*1*). The downstream link from financial protection to functional recovery, however, remains inferential.

Second, care continuity is policy-based and theoretically plausible. China's national LTCI service item catalog has standardized 36 service items, providing a common service vocabulary for home, community, and institutional long-term care. Whether this catalog can support effective transitional care after hospital discharge remains to be empirically evaluated (*15*). Yet direct evidence that LTCI-funded services achieve continuous care is limited.

Third, functional maintenance would distinguish a geriatric-syndrome-oriented LTCI model from a conventional compensation model. The WHO integrated care framework emphasizes identifying declines in intrinsic capacity and developing individualized care pathways (*16*). LTCI could potentially support packages for post-stroke swallowing and mobility care, dementia-related behavioral management and cognitive stimulation, fall-risk assessment, and home modification. This pathway is supported indirectly by geriatric intervention trials, but LTCI-specific evidence remains insufficient.

Fourth, caregiver support is partially supported by spillover evidence and caregiver-intervention research. Family caregivers are central to long-term care in China. LTCI may reduce caregiver burden by expanding formal services, but training and respite support are also needed. A meta-analysis of caregiver interventions suggests that professional support can reduce caregiver burden (*17*), but the LTCI-specific caregiver-mediated pathway remains unconfirmed.

Fifth, appropriate healthcare utilization is a downstream outcome, not the primary goal. Reduced hospitalization may represent fewer avoidable complications, but lower utilization should not be equated with better policy performance if necessary care is also reduced. Evaluation should therefore distinguish low-value utilization from appropriate unmet need.

4. Operational priorities for reform

The first priority is a two-level assessment model. Current LTCI eligibility assessment is primarily designed to determine severity of long-term functional dependency, with core domains including basic activities of daily living, cognition, and sensory-communication capacity. This eligibility-oriented assessment should remain the basis for determining severe-disability coverage. However, because it is not designed to capture modifiable geriatric risks before severe dependency develops, it should be complemented by rapid screening for high-priority geriatric risks. The first level could be performed by trained assessors in community or primary care settings and include ADL/IADL, brief cognitive

screening, fall history, nutritional risk, gait speed or timed up-and-go performance, depressive symptoms, swallowing risk, and caregiver burden. The goal is risk stratification, not full diagnosis. The second level should be professional comprehensive geriatric assessment for complex cases, involving geriatrics, rehabilitation, nursing, mental health, nutrition, and social work. Evidence from comprehensive geriatric assessment research suggests potential value, but implementation must be simplified and targeted to remain feasible outside hospital settings (*18*).

The second priority is service reorganization by population risk. The national service catalog provides a standardized foundation (*15*), but itemized services should be assembled into care packages. For post-stroke disability, this may include swallowing management, mobility training, pressure injury prevention, and caregiver guidance. For cognitive impairment, it may include safety assessment, cognitive stimulation, behavioral management, and caregiver training. For recurrent falls, it may include gait training, medication review, home modification, and osteoporosis management. These packages should not expand LTCI into an unlimited payer for all medical and rehabilitation services; rather, they should coordinate existing reimbursable services around functional risk.

The third priority is a minimum core outcome set. Administrative indicators such as fund expenditure, number of beneficiaries, and service counts are necessary but insufficient. LTCI evaluation should include ADL change, fall incidence, pressure injury incidence, unplanned hospitalization, caregiver burden, time living at home, and patient-reported outcomes. Provincial-level pooling, such as the emerging Hainan model, may provide an opportunity to build linked data systems connecting assessment, claims, service processes, and functional outcomes (*19*). However, currently available Hainan information remains administrative and process-oriented, and should be interpreted as an opportunity for future evaluation rather than evidence of health impact. Digital governance may improve assessment, service coordination, and policy feedback, but it also requires safeguards for data quality, privacy, algorithmic bias, and equity (*20*).

5. Conclusion

China's LTCI reform should not be viewed only as expansion of a reimbursement scheme for severe disability. Its broader policy potential lies in whether it can become a functional ability-oriented platform that links geriatric risk identification, coordinated care packages, caregiver support, and outcome-based evaluation. A geriatric-syndrome-oriented LTCI model offers a testable pathway for shifting long-term care from late-stage disability compensation toward functional maintenance and healthy aging. This transition, however, should be evaluated through linked assessment, claims, service delivery, clinical geriatric, caregiver-reported, and patient-reported outcome data before strong claims of effectiveness are made.

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Review

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Pathways for embedding digital health technologies and their governance mechanisms in long-term care insurance systems: A comparative review of Japan, South Korea, and China

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SUMMARY: Rapid population aging is increasing demand for long-term care (LTC), prompting many countries to institutionalize financing and service provision through long-term care insurance (LTCI). Digital health technologies are increasingly embedded into LTCI, and yet the pathways in which they are embedded and their governance effects differ across institutional contexts. This comparative review synthesizes evidence from Japan, South Korea, and China across five operational domains—institutional foundations, eligibility determination, service management, fund oversight, and policy steering—and uses a sociotechnical systems lens to analyze how technology and institutions co-evolve. We propose a three-layer model of institutional embedding linking welfare-boundary constraints, governance mechanisms shaping data-driven operations, and path dependence in policy and implementation. In the three countries, digital health technologies have not fundamentally expanded the welfare boundary of LTCI, but they have reshaped how LTCI is administered, shifting *i*) needs assessment from experience-led judgment toward data-driven decision-making support, *ii*) service management from flexible discretion toward rules and platform-based coordination, and *iii*) oversight from ex post auditing toward process-oriented monitoring. Distinct national pathways have emerged: a supplementary-technology pathway in Japan, a state-led integration pathway in South Korea, and an exploratory co-evolutionary pathway in China. These benefits are accompanied by practical risks, including algorithmic bias, inconsistent data quality, privacy and security concerns, and potential erosion of institutional flexibility. The proposed model helps explain cross-national divergence and provides a governance-oriented basis for selecting embedding strategies and safeguards in different LTCI contexts.

Keywords: sociotechnical systems theory, model of institutional embedding, data infrastructure integration, fund oversight, algorithmic bias, policy implementation

1. Introduction

Population aging has become one of the core trends in changes to the current composition of the global population. According to United Nations World Population Prospects 2024, the proportion of the global population age 65 years and older is projected to increase from 10.2% in 2024 to 20% in 2070 (*1*). With the increase in life expectancy and the decline in the fertility rate, the size of the elderly population continues to expand, and the need for long-term care caused by chronic diseases, functional decline, and disability continues to increase. Care issues are gradually being transformed family affairs into social problems requiring institutional responses (*2*). This is the background in which the long-term care insurance system (LTCI) has been gradually created, and it has become an important institutional arrangement to deal with the risk of geriatric care.

In terms of regional distribution, the aging process differs markedly in different countries (Figure 1). Europe and the US had an aging population earlier, and the level of aging was generally high. East Asian countries, as represented by Japan, South Korea and China, have experienced a more rapid demographic transition in a relatively short period of time (*3-6*). Japan

has a profoundly aging population, South Korea has a significantly accelerated rate of aging and is expected to surpass Japan's level of aging, and China has a large and continuously growing elderly population (Figure 2). The three countries are all located in East Asia and are influenced by traditional Confucian culture, where the family has long been responsible for providing care. With the reduction in family size and the increase in population mobility, however, the family's capacity to provide care has gradually weakened, hampering its ability to deal with the rapid growth of care needs (*7*). This transition prompted the three countries to establish LTCI systems in an institutionalized manner (*8*) to respond to the intense need for care.

As LTCI expands, its operation requires more sophisticated information integration. Digital health technologies (DHTs)—ranging from information systems and data platforms to sensors, wearable devices, assistive robotics, and AI-enabled analytics—have been introduced into LTCI-related processes (*9-12*). Japan has used systems and care robots to improve care workflows and quality (*13*), South Korea has used national data integration to link services and oversight (*10*), and China has developed pilot platforms that integrate needs assessment, service records, and fund settlement (*14*). The embedding of DHTs has therefore become a key

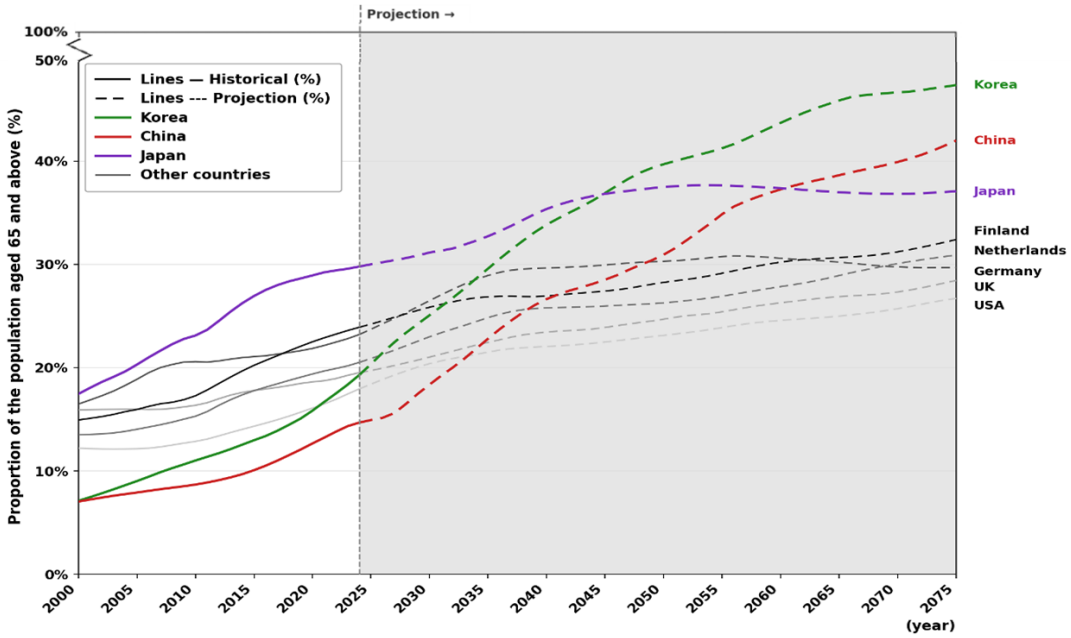

Figure 1. Levels of Aging in Japan, South Korea, and China Compared to Selected European and American Countries. *Data source*: United Nations (UN). World population prospects 2024. *https://population.un.org/wpp/Publications/Files/WPP2024_Highlights.pdf*

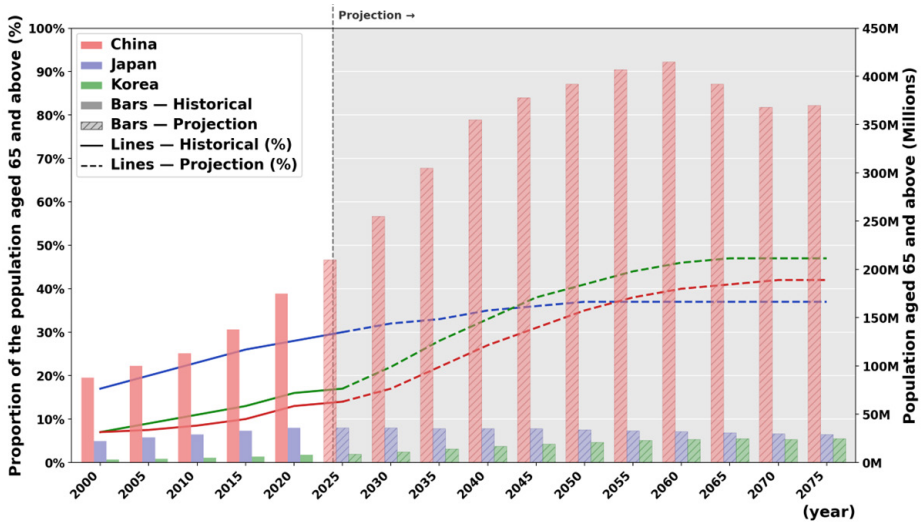

Figure 2. Population Size and Proportion of People Age 65 and Older in Japan, South Korea, and China. *Data source*: United Nations (UN). World population prospects 2024. *https://population.un.org/wpp/Publications/Files/WPP2024_Highlights.pdf*

driver of changing care governance (Figure 3).

Although a growing body of research has examined the use of DHTs in long-term care, cross-national comparisons that explain why similar technologies produce different governance effects remain relatively limited. Existing studies tend to focus on patterns of adoption or technological capabilities, while paying less attention to how institutional contexts shape the way in which these technologies operate in practice. To address this gap, this review compares Japan, South Korea, and China across five key operational domains and it develops a mechanism-oriented analytical framework to explain cross-national divergence.

2. Review design and analytical framework

2.1. Review design and information sources

This study is a comparative, policy-oriented narrative review. It synthesizes peer-reviewed articles and publicly available institutional materials, including laws, policy documents, official reports, yearbooks, and administrative guidance related to the creation of LTCI and use of DHTs in Japan, South Korea, and China. Source retrieval was updated through April 5, 2026, according to the access dates listed for the cited materials. This review used only publicly available documents and did not involve human participants, individual-level data, or animal experiments, so formal ethics approval and informed consent were not applicable.

2.2. Comparative analytical framework and pathway criteria

The comparison involved five operational domains: institutional foundations, eligibility determination, service management, fund oversight, and policy steering. Within each domain, we examined where DHTs are embedded, what aspects of governance they act upon, and the extent to which they reshape routine operations. To avoid impressionistic classification, national pathways were identified using three explicit criteria: *i*) the level of governance steering, referring to the degree of state or insurer control over standards and implementation; *ii*) data infrastructure integration, referring to the extent to which assessment, service, payment, and supervisory data are linked; and *iii*) institutional maturity and path dependence, referring to how strongly pre-existing organizational arrangements constrain new technical choices. These criteria are analytical rather than fixed labels, meaning that national pathways can evolve as institutional conditions change.

3. Key concepts and analytical dimensions

3.1. Defining DHTs in LTCI

In this review, DHTs refer to digital tools and systems used to support or transform health- and care-related activities such as data collection, information exchange, decision-making support, and coordination.

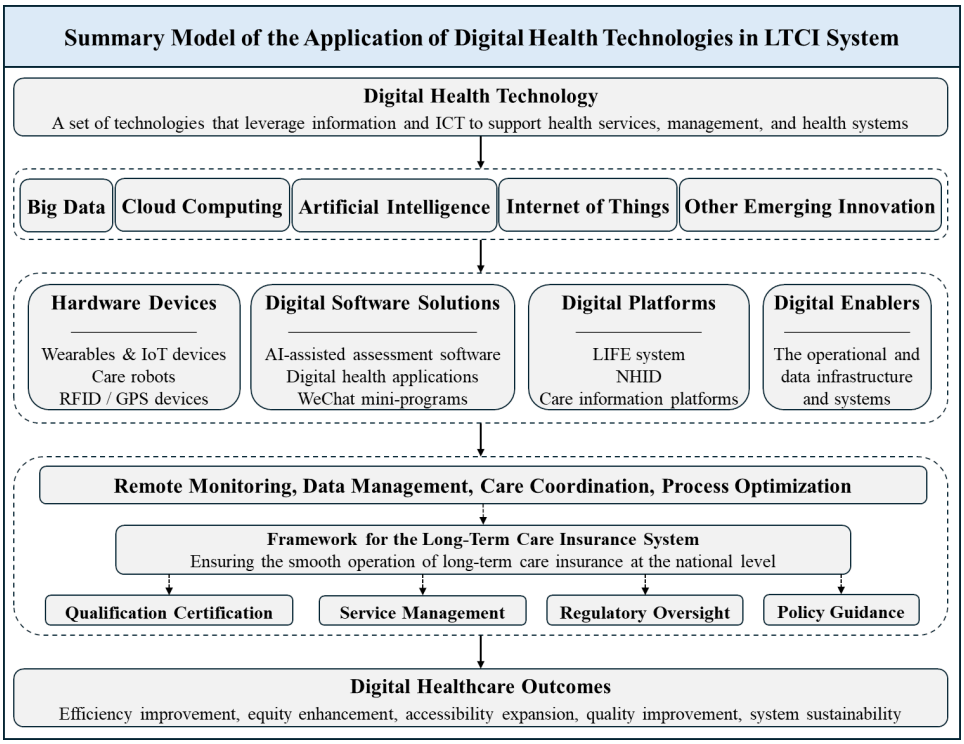

Figure 3. Diagram illustrating the integration of digital health technologies into LTCI. *Data source*: World Health Organization (WHO). Global strategy on digital health 2020-2027. *https://www.who.int/publications/i/item/9789240116870*. Status and Trends of the Digital Healthcare Industry. *https://doi.org/10.4258/hir.2024.30.3.172*

For analytical clarity, DHTs in LTCI are limited to technologies embedded in assessment, management, settlement, or oversight rather than all technologies used in elderly care. They are grouped into three functional categories: *i*) data capture and remote monitoring technologies, such as sensors and wearable devices; *ii*) information and workflow infrastructures, such as application systems, settlement platforms, and interoperable databases; and *iii*) intelligent decision and assistance technologies, such as AI-enabled scoring, fraud detection, care robots, or algorithm-assisted supervision.

3.2. Key LTCI operational links and governance effects

DHTs are not embedded into an abstract insurance system but into specific operational links: needs assessment and certification, care planning and service delivery, payment and settlement, and quality or fund supervision. Their governance effects depend on the aspects they act upon. In practice, DHTs reshape information flows, alter the basis of decision-making, and redistribute accountability by making some behaviors more evident, comparable, or auditable than before. This perspective helps distinguish between technology that merely supports existing tasks and technology that reorganizes how those tasks are governed.

3.3. Why a sociotechnical systems perspective?

The comparative findings described above require a framework that goes beyond simple adoption counts or policy diffusion narratives. Sociotechnical systems theory is useful because it treats technologies, organizational routines, decision rules, and governance arrangements as mutually constitutive rather than independent variables. In the present context, the question is not only whether a country uses AI, robotics, or platforms, but how these tools become operative within insurance eligibility, service coordination, and accountability relations. This perspective is especially suitable for explaining cross-national divergence because similar technical devices can have very different institutional effects when insurer composition, data governance, implementation authority, and policy priorities differ. It therefore provides the theoretical bridge between the descriptive comparison of systems and the later construction of an explanatory model.

4. Comparative findings: Institutional foundations and embedding of DHTs

4.1. Institutional foundations as enabling and constraining conditions

Japan, South Korea, and China differ substantially in when LTCI was introduced, how it is governed, and how mature the system is (Table 1). Japan has the longest-running LTCI system and a relatively stable division of

Table 1. Institutional foundations and governance structures of LTCI in Japan, South Korea, and China

Dimension	Japan	South Korea	China
System launch	Legislated and implemented in 2000	Legislated and implemented in 2008	Pilot efforts launched in 2016; moving toward nationwide unification[a]
Governance model	Municipalities serve as insurers	Unified administration by the NHIS	Central coordination with local implementation
Population covered	Age ≥ 65; age 40–64 with specified diseases	Age ≥ 65; below age 65 with specified geriatric conditions	Progressive expansion toward universal coverage, prioritizing severe disability[b]
Financing	Premiums plus taxes (50% each)	Premium-based financing plus about 20% fiscal subsidy	Multi-source financing (employers, individuals, and government)[c]
User co-payment	10% (20%-30% for higher-income groups)	15% for home care; 20% for institutional care	Dynamically adjusted[d]
Service types	Home care, institutional care, community-based integrated services (home care prioritized) (*16*)	Home care, institutional care, partial cash benefits (home care prioritized) (*19*)	Home, community, and institutional care ("9073" pattern of elderly care)
Benefit classification	Support levels 1–2; care levels 1–5	Levels 1–5 plus cognitive support level	Three disability levels: mild, moderate, severe[e]
System scale[f]	About 7.49 million beneficiaries certified; 2.40 million workers	About 1.16 million beneficiaries certified; 0.70 million workers	More than 308 million enrollees; over 3.3 million beneficiaries; nearly 0.37 million workers

Notes: [a]Pilot efforts began in 15 cities in 2016 and expanded to 49 cities in 2020; the 2026 Opinions marked a shift toward institutional implementation nationwide. [b]During the pilot phase, coverage mainly extended to employees and urban-rural residents, with priority given to people with a severe disability. [c]Pilot financing included proportional, fixed, and mixed models; the 2026 Opinions specify shared financing by employers, individuals, and government. [d]Local co-payment levels differed substantially during the pilot phase and are now subject to dynamic adjustment. [e]Earlier local standards were inconsistent; a unified national assessment framework is now being promoted. [f]Data dates: Japan (July 2025), South Korea (December 2024), China (March 2026).

Table 2. Eligibility assessment and use of digital health technologies in LTCI

Dimension	Japan	South Korea	China
Certifying body	Municipal governments	NHIS	Government-led with participation of multiple actors[a]
Assessment tools	Standardized questionnaire	Structured scale	Gradual rollout of unified national standards[b]
Technical use	Computer-assisted preliminary assessment	Computer analysis generating standardized scores	Information systems supporting application and review[c]
Assessment process	Computer pre-assessment followed by committee review	On-site assessment, computer analysis, committee review	Online application, administrative review, on-site assessment, further review and disclosure
Intelligent exploration	GPT-assisted pilot assessments	Information systems supporting eligibility review	Support from a national unified system[d]

Notes: [a]Includes government agencies, designated institutions, and third-party assessors. [b]Pilot practices used different scales and questionnaires; a unified national disability assessment standard is now being promoted. [c]Local exploration has included WeChat-based portals, mini-programs, and mobile applications; current arrangements are moving toward unified online application and review by medical insurance agencies. [d]The long-term care insurance subsystem under the national medical insurance information platform is expected to integrate intelligent assessment and data-validation.

responsibilities in which municipalities act as insurers (*15-17*). South Korea introduced LTCI later, but the system's reliance on the National Health Insurance Service (NHIS) and linked national databases allows it to be steered more centrally (*18,19*). China is still in the stage of pilot programs and scaling; localities have differed widely in the populations covered, financing arrangements, methods of assessment, and services supply, although recent national policy documents indicate movement toward a more unified system (*20-23*). These institutional differences are not background details alone. They shape the depth to and direction in which technologies are embedded by defining who can set standards, who controls data, and how easily routine workflows can be standardized across providers and regions.

4.2. Eligibility determination and assessment mechanisms

Eligibility determination is the entry point to LTCI because it converts care needs into certified benefit levels (Table 2). Japan has long used computerized preprocessing to support care-needs certification, while final decisions are reviewed through committee-based deliberation (*24,25*). South Korea uses structured assessment and system-supported scoring within a more centralized administrative framework (*26,27*). In China, assessment remains more inconsistent. Local pilot efforts have relied on different scales and administrative arrangements, while digital systems have primarily supported application receipt, documentation, and process control rather than fully standardized certification; national efforts are now directed toward harmonizing disability assessment standards and information support (*21,22,28,29*). In all three countries, DHTs are embedded first in data capture and preprocessing, but they have greater influence on the final decision where standards and institutional authority are more unified.

4.3. Service management, interoperability, and resource allocation

Service management involves care documentation, inter-organizational coordination, and payment-related data linkage (Table 3). In Japan, a system to exchange care plan data is used to connect providers and streamline the electronic flow of care management information (*30,31*). In South Korea, NHIS-linked data infrastructures facilitate integration between medical and LTC information and support the linking of service records and reimbursement processes (*32,33*). China has developed numerous local platforms for service records, dispatching, and settlement, but interoperability remains inconsistent across cities and provinces, and the quality of operational data depends greatly on local implementation capacity (*22,34,35*). The comparative pattern suggests a clear causal logic: where data infrastructures are nationally integrated, technology serves as a coordinating mechanism for services and payment; where systems remain locally fragmented, technology primarily supports recording and experimentation rather than fully standardized allocation.

4.4. Fund oversight and supervisory capacity

The embedding of DHTs is also changing how LTCI systems supervise quality and fund integrity (Table 4). Japan uses the LIFE system to collect and analyze care-related information and to link data use with quality improvement and payment adjustment (*36,37*). South Korea relies on centralized data comparison, claims review, and related supervisory mechanisms within the NHIS/NHID architecture (*32,33,38*). China has moved

Table 3. Use of digital health technologies in the management of LTCI services

Dimension	Japan	South Korea	China
Data carrier	System to exchange care plan data	National Health Information Database	National unified system being created[a]
Data integration	Inter-institutional exchange of business data	Unified integration of medical and LTC data	Primarily local platform integration; cross-regional interoperability still evolving[b]
Form of use	Electronic care plans and settlement	Automatic retrieval of service records with linked settlement	Promotion of full-process digital management
Use scenarios	Care planning, confirmation of service content, settlement	Retrieval of service records, claims submission, institutional assessment-result inquiry	Service-record management, intelligent dispatching, quality feedback[c]
Infrastructure character	Efficiency-oriented workflow optimization	Integration-oriented linkage of services and payment	Support-oriented, platform-driven standardization of operations

Notes: [a]During the pilot phase, local governments built their own platforms; a national LTCI subsystem is now being advanced under the national medical insurance information platform. [b]Some localities have achieved data integration, but cross-regional interoperability remains inconsistent. [c]Local exploration has included intelligent dispatching, cross-regional service coordination, and service-quality feedback; future national systems are expected to standardize operational workflows and data collection.

Table 4. Digital health technologies in LTCI supervision and governance

Dimension	Japan	South Korea	China
Supervisory body	Multi-level local supervision	Unified NHIS management	Central coordination, local implementation, multi-actor participation[a]
Supervisory tool	LIFE system	NHID	National unified system being created[b]
Technical use	LIFE-based analysis of the quality of care and functional improvement, linked to payment add-ons and electronic review	Automatic comparison and detection of anomalies in service records and claims, including fraud detection logic	Behavior recognition and intelligent verification approaches exploring real-time monitoring and data validation[c]
Supervisory process	Pre-set standards, in-process data recording, post hoc review and guidance	Uploading of service records, automated validation, centralized payment review, tracking of anomalies	Setting standards, recording processes, system review, ex post recovery
Supervisory focus	Appropriate benefit use and improvement of quality	Fund risk control and curtailment of improper claims	Fund security and fraud prevention[d]
Information disclosure	Institutional and policy information disclosed through LIFE and Q&A materials	Regular online disclosure of institutional assessments and regulatory information	Primarily local disclosure with gradual movement toward unified national disclosure

Notes: [a]Includes medical insurance administrative agencies and third parties. [b]Local pilot platforms remain in use while the national LTCI subsystem is being developed. [c]Local experimentation has included GPS tracking verification, facial recognition, video supervision, and cloud-based patrol systems. [d]Priority targets include fraudulent services, falsified assessments, identity theft, and improvement of performance evaluation and standardization.

toward digitally supported supervision through service-record platforms, post-payment review, and local experimentation with behavioral verification, video review, or intelligent monitoring, but these practices remain highly inconsistent across cities and are being gradually folded into a more unified national framework (*34,35,39-43*). This means that China is not simply "lagging behind"; rather, it illustrates how fragmented pilot efforts can generate innovation while also producing inconsistent data quality, inconsistent enforcement, and variable local governance capacity. This fragmentation is not only a technical issue but also reflects a broader governance structure characterized by decentralized experimentation and regionally differentiated policy implementation.

4.5. Policy steering and national development priorities

National policy priorities further shape the role assigned to DHTs (Table 5). Japan has emphasized care robots and Internet of Things (IoT) devices to relieve labor shortages and improve the quality and precision of care within an already mature insurance system (*44,45*). South Korea

Table 5. Policy orientation of and national pathways for use of digital health technologies

Dimension	Japan	South Korea	China
Service delivery focus	Care robots and IoT-based care devices	Smart elderly care platforms and AI remote terminals	Internet + nursing care and smart elderly care platforms[a]
Priority use	Supporting labor input and improving the precision of care	Enhancing data integration and linking services to payment	Expanding service coverage through remote nursing and regional coordination[b]
Role of technology	Improving the efficiency of services and quality of care	Enhancing fund supervision and standardizing system operation	Improving service accessibility and supporting institutional development[b]
Institutional effect	Embedded within the existing system as supplementation and optimization	Embedded in core institutional links and reshaping operational governance	Being promoted along with institutional implementation in a co-evolutionary manner
Pathway type	Supplementary technology pathway	State-led integration pathway	Exploratory co-evolutionary pathway

Notes: [a]Recent national policy has proposed exploring the inclusion of intelligent LTC services and supportive assistive devices within reimbursement arrangements, extending the focus of technology from service provision toward institutional support. [b]Because pilot areas face shortages of professional caregivers and an uneven distribution of services in urban and rural areas, DHTs in China partially compensate for supply shortages and limited services, which differs from the logic of technology use in more mature systems such as Japan and South Korea.

has prioritized national platform building, integrated service-payment linkage, and AI-IoT initiatives for older adults in local communities (*46,47*). China has promoted smart elderly care platforms and "Internet + nursing care" not only to improve efficiency but also to expand access amidst disparities in service availability and continuing institutional implementation (*48,49*). Policy orientation therefore interacts with institutional structure: mature systems tend to deploy technology for optimization, centralized systems for integration and rule enforcement, and pilot-based systems for both service expansion and organizational experimentation.

4.6. Interim synthesis: From institutional differences to pathway differences

Taken together, these findings suggest that differences in national pathways cannot be explained simply by the level of technological sophistication. In Japan, the combination of a mature system and decentralized insurers tends to channel DHTs into incremental and supportive roles. In contrast, South Korea's centralized governance and integrated data environment allow technology to be further incorporated in core institutional processes. China presents a different picture: ongoing institutional development creates room for experimentation but also results in fragmentation, inconsistent data quality, and variation in local implementation. These patterns highlight that the effects of DHTs are shaped as much by institutional conditions as by the technologies themselves. Differences in institutional structure, data infrastructure integration, and policy orientation jointly shape distinct national pathways by which DHTs are embedded (Figure 4).

5. Mechanisms and the three-layer model of institutional embedding

5.1. Why similar technologies have different governance effects

Describing national pathways alone is not sufficient without clarifying how technology actually interacts with institutional structures. From a sociotechnical perspective, DHTs do not operate on a neutral administrative foundation. Instead, they are interpreted and reshaped through existing welfare objectives, organizational arrangements, and governance rules (*50*). As a result, the same type of technology may play a limited, supportive role in one system while becoming structurally transformative in another. What matters, therefore, is not only the presence of technology, but how it becomes embedded within institutional processes.

5.2. Needs assessment: From experience-led judgement to data-supported decision-making

In early-stage LTCIs, needs assessment depended heavily on home visits, paper records, and expert judgement (*24*). As DHTs become embedded, information is recorded more systematically and processed more consistently, and digital scoring or algorithm-assisted suggestions increasingly support certification decisions (*25*). And yet this does not mean that human judgement disappears. Rather, the decision-making basis is rebalanced. In settings with more unified criteria, digital tools reinforce standardization and reduce inter-assessor variation; in settings where standards remain heterogeneous, digital systems coexist with case-by-case judgement and may expose inconsistencies rather than eliminate them (*21,22,51*).

5.3. Service management: From discretionary coordination to rule- and platform-based coordination

LTCI service management initially leaves room for

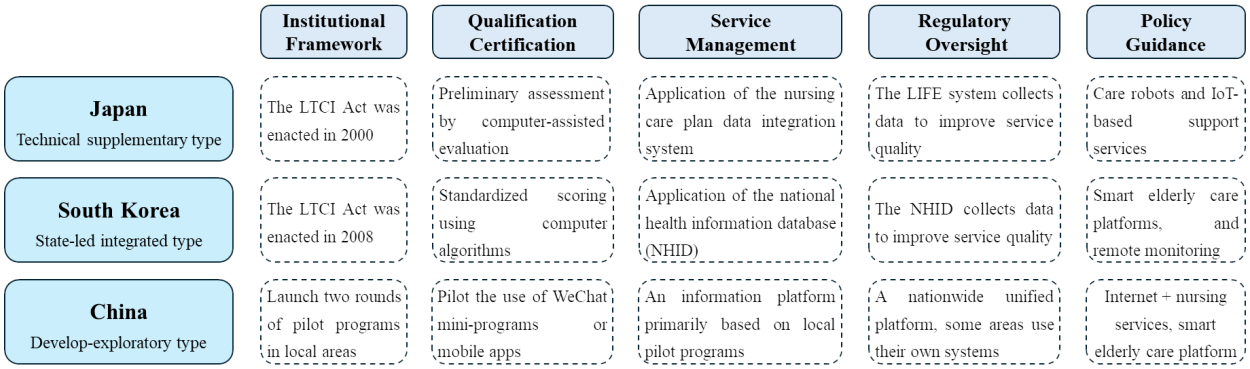

Figure 4. Summary of how digital health technologies are integrated into LTCI in different countries.

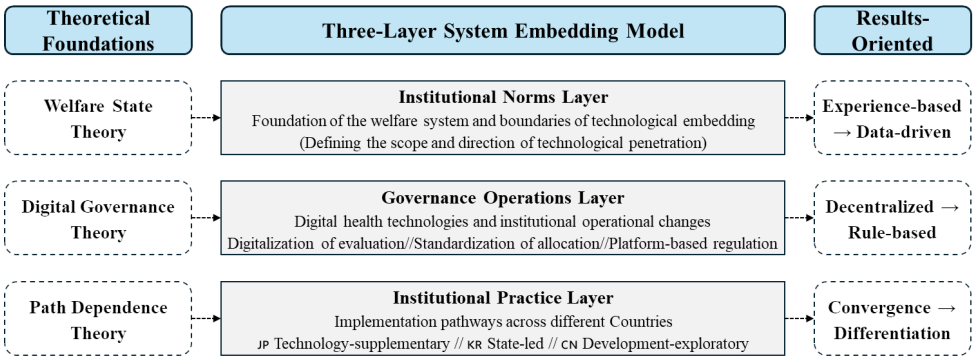

Figure 5. The three-layer model of institutional embedding and its mechanism of action.

discretionary adjustment because older adults have heterogeneous and changing needs (*52*). Once services, care plans, provider records, and settlement operations are combined into common digital infrastructures, coordination increasingly follows platform rules and standardized data formats (*53*). The result is greater traceability, faster settlement, and more comparable records across providers. However, these gains can also narrow the space for locally negotiated or professionally improvised adjustments, and especially when platform logic becomes tightly linked to payment rules (*54*). The shift is most visible where payer authority and data infrastructure are already centralized, but similar tendencies are emerging in China as local platforms are brought in line with the national information architecture.

5.4. Oversight: From ex post auditing to process-oriented monitoring

Conventional fund supervision often relies on ex post review, sampling inspection, or manual verification, which become increasingly difficult as system scale and claims become more complex (*55*). The embedding of DHTs changes this supervisory logic by allowing rapid comparison of service records, claim patterns, and behavioral tracking, thereby enabling earlier detection of anomalies and more continuous forms of monitoring (*32,33,36,37,56*). This does not simply make oversight faster. It also changes the temporal structure of governance by having control exercised closer to the point at which service is provided. In China, however, the move toward intelligent supervision has highlighted the importance of local data quality and implementation capacity; without stable standards and reliable inputs, real-time monitoring can increase the administrative burden without enabling equally reliable control.

5.5. The three-layer model of institutional embedding

To explain these differences systematically, we have integrated welfare state theory, digital governance theory, and path dependence to construct a three-layer model of institutional embedding (Figure 5) (*57-59*). The model is not a restatement of empirical findings. Rather, it explains how the findings are generated at the institutional level. Specifically, the institutional norms layer explains why the tripartite welfare boundary remains stable despite dramatic technological changes. The governance operations layer explains why the governance effects vary in intensity and direction between the areas of assessment, service management, and monitoring. The institutional practice layer explains why the three countries' paths diverge instead of converging on a single model.

5.5.1. Institutional norms layer

In the institutional norms layer, welfare boundaries define what technology is allowed to do. LTCI is a welfare system designed to socialize the risk of care through collectively organized financing and entitlement rules. DHTs can improve how the system functions, but they do not themselves redefine who is covered, what risks are collectively pooled, or where the political boundary of entitlement lies (*57,60,61*). This is why technology in all three countries operates primarily within, rather than beyond, the welfare logic of LTCI.

5.5.2. Governance operations layer

In the governance operations layer, digital infrastructures reshape decision-making bases, workflow coordination, and accountability structures (*58*). Here, DHTs have the greatest impact: data platforms standardize inputs, algorithmic tools support certification and detection of anomalies, and interoperable systems connect assessment, service delivery, and payment. The key point is that governance effects occur not as a result of technology alone but from the coupling of technology with administrative authority, database architecture, and enforcement rules. This explains why greater integration is evident in South Korea than in Japan and why integration is more inconsistent in China despite rapid experimentation.

5.5.3. Institutional practice layer

In the institutional practice layer, earlier institutional choices lock in subsequent trajectories (*59*). Mature municipal insurer arrangements in Japan channel DHTs into the supplementary optimization of existing routines (*30,31,44,45*). South Korea's centralized governance reinforces state-led integration because new tools can be incorporated into already unified administrative pathways (*32,33,46,47*). China's pilot program-based evolution produces a more exploratory co-evolutionary pathway in which technical systems and institutional rules are still being shaped together, but this same openness also leads to fragmentation and inconsistent implementation (*22,34,35,39*).

5.5.4. Explanatory power of the model

The model clarifies why the three pathways should not be treated as fixed descriptive labels alone. They are the practical outcome of how welfare boundaries, governance mechanisms, and path dependence interact. If governance steering is more centralized, if data infrastructures are more interoperable, or if institutional routines stabilize, the pathway by which technologies are embedded in a country may also shift. The model therefore explains both cross-national divergence and the conditions under which future convergence might occur. For example, a decentralized system that becomes more data-integrated and centrally coordinated may shift from a supplementary pathway toward a more state-led integration pathway.

6. Risks and governance challenges

6.1. Algorithmic bias and assessment inequity

As DHTs become more deeply involved in assessment and supervision, LTCI operations rely more heavily on data quality, variable selection, and model design. If underlying datasets are incomplete or systematically skewed, algorithm-assisted tools can reproduce or amplify inequities in certification and service allocation (*62-64*). This concern is not abstract. In Japan, emerging discussion around AI-assisted care-needs assessment has already raised questions about accuracy, explainability, and the appropriate boundary between algorithmic recommendation and committee judgement (*25*). In South Korea, the automated fraud detection logic embedded in the NHIS claims review raises similar issues of false positives, as well as procedural burdens on providers when challenging algorithmic results (*38*). In China, local pilot adoption of facial recognition, GPS tracking verification, and video surveillance has raised questions about the proportionality of biometric data collection and the accountability framework for use in monitoring at the benefits level (*39-43*).

6.2. Data quality, fragmentation, and differing local capacity

A second challenge concerns inconsistent data quality and institutional capacity. China is the clearest example because local pilot programs have adopted different assessment instruments, service platforms, and supervisory tools, which makes cross-regional comparability difficult and complicates national scaling (*21,22,34,35*). But fragmentation is not only a Chinese issue; even in more mature systems, inconsistent coding practices, incomplete records, or provider-level variation can diminish the reliability of digitally mediated governance. Without clear standards, better technology may merely digitize existing inconsistencies.

6.3. Privacy and security

Large-scale collection and linkage of sensitive data results in substantial privacy and security issues (*65*). LTCI systems increasingly handle information on disability, family support, service use, and sometimes behavioral or biometric patterns. The more that assessment, payment, and supervision are integrated, the more important that governance safeguards regarding legitimate access, data minimization, cross-departmental

sharing, and accountability for breaches become. Privacy protection is therefore not an external ethical add-on; it is an essential element of the justification for embedding DHTs.

6.4. Standardization versus institutional flexibility

Finally, digital governance can erode institutional flexibility. Standardized platforms improve comparability and administrative efficiency but they may also narrow the discretionary space needed to accommodate heterogeneous and changing care needs. In LTC, some degree of professional judgement and local adjustment remains essential. The governance challenge is therefore not to choose between digitization and flexibility, but to specify which decisions should be standardized, which should remain reviewable by human actors, and how appeal or override mechanisms should be designed.

7. Institutional embedding and cross-national variation in DHTs

This review shifts the analytical focus from technology adoption to institutional embedding. Existing studies often catalogue digital tools used in elderly care or discuss general digital transformation in healthcare systems. In contrast, the present review explains how DHTs become consequential only when they are linked to welfare objectives, administrative authority, and operating rules. A comparison of Japan, South Korea, and China has shown that cross-national divergence is best understood through the joint effects of the level of governance steering, data infrastructure integration, and institutional maturity rather than through any simple hierarchy of technological advancement.

The findings also have practical implications. In mature but decentralized systems such as Japan's, the priority is not wholesale technological overhaul but interoperability, coordination, and careful integration that does not undermine professional discretion. In highly centralized systems such as South Korea's, the main challenge is to balance efficiency gains from integration with transparency, fairness, and safeguards against excessive dependence on automated classification or monitoring. In pilot program-to-scaling systems such as China's, the first-order tasks are harmonizing standards, enhancing local implementation capacity, and staged governance arrangements that improve data quality before expanding algorithmic control.

Several limitations should be acknowledged. First, this is a narrative review rather than a formal systematic review or meta-analysis, so the purpose is explanation and synthesis rather than exhaustive estimation of effects. Second, this analysis has focused on three East Asian countries and therefore does not cover European LTCI models or mixed public-private arrangements elsewhere. Third, China is still in an evolving policy phase, so some institutional effects are still emerging. Nevertheless, these limitations do not diminish the value of the proposed model as a framework for future comparative work on digitalization in welfare systems.

8. Conclusions

DHTs are increasingly embedded in LTCI in Japan, South Korea, and China. They have not fundamentally expanded the welfare boundary of LTCI, but they have changed how eligibility is assessed, how services are coordinated, and how fund use is supervised. The three national pathways - supplementary technology in Japan, state-led integration in South Korea, and exploratory co-evolution in China - reflect not only different technological choices but also different welfare boundaries, governance mechanisms, and institutional trajectories. The three-layer model of institutional embedding developed here helps explain that divergence and underscores a central policy lesson: digitalization in LTCI should be designed not only for efficiency but also for fairness, privacy, data reliability, and the preservation of appropriate institutional flexibility.

Although our analysis has focused on East Asia, the three-layer model may also offer a transferable analytical framework for welfare systems in other countries undergoing a transition in digital governance. By breaking down institutional embedding into an institutional norms layer, a governance operations layer, and an institutional practice layer, researchers can more clearly judge how to more accurately assess governance interventions in specific situations.

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Review

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Clinical translation and accessibility of brain-computer interfaces: From technology development to clinical application

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SUMMARY: Brain-computer interface (BCI) technology establishes a direct communication pathway between neural activity and external devices. Driven by advances in neuroscience, artificial intelligence (AI), neural signal acquisition, decoding algorithms, and implantable system design, BCIs have progressed rapidly from experimental prototypes toward clinically relevant neurotechnologies. However, the translation of these technical advances into routine clinical practice and equitable real-world access remains substantially slower than technological innovation. This review summarizes the major technological pathways of BCIs and their clinical applications, and it then examines BCI development from the perspective of clinical translation and accessibility. We focus on key barriers across the translational chain, including long-term technical stability, quality of clinical evidence, evaluation standards, reimbursement mechanisms, health-economic evidence, and the feasibility of implementation in real-world healthcare settings. We argue that the central challenge in BCI development has shifted from improving technical performance alone to building the translational infrastructure required for safe, effective, affordable, and sustainable clinical integration.

Keywords: brain-computer interface, technology development, clinical application, clinical translation, accessibility

1. Introduction

Brain-computer interface (BCI) technology aims to establish a direct communication pathway between the brain and external devices by recording neural activity, decoding neural states or intentions, and converting these signals into commands for assistive, rehabilitative, or therapeutic systems (*1*). A typical BCI system includes neural signal acquisition, signal preprocessing, feature extraction, algorithmic decoding, command generation, device control, and, in closed-loop systems, sensory or neural feedback (*1,2*). Most BCIs currently in use are non-invasive and rely primarily on electroencephalography (EEG). Implantable electrode systems, including electrocorticographic and intracortical interfaces, provide higher-fidelity neural signals and have particular relevance for patients with severe motor, sensory, or communication impairments (*3,4*).

Recent advances in neuroscience, AI, flexible electronics, and computing hardware have transformed BCI signal processing, system miniaturization, and decoding performance (*5,6*). Deep learning and generative AI have expanded the scope of BCI research beyond simple motor-intention decoding toward the reconstruction of speech, handwriting, and other high-order cognitive or communicative processes (*7*). At the same time, improved non-invasive and wearable systems, including EEG-functional near-infrared spectroscopy (fNIRS) hybrid platforms, are being developed to partly address the signal-to-noise ratio, spatial-resolution, and robustness limitations of conventional EEG-based BCIs (*8,9*). Clinically, BCIs exhibit substantial potential in stroke rehabilitation, spinal cord injury, Parkinson's disease, epilepsy, disorders of consciousness, and other neurological conditions, and particularly in communication restoration, motor control, functional rehabilitation, and closed-loop neuromodulation (*10,11*).

In China, a notable milestone in BCI clinical translation was reported on March 13, 2026, when the National Medical Products Administration approved an implantable BCI medical device, the Implantable BCI Hand Motor Function Compensation System, for tetraplegia caused by cervical spinal cord injury. The system supports hand grasping through a pneumatic glove and was subsequently incorporated into Shanghai's medical service catalogue by the Shanghai Healthcare Security Administration through an expedited process

aligned with national BCI coding guidance (*12*). This case provides a useful policy and payment example for examining how BCI technologies may move from regulatory approval toward reimbursable clinical services.

Internationally, China has identified BCI as a future-industry priority, and coordinated policy, industrial, and clinical drivers are accelerating development. The United States and the European Union have also incorporated neurotechnology and BCI-related research into their strategic science and technology agendas. Despite increasing research output and investment, BCI translation continues to face multiple bottlenecks (*13*). Technical challenges include limited long-term signal stability, degradation at the electrode-tissue interface, signal non-stationarity, and low signal-to-noise ratio, all of which limit reliability in real-world use (*14,15*). Standardized clinical assessment metrics and reproducible multicenter protocols remain insufficient, limiting cross-study comparison and scalable validation (*13,16*). Regulatory and market-access pathways are also incompletely defined, and harmonized standards for BCI products have not yet been established across jurisdictions (*17*).

Contemporary BCI research is characterized by convergence across neural engineering, machine learning, materials science, clinical medicine, rehabilitation, ethics, regulation, and health economics (*18*). Although many reviews have addressed BCI signal processing, neural interfaces, and hardware development (*19*), fewer have examined the full clinical translation chain from research and development to regulatory approval, reimbursement, health technology assessment (HTA), and real-world implementation. This gap is important because promising technical performance does not automatically translate into sustainable clinical value. This review therefore adopts a clinical translation and accessibility perspective. Using recent Chinese regulatory and payment developments as an illustrative framework, we summarize major BCI technology pathways, global research landscapes, clinical applications, and translational bottlenecks. We then identify priorities for evaluation, reimbursement, policy design, and healthcare-system integration that may help accelerate responsible clinical implementation and improve access to neurorehabilitation and assistive neurotechnology.

2. Technology pathways and current translation stages of BCIs

2.1. Major technology pathways

The term BCI was introduced by Jacques Vidal in the 1970s to describe computer systems capable of extracting information from brain activity and using it for external communication or control (*20*). A typical BCI consists of six core modules: neural signal acquisition, signal preprocessing, feature extraction, algorithmic decoding, output control, and sensory or neural feedback. The acquisition module captures neural activity through electrodes or other sensors; preprocessing amplifies low-amplitude signals and reduces noise; feature extraction identifies biologically relevant neural signatures; decoding algorithms translate these signatures into interpretable intentions or states; output modules drive external devices such as robotic arms, wheelchairs, computers, or functional electrical stimulation systems; and feedback modules support closed-loop adaptation by delivering sensory, electrical, or other forms of stimulation (*21,22*) (Figure 1).

Depending to the mode and anatomical level of signal acquisition, BCIs can be broadly divided into five major pathways: non-invasive BCI, electrocorticography (ECoG)-based BCI, intracortical BCI (iBCI), endovascular BCI (EBCI), and neuromodulation-based BCI (*23,24*). These categories differ in invasiveness, signal fidelity, clinical risk, achievable bandwidth, and translational maturity.

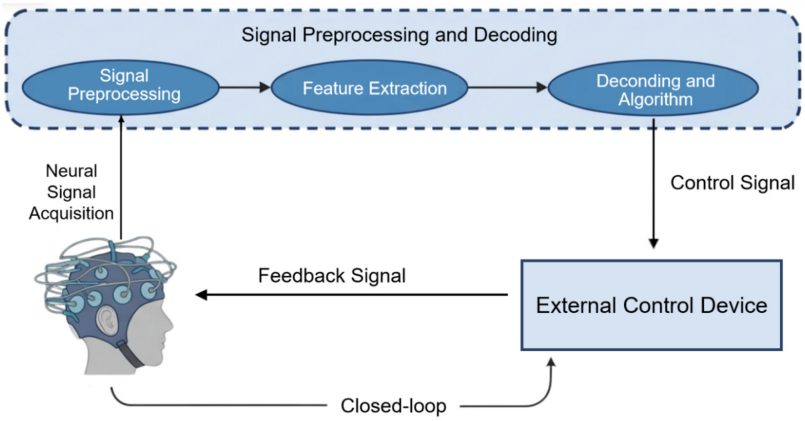

Figure 1. Schematic example of a typical BCI system. Neural signals are processed through preprocessing, feature extraction, and decoding to generate control commands for an external device. Feedback from the device forms a closed-loop system, enabling real-time interaction and control in BCI applications. *Abbreviation:* BCI, brain-computer interface.

2.1.1. Non-invasive BCI

Non-invasive BCIs are the most mature and widely deployed modality. They typically acquire EEG signals from scalp electrodes and may incorporate complementary modalities such as fNIRS or magnetoencephalography. Wet, dry, and hydrogel electrodes offer different trade-offs among signal quality, comfort, preparation time, and long-term wearability. Non-invasive BCIs are safe, relatively low-cost, scalable, and suitable for rehabilitation training, assistive communication, home monitoring, and consumer human-computer interaction. However, neural signals are attenuated by the scalp and skull and are vulnerable to motion artifacts, environmental noise, and inter-individual variability. As a result, non-invasive BCIs generally have limited spatial resolution, reduced localization precision, and lower decoding accuracy and stability than implanted interfaces (*25,26*). Improvements therefore depend on optimized experimental paradigms, robust signal processing, adaptive algorithms, and hybrid designs. EEG-fNIRS systems are an important strategy because they combine the high temporal resolution of EEG with hemodynamic information that can improve spatial and physiological interpretation (*27*).

2.1.2. ECoG BCI

ECoG BCIs use epidural or subdural electrodes placed close to cortical neural sources, often in the form of flexible cortical surface arrays. Compared to scalp EEG, ECoG provides higher spatial resolution, stronger signal-to-noise ratio, and better localization while retaining millisecond-level temporal resolution. It has clear utility in motor decoding, speech reconstruction, and epileptic focus localization (*28*). Recent high-density ECoG systems have enabled long-term spelling and speech neuroprostheses, indicating the feasibility of continuous high-performance communication. Nevertheless, ECoG requires cranial surgery and carries non-negligible risks, including bleeding, infection, tissue reaction, and device-related complications. Long-term performance may also be affected by signal decay, electrode aging, hardware failure, or the need for revision surgery (*26,29*).

2.1.3. iBCI

Intracortical BCIs use microelectrode arrays to record single-unit, multi-unit, or local field potential activity directly from the cortex. Among current BCI modalities, iBCIs offer the highest spatial resolution, signal fidelity, and information bandwidth, enabling precise real-time decoding for robotic arm control, cursor control, handwriting and typing, speech restoration, and fine motor reconstruction. Their major advantage is access to neural activity at the single-neuron or local microcircuit level, which facilitates high-dimensional decoding of motor and communicative intentions. Landmark studies have demonstrated high-performance speech and handwriting decoding in people with severe paralysis or amyotrophic lateral sclerosis (ALS), underscoring the unique value of iBCIs for high-bandwidth neuroprosthetics (*30,31*). However, iBCIs require highly invasive implantation, are vulnerable to foreign-body reactions and glial scarring, and generally sample localized cortical populations rather than distributed whole-brain activity. These limitations present challenges in terms of long-term stability, device maintenance, and broad clinical adoption (*32*).

2.1.4. EBCI

Endovascular BCIs record neural signals through stent-mounted electrode arrays deployed within cerebral blood vessels. This approach avoids conventional open-cranial implantation and therefore offers a less invasive route to implanted neural recording, while maintaining closer proximity to cortical sources than scalp EEG (*33*). Early clinical studies have suggested that endovascular BCIs can be implanted safely in selected patients with severe paralysis and can support digital control tasks such as texting, emailing, online shopping, and communication of care needs (*34*). However, EBCI remains in an early stage of clinical development. Wider translation will require stronger evidence on anatomical suitability, thrombotic and vascular complications, implant stability, long-term biocompatibility, signal quality, and long-term usability in daily environments (*35*).

2.1.5. Neuromodulation-based BCI

Neuromodulation-based BCIs integrate neural recording, state decoding, and stimulation into closed-loop systems. These systems detect neural states in real time and deliver adaptive stimulation through approaches such as closed-loop deep brain stimulation (DBS), responsive neurostimulation (RNS), BCI-functional electrical stimulation (BCI-FES), and EEG- or transcranial magnetic stimulation-based closed-loop frameworks. Compared to conventional assistive BCIs that focus primarily on external device control, neuromodulation-based BCIs aim to identify pathological or functional brain states and intervene dynamically. They have substantial potential in epilepsy, Parkinson's disease, stroke rehabilitation, chronic pain, disorders of consciousness, and functional restoration (*36,37*). Guozhen Liu's team has developed flexible, implantable electrochemical sensors capable of high-sensitivity, long-term monitoring of multiple cytokines and neurotransmitters in the brain. Validation in animal models has demonstrated the utility of this technology in tracking Parkinson's disease and neuropathic pain, offering a novel tool to aid in the diagnosis and management of neurological disorders (*38,39*). The conceptual boundary between BCI and neuromodulation

remains a subject of debate. Narrow definitions restrict BCIs to direct central nervous system signal acquisition for external device control, whereas broader definitions include closed-loop systems that decode neural activity to guide therapeutic stimulation. In this review, DBS, RNS, and related technologies are discussed within this broader BCI-related framework when they include record-decode-stimulate closed-loop functions.

2.2. From technology to the clinic: Translation stages and key transitions in BCI development

BCI development is moving from a primarily technology-driven phase toward a clinically and regulatorily oriented phase. Non-invasive BCIs have been commercialized to an extent and are increasingly used in rehabilitation and consumer settings, although their clinical value still depends on standardization, outcome evidence, and reimbursement integration. ECoG and iBCIs represent high-performance implantable pathways with clear advantages in motor decoding, speech restoration, and neuroprosthetic control, but they remain concentrated in specialized clinical trials and selected patient populations. Their broader clinical adoption is limited by invasiveness, long-term signal stability, postoperative management, their maintenance burden, and the reproducibility of outcomes across centers. EBCI offers a less invasive route of implantation, but it remains largely in the proof-of-concept and early feasibility stages. Neuromodulation-based BCIs are more mature for selected indications, and especially epilepsy and Parkinson's disease, but dissemination of adaptive closed-loop systems still depends on algorithm optimization, evidence of their long-term benefit, regulatory clarity, and reimbursement pathways.

Overall, non-invasive BCIs are closest to scalable clinical implementation, and particularly in rehabilitation and home-based training. ECoG and iBCIs provide higher performance but require more demanding surgical, ethical, and maintenance infrastructures. Endovascular systems are promising but still require longitudinal safety and effectiveness evidence. Closed-loop neuromodulation has already entered into clinical use in certain disease contexts, but its classification as BCI depends on the degree to which it incorporates neural decoding and adaptive control. Overall, the clinical translation of BCIs depends not only on their decoding performance but also on their safety, sustained reliability, usability, training burden, clinical workflow compatibility, patient selection, cost, and reimbursement (Table 1).

To indicate the logical transition from technology to clinical use, this review uses a technology-clinical-translation framework (Figure 2). Different BCI pathways occupy distinct positions along this continuum: non-invasive BCIs are in preliminary clinical use in rehabilitation and assistive communication; semi-invasive and minimally invasive systems are mostly used in early or exploratory clinical trials; and highly invasive BCIs are concentrated in carefully selected populations and specialized centers. These differences show that the clinical prospects of BCIs depend not only on signal fidelity or decoding accuracy but also on safety, long-term stability, operational complexity, patient adherence, and compatibility with existing healthcare systems.

3. Major areas of application and progress made by BCIs

3.1. Motor function restoration

BCIs are widely examined in neurorehabilitation after stroke, and especially for improving upper-limb motor function. A multicenter, randomized, open-label, controlled trial conducted across 17 centers in China showed that patients with ischemic stroke receiving BCI-based rehabilitation had significantly greater improvement in upper-limb Fugl-Meyer scores at one month than those undergoing conventional rehabilitation (*39*). Another randomized study suggested that combining BCI with functional electrical stimulation could improve post-stroke motor outcomes (*40*). A systematic review has further indicated that EEG-based neurofeedback can support motor recovery, with therapeutic benefit influenced by training intensity, feedback quality, and patient engagement (*41*). Motor-imagery BCIs combined with advanced signal processing can also detect functional changes before and after rehabilitation, providing both therapeutic and assessment value (*42*). BCIs may also restore communication and environmental control for patients with severe paralysis caused by spinal cord injury. In a first-in-human study, an endovascular BCI was implanted through the internal jugular venous route in four patients with severe bilateral upper-limb paralysis. During 12 months of follow-up, the system remained safe and stable, and participants were able to control a computer using thought-driven commands, indicating the feasibility of this less invasive approach to implantation (*33*). In addition, transcutaneous cervical spinal cord stimulation has been reported to enhance sensorimotor rhythms and accelerate BCI skill acquisition in people with spinal cord injury, suggesting a possible role for combined neuromodulation and BCI training in motor rehabilitation (*43*).

3.2. Communication restoration

BCIs provide a potential communication pathway for patients with severe speech or motor impairment caused by neurological injury or degenerative disease. Direct decoding of neural activity into text, speech, or speech-related articulatory representations has become a major clinical frontier, with rapid advances in both discrete and continuous speech decoding (*44*). For tonal languages,

Table 1. Core characteristics, translation stages, and limitations of major BCI technology pathways

Technology pathway	Signals and acquisition	Spatiotemporal resolution	Invasiveness/risk	Typical applications	Current stage	Translation potential	Key limitations
Non-invasive BCI	Scalp EEG and/or fNIRS acquisition of electrical or hemodynamic signals	Low spatial resolution; millisecond temporal resolution for EEG	Non-invasive	Rehabilitation training; disorders-of-consciousness assessment; assistive communication; consumer human-computer interaction; home monitoring	Clinical use / partial commercialization	High	Signal quality; artifact sensitivity; standardization; reimbursement integration
ECoG BCI	Epidural or subdural recording of cortical local field potentials	Intermediate to high; millisecond-level temporal resolution	Moderate; requires cranial surgery	Epilepsy localization; speech decoding; motor-intention decoding; intraoperative functional mapping; semi-implantable communication	Clinical trials / feasibility validation	Moderate	Invasiveness; long-term signal stability; postoperative management
Intracortical BCI	Microelectrode-array recording of single-unit, multi-unit, and local field potential activity	High; micrometer-scale spatial resolution and sub-millisecond to millisecond temporal resolution	High; requires intracortical implantation	Communication and typing for severe paralysis; robotic arm control; fine motor reconstruction; speech and handwriting decoding	Clinical trials / early translation	Moderate	High invasiveness; immune response; hardware lifespan; maintenance burden
Endovascular BCI	Stent-electrode recording of neural signals from cerebral vessels	Intermediate; generally below intracortical and surface interfaces but above conventional scalp recording	Lower than open-cranial implanted interfaces, but with vascular risks	Digital communication; environmental control; assistive interaction for severe paralysis	Early exploration / feasibility testing	Low to moderate	Long-term vascular safety; implant stability; limited clinical evidence
Neuromodulation-based BCI	Record-decode-stimulate systems using EEG, ECoG, local field potentials, or other neural signals	Depends on recording and stimulation modality	Depends on implementation	Epilepsy; Parkinson's disease; chronic pain; stroke rehabilitation; consciousness modulation; functional reconstruction	More mature for selected indications	Context-dependent	Conceptual boundaries; algorithm validation; reimbursement and regulatory pathways

Abbreviations: BCI, brain-computer interface; ECoG, electrocorticography; EEG, electroencephalography; fNIRS, functional near-infrared spectroscopy.

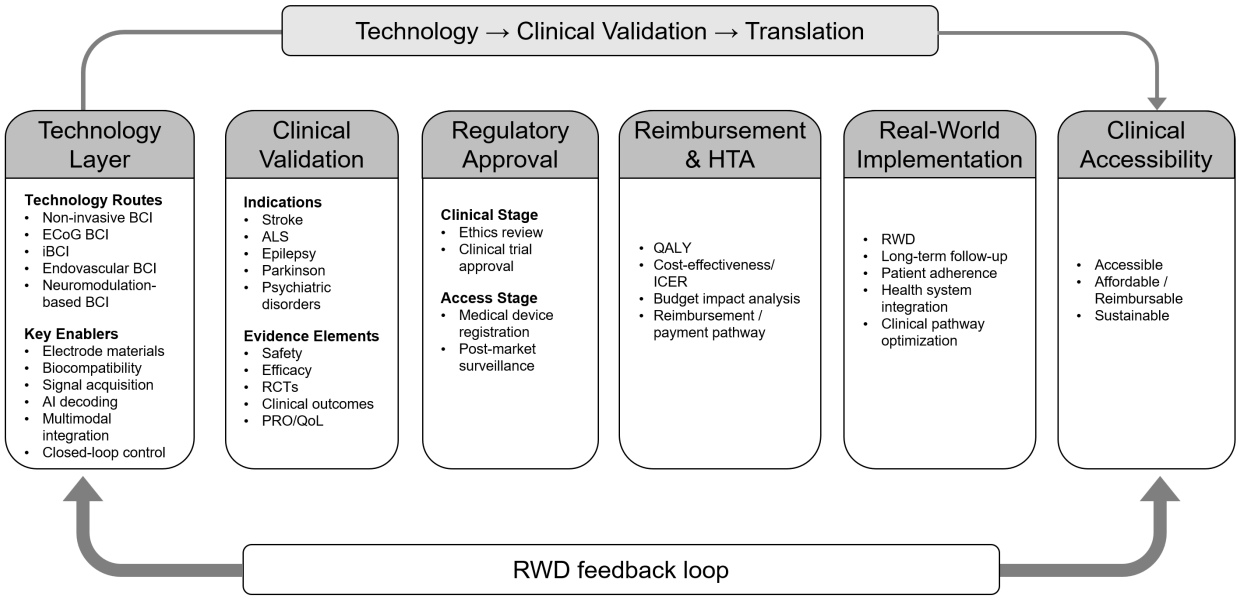

Figure 2. Framework for the clinical translation pathway of BCI. This pathway illustrates the progression of BCIs from fundamental technology development, clinical validation, regulatory approval, and health technology assessment, to real-world implementation and clinical accessibility. It emphasizes a closed-loop iterative system driven by real-world data to continuously optimize translation outcomes. *Abbreviation:* AI, artificial intelligence; ALS, amyotrophic lateral sclerosis; BCI, brain–computer interface; ECoG, electrocorticography; HTA, health technology assessment; iBCI, intracortical brain–computer interface; ICER, incremental cost-effectiveness ratio; PRO, patient-reported outcome; QALY, quality-adjusted life year; QoL, quality of life; RCT, randomized controlled trial; RWD, real-world data.

hybrid EEG-EMG BCIs have shown promise in decoding neural and muscular representations during silent and audible speech. Studies of Mandarin tone decoding have reported classification accuracies ranging from 71.22 to 91.00%, suggesting that language-specific features should be considered when developing communication BCIs for diverse patient populations (*45*).

3.3. Neuromodulation-related functional restoration

Closed-loop BCI-related neuromodulation is reshaping therapeutic strategies for neurological and neuropsychiatric disorders. In epilepsy, responsive and closed-loop systems can detect pathological activity and deliver stimulation when needed. A preclinical study in epileptic rats developed a non-invasive closed-loop acoustic BCI that showed antiepileptic efficacy superior to conventional vagus nerve stimulation, with effects eliminated by vagal pathway disruption, indicating the importance of mechanism-guided closed-loop design (*46*). In Parkinson's disease, BCI-related approaches aim to restore impaired motor or cognitive function by decoding cortical or subcortical activity and translating it into adaptive stimulation or corrective commands (*47*). In psychiatry, sensing-enabled DBS and related closed-loop neuromodulation technologies are advancing circuit-based treatment concepts. For refractory obsessive-compulsive disorder (OCD), long-term intracranial monitoring using sensing-enabled DBS has identified biomarkers associated with clinical states and treatment response, which may guide adaptive stimulation (*48*). Connectivity-guided targeting may further improve therapeutic precision in OCD and related disorders (*49*). For post-traumatic stress disorder and other conditions involving emotional dysregulation, DBS-related studies have focused on cortico-striato-thalamo-cortical circuits and transdiagnostic network targets (*50,51*). Although these approaches are not always classified as BCIs in a narrow sense, they are highly relevant to the broader BCI framework when neural signals are recorded, decoded, and used to guide closed-loop intervention.

BCI-related technologies are also being explored in disorders of consciousness, sensory dysfunction, cognitive impairment, neurodegenerative disease, sleep disorders, anesthesia monitoring, brain resuscitation, and affective-state recognition (*33*). In subacute stroke, for example, single-channel EEG-BCI systems have been used to classify selective tactile attention online, assist sensory training, and assess changes in cortical excitability (*44*). These applications illustrate a broader shift from device control alone toward neural-state monitoring, rehabilitation guidance, and adaptive therapy (Figure 3).

4. Research translation and clinical evaluation of BCIs

4.1. Research landscape and translation

BCI has become a strategic priority for several major economies, accompanied by increasing scientific output, industrial investment, and policy attention (*52*). China,

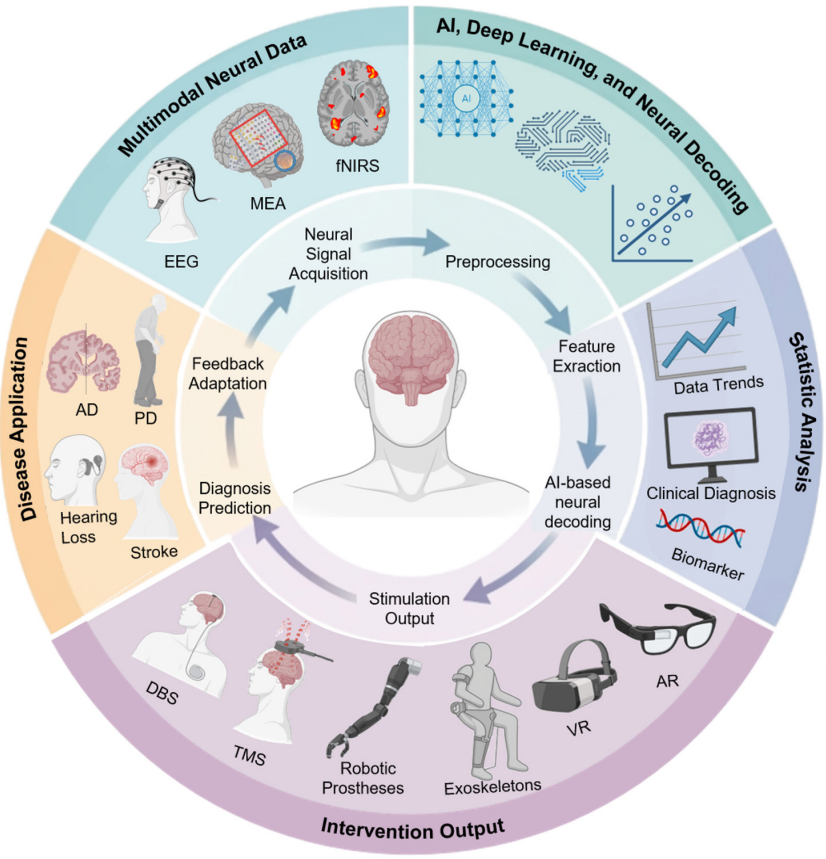

Figure 3. Main disease areas and clinical application processes for BCI-based intervention. Application scenario symbols guide related results throughout this study. Partially created with Biorender.com. *Abbreviations*: AD, Alzheimer's disease; AI, artificial intelligence; AR, augmented reality; DBS, deep brain stimulation; EEG, electroencephalography; fNIRS, functional near-infrared spectroscopy; MEA, microelectrode array; PD, Parkinson's disease; TMS, transcranial magnetic stimulation; VR, virtual reality.

the United States, the European Union, Japan, and South Korea are among the major contributors, although their development models and technical strengths differ.

China has a strong capacity in non-invasive BCI research and translation, supported by vast clinical resources, extensive EEG datasets, and a rapidly developing industrial ecosystem (*53*). National initiatives, including the China Brain Project and future-industry strategies, have elevated BCI to a priority frontier technology (*35*). China has also conducted prospective clinical testing of invasive BCIs (*54*) and is developing domestic industrial chains spanning chips, electrodes, algorithms, devices, and system integration (*55*). Rehabilitation medicine has been a major field of application, enabling the relatively rapid commercialization of non-invasive BCI systems and the accelerated development of implantable devices (*56*). The approval of an implantable BCI Class III medical device in 2026 represents an important translational milestone within this context (*57*).

The United States leads in many invasive BCI technologies, including high-channel-count neural acquisition, flexible electrodes, wireless implantable devices, and human neuroprosthetic trials (*58*). Its development model is powerfully driven by academic innovation, private capital, start-up companies, and close collaboration among engineering, industry, and clinical centers (*22*). The European Union (EU) has contributed substantially to neural coding, biocompatible materials, closed-loop neuromodulation, and hybrid brain-silicon systems designed to restore network connectivity in neurological disease (*59*). The EU also places a strong emphasis on ethical, privacy, and safety governance, with regulatory frameworks such as the AI Act and the General Data Protection Regulation shaping neurodata governance and patient protection (*60*). Large-scale infrastructures, including the Human Brain Project, have supported multicenter collaboration and public-interest translation (*61,62*), although commercialization has generally proceeded more slowly than in the United States (*63*).

Japan has integrated basic neuroscience with clinical rehabilitation, emphasizing neuroplasticity, neural decoding, and post-stroke recovery. The Hybrid Assistive Limb (HAL) in Japan has completed multiple phase III clinical trials. Randomized controlled studies in patients with neuromuscular disorders and spinal cord lesions demonstrated that HAL significantly improves walking distance and speed, alleviates limb spasticity, and enhances activities of daily living. Similar

positive rehabilitation outcomes were observed in stroke populations. The overall incidence of adverse events was below 5%, and those events were predominantly mild localized muscle soreness and minor skin discomfort, with no serious safety events reported. Long-term application appears safe and reliable. HAL is currently commercially available in Japan and covered by national health insurance (*64-66*). A study from a Japanese group has shown that BCI training combined with hybrid assistive neuromuscular stimulation can improve upper-limb function in severe post-stroke hemiplegia through induced neuroplasticity (*67*). A systematic review corroborates the role of EEG neurofeedback and motor-imagery paradigms in promoting cortical reorganization (*68*), while basic research has identified overlapping neural correlates of real and imagined movements that may contribute to BCI performance (*69*). South Korea has incorporated brain-machine interaction and digital therapeutics into its national biotechnology strategies, with investment in BCI, digital bioinnovation, neurotechnology ethics, and standardization (*70-73*) (Table 2).

Table 2. Global landscape of BCI research in selected countries and regions

Country/region	Strategic programs	Core strengths	Representative institutions	Technical focus
China	Sci-Tech Innovation 2030 - Brain Science and Brain-inspired Intelligence; future-industry policies	Vast clinical resources; non-invasive BCI deployment; industry-academia-clinical collaboration	Tianjin University; Tsinghua University; clinical rehabilitation centers	Minimally invasive BCI; non-invasive rehabilitation systems; medical translation
United States	BRAIN Initiative and related neurotechnology programs	High-performance invasive interfaces; strong commercialization capacity; extensive human trials	Stanford University; BrainGate; Neuralink and other neurotechnology companies	Invasive BCI; neuroprosthetics; speech and motor decoding; medical applications
European Union	Human Brain Project; neurotechnology and AI governance frameworks	Basic neuroscience; ethical and regulatory governance; international collaboration	Federal Polytechnic School of Lausanne; University and industry consortia	Non-invasive and hybrid systems; brain modeling; closed-loop neuromodulation
Japan	Long-term brain science and rehabilitation research programs	Neuroplasticity research; rehabilitation-oriented translation	University of Tokyo; Kyoto University; Keio University	Neural repair; motor rehabilitation; disease mechanisms
South Korea	Digital Bio Innovation Strategy	Integration of BCI with digital therapeutics and bioinnovation policy	KAIST and national research institutes	Brain-computer interaction; brain-function visualization; digital therapeutics

Abbreviations: AI, artificial intelligence; BCI, brain-computer interface; KAIST, Korea advanced institute of science and technology.

4.2. Clinical evaluation

Clinical evaluation of BCIs remains dominated by technical performance metrics, whereas frameworks centered on patient benefit, quality of life, functional independence, and long-term clinical value remain underdeveloped. Many studies use decoding accuracy, information transfer rate, task completion, or device-control performance as primary endpoints but report limited data on quality of life, the caregiver burden, long-term functional improvement, or sustained use in home settings. A systematic review of implantable BCIs found that only 17.9% of studies reported clinical outcomes, with technical metrics predominating (*74*). This imbalance is a major barrier to regulatory decision-making, payer evaluation, and routine clinical adoption.

As BCIs enter a more clinically oriented stage, evaluation should go beyond engineering metrics to include health-economic dimensions such as quality-adjusted life-years (QALYs), incremental cost-effectiveness ratios (ICERs), and budget impact. Related neuromodulation technologies provide useful precedents. A Japanese health-economic study of DBS for Parkinson's disease estimated that DBS could generate an additional 3.2 QALYs compared to conventional treatment and could be cost-effective under certain assumptions (*75*). Similarly, a cost-effectiveness analysis of responsive neurostimulation for drug-resistant focal epilepsy suggested that such systems may achieve acceptable ICERs compared to medication alone (*76*). Although these technologies are not identical to BCIs, they offer relevant methodological models for evaluating high-cost, implantable, and long-term neurotechnologies. Patient adherence, the training burden, usability, and

technological appropriateness should also be treated as core dimensions for evaluation. Evidence from a systematic review suggests that, although BCI performance may now exceed some patients' minimum expectations, prolonged training, daily-use complexity, equipment maintenance, and caregiver support requirements remain major obstacles to its sustained adoption (*77*). Clinical evaluation should therefore assess not only whether a BCI works in a controlled setting but also whether patients can learn, tolerate, maintain, and benefit from it in daily life.

5. Challenges in clinical translation and application

BCI translation faces several interconnected bottlenecks. Technical limitations include insufficient long-term stability, degradation at the electrode-tissue interface, signal non-stationarity, and a low signal-to-noise ratio, all of which constrain real-world reliability and practical utility (*78,79*). In parallel, the absence of standardized clinical outcome measures and reproducible multicenter protocols makes results difficult to compare, validate, and scale (*13,80*). Economic evidence, reimbursement mechanisms, regulatory pathways, and market-access models remain incompletely defined, while internationally harmonized standards for BCI products are still lacking (*81*).

5.1. Long-term technical safety and stability remain insufficiently validated

At the hardware level, conventional rigid electrodes can trigger foreign-body responses, causing tissue injury, glial scarring, signal attenuation, and an eventual decline in performance. Flexible electrodes, hydrogels, and biomimetic neural probes have improved mechanical matching and biocompatibility, but many remain insufficiently validated in sustained functional settings. Non-invasive EEG is safer but suffers from a low signal-to-noise ratio, artifact contamination, and limited spatial resolution; denoising algorithms can reduce but not fully eliminate these problems. Inter-individual variability further reduces robustness across users, sessions, and clinical settings (*82*). At the algorithmic level, AI and transfer learning have improved decoding accuracy but have not fully solved the problem of generalizability across individuals, devices, disease states, and real-world conditions (*83*). Long-term training and adjunctive neuromodulation may enhance neuroplasticity and improve device control, and closed-loop control has begun to show practical value in both therapeutic and assistive contexts. Nevertheless, large-scale, long-term controlled trials remain limited, and particularly in severely affected populations and home-based settings (*84*). Overall, non-invasive BCIs still face limitations in decoding accuracy and stability; iBCIs remain constrained by invasiveness and long-term device performance; and EBCIs require additional validation of long-term safety, signal stability, and vascular biocompatibility. Broader implementation will require progress in long-term stability, user adaptability, device reliability, and clinical standardization.

5.2. Monitoring systems for the effects of BCIs remain inadequate

Most BCI studies emphasize classification accuracy, hit rate, task performance, cortical activation, or functional connectivity but lack unified and clinically meaningful outcome measures that capture real patient benefit (*52,85,86*). A systematic review of 112 implantable BCI studies reported that only 17.9% assessed clinical outcomes, and the methods used to evaluate outcomes were highly heterogeneous (*74*). Standardized tools for monitoring long-term effectiveness, tolerability, quality of life, caregiver burden, and sustained use are also lacking (*87*). In patients with end-stage neurodegenerative diseases such as ALS, BCIs may support communication and daily assistance, but robust frameworks for quantifying their effects on quality of survival, autonomy, and the caregiver burden remain limited (*88*). Real-world evidence is fragmented because centers often differ in electrode layouts, sampling rates, preprocessing pipelines, experimental paradigms, methods of annotation, and outcome definitions. This heterogeneity limits cross-center comparison, compilation of evidence from multiple centers, and external validation. The lack of post-marketing real-world data and standardized follow-up frameworks further impedes the systematic assessment of BCIs' long-term effectiveness, safety, adherence, maintenance burden, and reasons for discontinued use in routine clinical and home settings (*89*).

5.3. Technical evaluation standards for algorithms and training protocols are not yet unified

Clinical translation is also hindered by the lack of standardized technical evaluation protocols. Studies differ substantially in paradigms, devices, algorithms, patient populations, calibration methods, feedback modalities, and training programs, making horizontal comparison difficult (*90*). Advanced algorithms, including Ensemble RCSSP (*91*), McRFS-IBiRNN (*92*), and OADANN (*92*), may achieve a high level of accuracy on specific datasets, but their generalizability in multicenter and real-world settings remains insufficiently demonstrated. In addition, user learning effects (*2*), differences in neuroplastic potential, fatigue, motivation, cognitive capacity, and the phenomenon often described as BCI illiteracy further complicate evaluation (*93,94*). Standardized benchmark datasets, reporting guidelines, patient-stratification criteria, and clinically meaningful performance thresholds are

needed to determine whether algorithmic improvements translate into practical benefit.

5.4. Costs are high and health-economic evidence remains insufficient

EEG-based non-invasive BCIs are often considered the most feasible route for near-term clinical translation because they are relatively low-cost, non-invasive, and easier to deploy than implanted systems (*95*). However, the overall costs of development, deployment, maintenance, training, and service delivery remain substantial (*96*). High-performance wearable EEG devices, real-time signal-processing hardware, AI-driven decoding engines, and integration with functional electrical stimulation, robotic systems, or remote monitoring platforms all require complex hardware-software co-design. Implantable BCIs provide higher signal quality but involve much higher costs for surgery, long-term device management, maintenance, and treatment of complications, all of which constrain their broad adoption (*97*). Even when novel bioelectronic materials such as conductive hydrogel electrodes improve biocompatibility and mechanical matching, clinical-grade manufacturing, quality control, sterilization, and regulatory testing remain costly (*98*). Overall, rigorous health-economic evidence for BCIs remains sparse, limiting payer confidence and reimbursement decisions.

5.5. Established reimbursement pathways are still lacking

Globally, clear and widely established reimbursement pathways for BCI technologies remain limited. Many BCI systems are still in the research or early clinical testing stage and have not been incorporated into routine fee schedules. Existing payment items often cover basic procedures or adaptation services but may not include essential costs such as device consumables, long-term maintenance, software updates, rehabilitation training, or home-use support. Payment standards vary across jurisdictions and lack harmonization (*99*). Current payment models remain largely fee-for-service and rarely incorporate value-based approaches that link reimbursement to functional outcomes, quality of life, or long-term cost offsets. Because high-quality evidence of their clinical value remains limited, the relationship between outcomes and charges is weak, yielding insufficient evidence for pricing and reimbursement adjustment (*100)*. Although several randomized controlled trials have shown that BCI-based rehabilitation can improve upper-limb motor function after stroke (*101,102*), these interventions have not yet been widely recognized by payers as standard treatment. The absence of payment mechanisms places substantial financial burdens on facilities and patients and directly limits real-world implementation.

6. Future perspectives

6.1. Accelerating the technological transition toward clinical application

BCI is undergoing a critical transition from laboratory research to real-world clinical application. This transition requires coordinated progress in technological innovation, clinical evidence, health economics, ethics, regulation, and reimbursement. Technologically, flexible electronics may improve their biocompatibility, mechanical matching, and long-term signal stability; deep learning, generative AI, and transfer learning may improve their decoding accuracy, robustness, and cross-individual generalization; and multimodal integration, closed-loop control, and adaptive design may expand their functional scope. Clinically, BCIs show great promise in stroke rehabilitation, communication support for ALS and severe paralysis, epilepsy interventions, and care for Parkinson's disease. Randomized trials substantiate the possibility of improving upper-limb function and activities of daily living, and particularly when a BCI is combined with functional electrical stimulation or robotic assistance. However, clinical research remains constrained by heterogeneous outcomes, insufficient long-term evidence, non-standardized protocols, and immature evaluation systems. Unified assessment frameworks and high-quality multicenter trials are urgently needed.

6.2. Improving HTA and reimbursement design to overcome implementation barriers

Scalable BCI implementation depends not only on technical maturity but also on HTA, reimbursement policies, ethical governance, and healthcare-system integration. Evidence on their cost-effectiveness, budget impact, payment design, and resource allocation remains insufficient. Ethical and legal questions also remain unresolved, including patient autonomy, informed consent, neurodata privacy, cybersecurity, algorithmic transparency, and risks associated with long-term neural interventions. Interdisciplinary collaboration among engineers, clinicians, rehabilitation specialists, health economists, ethicists, regulators, payers, and patient communities is necessary to develop evidence-based policies and transparent regulatory frameworks. Future BCI development should integrate neuroscience, AI, flexible electronics, clinical medicine, and implementation science to optimize hardware-software co-design, closed-loop personalized interventions, real-world robustness, and equitable access.

6.3. Aligning BCI development with clinical needs and accessible care

The next phase of BCI development should redefine their clinical goals, system architecture, and translational

logic. The field is likely to move beyond focal motor restoration toward brain-network state recognition, adaptive regulation, and precision neurorehabilitation. These advances may facilitate closed-loop interventions for epilepsy, Parkinson's disease, disorders of consciousness, psychiatric disorders, chronic pain, and other complex neurological conditions. Clinical BCI delivery will also evolve from standalone devices into integrated care systems that combine signal acquisition, intelligent decoding, closed-loop feedback, rehabilitation training, remote monitoring, device maintenance, and long-term follow-up. This systems-level model is essential for improving their real-world feasibility and sustained benefit.

The central mission of BCI development is therefore no longer simply to increase decoding speed, channel count, or spatial resolution. Rather, the goal is to match each technological pathway to appropriate clinical scenarios, patient populations, healthcare workflows, and payment models. High-quality BCI research must integrate technical optimization with evidence of their economic value, real-world effectiveness, patient adherence, usability, long-term safety, and ethical governance. Only through this integrated translational framework can BCIs move from impressive engineering achievements to accessible, affordable, and sustainable clinical neurotechnologies.

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Review

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Liver transplantation in Japan: Achievements, limitations, and future perspectives

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SUMMARY: Liver cirrhosis (LC) represents a substantial and growing global health burden, driving high mortality through liver failure and hepatocellular carcinoma (HCC), for which liver transplantation (LT) remains the only definitive and life-saving therapy. Despite continuous technical and perioperative advances, a critical unmet need persists due to the imbalance between organ demand and availability. In Japan, the practice of LT is uniquely shaped by the predominance of living donor transplantation and a marked epidemiological transition: the burden of viral hepatitis-related cirrhosis has declined with antiviral therapies, while metabolic dysfunction–associated steatohepatitis (MASH) and alcohol-associated liver disease (ALD) are emerging as leading indications. This paradigm shift necessitates refinement of transplant strategies, including improved candidate selection for HCC through integration of tumor biology and novel biomarkers and careful consideration of immunotherapy-related risks. Moreover, MASH introduces complex challenges related to obesity, disease recurrence, and the role and timing of metabolic interventions, whereas ALD raises ongoing clinical and ethical questions regarding early transplantation and relapse prevention. Future progress will depend on expanding the donor pool through innovations such as machine perfusion and xenotransplantation as well as expanding indications to selected non-HCC malignancies and adopting advanced surgical technologies. Collectively, LT is transitioning toward a precision-based, multidisciplinary, and innovation-driven paradigm.

Keywords: liver transplantation, living donor, hepatocellular carcinoma, metabolic dysfunction-associated steatohepatitis, bariatric surgery

1. Introduction

Cirrhosis is a consequence of chronic inflammation and diffuse fibrosis, in which regenerative hepatic nodules replace the normal hepatic structure. It will ultimately lead to failure of liver function (*1*). It involves various etiologies, including hepatitis B virus (HBV) or hepatitis C virus (HCV) infection, autoimmune liver diseases, alcoholic-related disease (ALD) and metabolic dysfunction-associated steatohepatitis (MASH) (*2*). HBV infection is one of the widespread causes of liver cirrhosis (LC) in Asia and Africa. HCV is responsible for LC in other areas.

Globally, the rates of LC have increased. About two million deaths worldwide annually are attributable to liver disease, with one million due to cirrhosis and the remaining one million due to hepatocellular carcinoma (HCC) (*3*). The high cirrhosis burden has increased the need for liver transplantation (LT). In 2021, 34694 liver transplants have been performed globally, marking an increase of 7% from 2020 and a 20% increase from 2015 (*4*).

Etiologies of cirrhosis leading to LT have changed over time in Japan. Data from 36 hospitals with datasets for 2008–2016 (n = 18,358) has indicated that HCV infection (48%) was the leading cause of cirrhosis. HBV infection (12%) was the third most common cause. During that period, the contribution of viral hepatitis to cirrhosis dropped from 73 to 50%. Since 2014, there has been a drastic decline in the number of patients who underwent LT for HCV as direct-acting antivirals have become available. In its place, cirrhosis due to ALD and MASH has increased markedly (from 14 to 25% and from 2 to 9%, respectively) during that period. Accordingly, the proportion of liver transplants for MASH increased from 1% in 2002 to 8% in 2016 (*5*).

2. Current challenges in LT

2.1. HCC

2.1.1. Epidemiology

HCC is the sixth most malignant tumor in the world.

More than 800,000 new cases are reported per year. The 5-year survival rate has remained low. There are about 900,000 deaths per year, making HCC the fourth most common cause of cancer deaths worldwide. The potential for LT to treat HCC, removing the tumor and restoring liver function, has long been anticipated. The first liver transplants were for HCC (*6*).

2.1.2. Japan criteria (5-5-500 rule)

A recent study (*7*) examined the 965 patients who underwent living donor liver transplantation (LDLT) for HCC between 1990 and 2005 in Japan. Of those patients, 664 met the Milan criteria while 301 did not. The criteria (the 5-5-500 rule) consisted of a tumor number ≤ 5, a tumor size ≤ 5 cm, and a serum alpha-fetoprotein level ≤ 500 ng/mL. Adoption of those criteria increased the number of LT candidates (n = 725) and resulted in a 5-year recurrence rate ≤ 10%. The cost of transplantation when the 5-5-500 rule for LDLT and deceased donor liver transplantation is adopted is now covered by the insurance system.

2.1.3. Current challenges in LT for HCC

Criteria for LT to treat HCC have basically consisted of the number and the size of HCC. The recurrence risk will increase with the level of alpha-fetoprotein, tumor size, and tumor number (*8*). Vascular endothelial growth factor (*9*), lens culinaris agglutinin-reactive AFP (AFPL3) (*10*), des-gamma-carboxy prothrombin (*11*), and neutrophil-to-lymphocyte ratio (*12*) are biomarkers that reflect tumor biology. Molecular biomarkers, such as circulating tumor cells, have been discussed in terms of predicting HCC recurrence. They may be useful in patient selection and post-LT management (*13*).

Another challenge is better understanding of how to manage HCC before LT. The emerging standards include vascular endothelial growth factor inhibitors and immune checkpoint inhibitors (ICIs) or a combination of both. However ICIs are associated with a risk of T cell-mediated rejection (*14*); that rejection is difficult to treated and often results in graft failure (*15-17*). Optimal doses of ICI and the duration between the administration of ICIs and LT are issues that require further analyses.

2.2. MASH as an indication for LT

2.2.1. Epidemiology

MASH is a manifestation of metabolic syndrome in the liver, which affects around 25% of the global population (*18*). MASH cases are estimated to total as many as 15 million (6% of adults) in the US. The number of those cases with ≥ F2 is estimated to be 7 million (*19*). According to the registry of United Network for Organ Sharing and Organ Procurement and Transplantation Network, the number of listed MASH patients has almost tripled in ten years. MASH is now one of the most common indications for LT (*20,21*).

A study by Hagström *et al*. (*22*) found that a liver suffering from MASH developed F0–1 fibrosis in 25 years, F2 in 9 years, F3 in 2 years, and F4 in 1 year. The MASH epidemic will presumably reduce the pool of donors, increase risk for LT recipients, increase the technical demands of surgery, and increase consequent complications (*23*).

2.2.2. Outcomes of LT

A recent analysis (*24*) of MASH and other conditions noted comparable outcomes of LT in terms of patient and graft survival. A point of note, however, is that obese LT candidates have a lower transplantation rate and a higher mortality rate while on the list. Recurrence of MASH post-LT is common and its management is challenging (*25*), which can unfavorably affect post-LT outcomes long-term (*26,27*).

2.2.3. Relationship between bariatric surgery (BS) and LT

LT and BS procedures are a reliable combination for weight loss. Sleeve gastrectomy is an effective therapy for weight loss (*23*) that will not cause malabsorption, it will not hamper an endoscopic approach to the bile ducts, and it will not affect the pharmacokinetics of immunosuppressive drugs. Complications include bleeding and leakage from the lines of the staple closure.

The most effective treatment for weight loss is *via* a small bowel Roux-en-Y bypass, which is more invasive but which will result in prolonged weight loss. In contrast to a sleeve gastrectomy, a Roux-en-Y bypass makes an endoscopic approach to the bile duct difficult and it affects the pharmacokinetics of immunosuppressive drugs. Malabsorption and sarcopenia are complications of the bypass procedure (*23*).

2.2.4. Timing: BS and LT

The ideal timing of BS - before, after, or at the same time as LT - has not established (*23*). Decompensated cirrhosis is a contraindication for BS because of the high risk of postoperative death (*28*). Outcomes are influenced by the degree of liver dysfunction and/or portal hypertension among individuals with compensated cirrhosis. Some patients with compensated cirrhosis have actually undergone BS successfully but with higher complication rates (*29*). A study (*30*) found that patients listed for LT who underwent laparoscopic sleeve gastrectomy had successful weight loss with no postoperative mortality. That study involved 32 patients who had an average Model for End-stage Liver Disease (MELD) score of 12.

In contrast, LT candidates who underwent BS

beforehand (n = 78) had a higher waitlist mortality rate (33% *vs* 10%, p = 0.002) and a lower transplantation rate (49% *vs* 65%, p = 0.02) than a matched LT cohort not undergoing BS (*31*). A limitation of this strategy is that obesity is less prevalent among LT candidates than the general public (*32*). Postoperatively, one-third of recipients become obese. Whether BS prior to LT affects the natural course of obese patients is not clear.

Simultaneous BS and LT would reduce the number of surgeries required (*33,34*). In some series, satisfactory short- and long-term outcomes were reported. Those series have demonstrated that the procedure is safe and effective over the long term and that it reduces the rate of steatosis and diabetes recurrence (*35-37*). The procedure has the advantages of rapidly dealing with obesity and reducing comorbidities.

An advantage of BS after LT (*38,39*) is that LT survivors who become obese post-LT can be selected. The surgery is, however, technically demanding and an open approach has a high morbidity rate of up to 45% (*39*). The reoperation rate is as high as 33%. A total of 14% of patients died within one year of BS (*39*). A study of 15 patients who underwent sleeve gastrectomy after LT (median duration: 2 years) found that weight was effectively reduced with a lower complication rate (*40*).

2.2.5. Non-surgical strategy for weight loss

Treatments for weight loss other than surgery are playing a non-negligible role in the management of obese patients undergoing LT. Tirzepatide (an agent combining a glucose-dependent insulinotropic peptide receptor agonist and glucagon-like peptide-1 receptor agonist) results in body weight loss of about 25% (*41-43*). Tirzepatide is followed by semaglutide and liraglutide, which are solely glucagon-like peptide-1 agonists. A recent study (*44*) showed that endoscopic sleeve gastroplasty is more cost-effective compared to semaglutide in the treatment of obesity indicated by a body mass index (BMI) > 30. Nonetheless, there are no available data on the clinical use of these medicines in patients with decompensated cirrhosis or those post-LT.

2.3. Alcoholic cirrhosis

2.3.1. Epidemiology

ALD poses a substantial burden around the world. Of the 2.3 billion people who drink alcohol, approximately 40% are heavy drinkers. The number of younger people with ALD has increased. Due to liver disease's relationship with obesity (*18*), the severity of alcohol use disorder has increased and the incidence of ALD (*45*) has increased, along with increased hospital admissions for alcohol-associated hepatitis (AH) (*46*) and consequent alcohol- and liver disease-related deaths (*47*). Now, ALD accounts for around 40% of all liver transplants in North America, which is more prevalent than MASH or HCV cirrhosis (*48*).

2.3.2. Outcomes of LT

Patients with ALD who underwent LT have comparable survival post-LT compared to that for patients with other conditions (*49,50*). Diabetes was one of the prognostic factors for patients who underwent LT for alcoholic cirrhosis (*51*). Around the 50% of the recipients resumed consuming alcohol to some degree. However, only a small proportion of patient deaths is due to alcohol abuse. Patients who are abstinent for a prolonged period can be adequately selected for LT (*52*). The 6-month rule is not always evidence-based. Decisions on LT candidacy might not be decided solely on the duration of abstinence (*49*).

2.3.3. LT for AH

LT for severe AH has promising outcomes when highly selective (*52-55*). A multicenter study examined three groups of patients: 1. Transplant patients with severe AH, 2. Those with AH who were rejected for LT due to sociopsychological contraindications, and 3. Those with alcohol-associated cirrhosis who were abstinent pre-transplant for ≥ 6 months) (*55*). According to that study, patients who underwent LT for AH not responding to steroids had a better survival than those not undergoing LT (83% *vs* 28% at 2 years). The two-year survival after LT was comparable between patients with ALD cirrhosis who were abstinent for ≥ 6 months and those with AH (*55*). An American study (ACCELERATE-AH) showed that early LT for AH had satisfactory outcomes (*56*).

A concern when performing LT for severe AH (*57*) is that there are few predictors of outcome. Not all centers apply uniform criteria. The stringency of the criteria

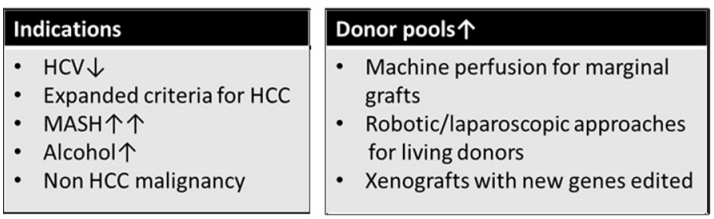

Figure 1. Changing indications and expanding donor pools. *Abbreviations*: HCV, hepatitis C virus; HCC, hepatocellular carcinoma; MASH, metabolic dysfunction-associated steatohepatitis.

will depend on the expertise in medical management, the existence of an infrastructure with multidisciplinary teams, and the evaluation process (*53*). Another concern is the difficulty in defining the best indicator of outcome. It may be survival or relapse. The difference between a slipup and sustained harmful drinking is important. Sustained harmful drinking is related to a poor prognosis (*58*).

If they do not undergo LT, patients with severe AH are at risk of a fatal outcome. A meta-analysis (*59*) showed that corticosteroids reduced mortality in patients with AH and a Maddrey score > 32. Patients with severe AH who did not receive them had a mortality of 35–40% in one month, while mortality decreased to 20% for those in the treatment arm with treatment (*60*). Patients with a MELD score of 25–39 had the best outcomes with corticosteroid therapy (*59*). Outcomes differed with the Lille score: patients with a score > 0.56 (1-month survival rate of 50%) had a poor outcome while those with a score of 0.16-0.56 had better survival (1-month survival rate of 79%) (*61*). The MELD score is better than the Maddrey score at predicting death post-LT in patients with AH. In addition, the MELD-Na score is not superior to the MELD score (*62*).

2.3.4. Long-term abstinence and relapse

AUD is a chronic disorder with remission and relapse. Sustained abstinence post-LT determines the outcome after LT. Several studies have shown that relapse rate was 10-25% within 2 to 3 years of LT (*55,63*). In patients with alcohol-associated cirrhosis who were abstinent for 6 months before LT, the rate was 25% (*61*). The rate of alcohol relapse was 22% in patients soon after LT while the rate of heavy alcohol relapse was 5%. The cumulative incidence of heavy alcohol consumption is reported to increase from 2% 1 year after LT to 29% after 10 years (*64*).

Instruments used to select patients for LT include the High-Risk Alcoholism Relapse (HRAR) scale and the Stanford Integrated Psychosocial Assessment for Transplant (*64,65*). They consist of items regarding psychosocial stability, psychosocial assessment, social support, abuse of other substances, and motivation. Experts in addiction and transplantation need to be involved in pre- and post-transplant settings. Effective therapies for AUD are offered after LT (*66*). Multidisciplinary teams including addiction specialists can help patients with long-term abstinence.

3. Future directions in LT

3.1. More donor organs

The demand for organs far exceeds the supply. The consequence of this disparity in organ needs versus availability has resulted in the deaths of many patients on the waiting list. Increasing the number of available deceased donors by reducing the rate of organ discard is crucial to increasing donors as well as expanding living donor LT.

3.1.1. Machine perfusion of deceased donor organs

With the standard criteria, the graft survival rate is around 90% 1 year after LT. However, it decreases when using after circulatory death (DCD) grafts and grafts from donors with high-risk indices. Organ preservation was conventionally done with static cold storage, which slows graft metabolism without completely stopping metabolism. Greater attention is being paid to advances in machine perfusion for organ preservation that enhance organ utility and improve graft survival (*67*).

Techniques for liver graft preconditioning, oxygenation systems, and graft perfusion with hypothermic (HMP) or normothermic machine perfusion (NMP) have garnered attention. HMP can be divided, from the point of oxygen supplementation, into hypothermic oxygenated machine perfusion (HOPE) (delivery of an oxygenated perfusion solution only through the portal vein) or dual HOPE (delivery simultaneously through both the hepatic artery and portal vein).

An NMP system consists of a circuit and a perfusate (a priming solution and a maintenance infusion) (*68*). NMP systems can be maintained for several hours without oxygen carriers, but most perfusates include a carrier to provide oxygenation. Benefits of these techniques are that they enable assessment of graft viability through measurement of glucose, lactate, flavin mononucleotide, and pH (*69*), they lower the non-anastomotic biliary stricture risk of DCD grafts (*70*), and they remove lipids from steatotic grafts (*71*).

3.1.2. Xenografting

Xenotransplantation has a relatively long history (*72*), but only recently has the field made progress. Due to acceptable similarities in genetics, similarities in organ size, and rapid maturation, pigs have been ideal donors (*73*). Genetically engineered pig kidney and heart (*74*) grafts have been successfully used in non-human primates. In contrast, pig liver grafts are not satisfactory (survival of non-human primate < one month) (*75,76*). Heterotopic auxiliary transplantation of a six-gene-edited pig liver graft into a brain-dead recipient took place in 2025 (*77*). Hemodynamics, immune and inflammatory responses, and graft function were monitored for 10 days after LT. A patient with a massive HCC underwent heterotopic auxiliary transplantation of a ten-gene-edited pig liver graft but died due to xenotransplantation-associated thrombotic microangiopathy on day 171 (*78*).

CRISPR/Cas-9 allows genetic knock-outs of highly immunogenic epitopes and engineered knock-ins, thus enabling the expression of human transgenes regulating

the complement regulatory proteins and the coagulation cascade. Donor viability has been maintained in pigs that received multiple gene knockouts and knock-ins (*79*). In xenotransplantation, ethical considerations and safety are major issues. The welfare of animal donors is important and the animals must be reared in highly monitored settings. The risk of zoonotic infections by retroviruses in particular is a concern. Protocols for screening, prevention, and risk mitigation of recipients of xenografts are mandatory (*80*).

3.2. Non-hepatocellular carcinoma malignancy

3.2.1. Peri-hilar cholangiocarcinoma (CCA)

Patients with peri-hilar CCA undergo neoadjuvant chemoradiotherapy. Protocols include those from Toronto, Mayo, and the University of Michigan (*81*). LT for peri-hilar CCA in line with the Mayo protocol had a satisfactory outcome, with a disease-free survival rate of 62% at 5 years (*82,83*).

A MELD score exception for peri-hilar CCA is offered by the United Network of Organ Sharing (UNOS). The recurrence-free survival rate at 5 years was 65% according to 12 transplantation centers in the US (n = 287) (*84*). A prior malignancy or falling outside the UNOS criteria (tumor diameter > 3 cm, metastatic lesions) indicated a poor prognosis. The cumulative incidence of drop-outs from the waiting list was 13% at 6 months and 24% at 12 months (rates for HCC were 7% and 13%) (*85*). Eight Italian centers (*86*) reported on 25 patients who received neoadjuvant radio-chemotherapy and who underwent LT from 1986 to 2021. Recurrence-free survival was 91% at 1 year, 61% at 3 years, and 47% at 5 years.

3.2.2. Intrahepatic CCA

Another primary liver malignancy that LT is indicated for is early-stage intrahepatic CCA (single tumor, less than 2 cm in size) that is unresectable due to poor liver functional reserve or the location of the tumor. A multicenter study (*83*) of 48 patients found that 31% had an early-stage tumor (single tumor, less than 2 cm in size). The recurrence rate in patients with early-stage CCA was 7% at 1 year, 18% at 3 years, and 18% at 5 years versus 30% at 1 year, 47% at 3 years, and 61% at 5 years for patients with tumors in other stages. The median follow-up was 35 months. The 5-year survival rate was 65% in patients with an early-stage tumor, which was higher than the rate in patients with tumors in other stages (45%, p = 0.02).

A French study (*87*) compared the survival of patients who had intrahepatic CCA < 5 cm and who underwent LT (n = 49) or liver partial resection (n = 26). Patients who underwent LT had a higher 5-year recurrence-free survival (75% *vs* 36%; p = 0.004). Another study (*4*) examines the outcomes of 18 patients with intrahepatic CCA who received neoadjuvant therapy and who underwent LT. The overall survival rate was 100% at 1 year, 71% at 3 years, and 57% at 5 years. The recurrence rate was 39%.

A therapeutic protocol for patients with unresectable CCA was developed by a US center, which included normal functional liver, no extrahepatic lesions or vascular involvement, and gemcitabine-based neoadjuvant chemotherapy with a minimum of 6 months of radiographic response or stability before listing (*88*). Of 12 patients eligible for LT, a total of 6 underwent LT. The median time from diagnosis of CCA to LT was 26 months. The overall survival was 100% at 1 year and 83.3% at 3 years. The recurrence-free survival at 3 years was 50%.

3.2.3. Neuroendocrine tumor (NET)

The UNOS guidelines for NET [89] include lymph node metastatic lesions turning negative confirmed by a positron emission tomography scan at least 6 months before listing, and a recurrence-free duration > 3 months. A UNOS data-based study (*90*) showed that the overall survival rate of patients undergoing LT (n = 184) at 5 years was 49%. Adoption of the MELD score improved outcomes. After its adoption, the overall survival rate was 85% at 1 year, 65% at 3 years, and 58% at 5 years.

The European Liver Transplant Registry (ELTR) found that 213 patients underwent LT for NET over a period of 27 years. Of those patients, 83% underwent resection of the tumor before LT. The tumors were synchronous in 119 patients. Of the total patients, 76% received nonoperative treatment including somatostatin analogues and trans-arterial chemoembolization. The overall survival rate was 81%, 65% and 52% at 1, 3, and 5 years, respectively, and the disease-free survival rate was 65%, 40% and 30%, respectively.

A study by the University of Göteborg (*91*) examined 15 patients who underwent LT (n = 10) or multi-visceral transplantation (n = 5). The 5-year overall survival rate was 90% and the 1-year recurrence-free survival rate was 70%.

Mazzaferro *et al*. (*92*) reported that patients who were within the Milan NET criteria and who underwent LT (n = 42) had a 5-year overall survival rate of 97% and a disease-free survival rate of 89%. Lim *et al*. (*93*) found that patients with NET who underwent LT had a 5-year overall survival rate ranging from 41 to 71%, which was similar to the rate for patients with other conditions undergoing LT. In contrast, the recurrence rate (31–57%) was much higher than that for patients with other conditions.

A Spanish multi-center study (*94*) included 91 patients with NET who underwent LT. Of those patients, 71 met the Milan criteria while 20 did not. The recurrence rate was 57% and overall mortality was 52%.

Five-year overall survival was 71% among patients meeting the Milan criteria and 58% among those who did not meet those criteria. The 5-year disease-free survival rate was 59% among patients meeting the Milan criteria and 36% among those who did not meet those criteria.

3.2.4. Colorectal liver metastasis (CRLM)

In the SECA-I study (*95*) in Norway, 21 patients who underwent LT were compared to 47 patients receiving chemotherapy. The 5-year survival rate of LT recipients was higher than the rate of patients receiving chemotherapy alone (56% and 9%, $p < 0.001$). In contrast, there were no significant differences between the two groups in terms of median disease-free survival (10 and 8 months, respectively). In the patients who underwent LT, a better prognosis was related to a short duration between diagnosis of the primary tumor and LT, a tumor small in size (< 5.5 cm), stable disease or tumor shrinkage in response to neoadjuvant therapy, and a serum carcinoembryonic antigen level < 80 mg/L.

Rajendran *et al*. (*96*) reported on the outcomes of LDLT for CRLM ($n = 7$). Six patients had received chemotherapy and two underwent partial liver resection before LDLT. The Oslo score was 0–2. The recurrence-free survival rate was 86% 1 year after LDLT and 69% 3 years afterwards. Favorable prognostic factors included a long duration from diagnosis of the primary tumor to LT (> 2 years), a tumor < 5.5 cm in size, a carcinoembryonic antigen level < 80 mg/L, and stable disease or shrinkage in response to neoadjuvant chemotherapy.

A North American multi-center study (*97*) examined 10 patients who underwent LDLT for CRLM (9 with synchronous lesions and 1 with metachronous lesions). Three patients had undergone partial liver resection and three had receive trans-hepatic arterial chemotherapy before LDLT. The overall survival rate was 100% and the recurrence-free survival rate was 62%.

A French multi-center study (*98*) examined the outcomes of LT for extensive colorectal liver metastases in both lobes. The overall survival rate at 5 years was 84%, the recurrence-free survival rate was 24%, and the time to surgical failure was 61%.

3.3. Robotic surgery for LT

Robotic liver surgery is now playing a more important role in LT. A stable camera platform, elimination of tremors, enhanced dexterity, and improved ergonomics enable complex liver procedures that require accurate tissue dissection and hemostasis (*99*). Robotic surgery is performed in LT at some centers around the world. Eligible patients are now limited to those with low MELD scores.

In 2023, the King Faisal Specialist Hospital in Saudi Arabia performed robotic donor and recipient hepatectomy and liver graft implantation in three cases (*100*). The candidates for robotic LT include recipients with a liver graft less than 900 g as well as an anticipated graft-to-recipient weight ratio of more than 0.80%. Khan *et al*. (*101*) subsequently reported robotic LT. A whole graft from a deceased donor was transplanted into a 62-year-old man with HCV and HCC. Lisbon and Modena University (*102*) performed robotic LT in six cases using a whole liver from deceased donors. Eligible patients included those with low MELD scores.

Laparoscopic techniques in LT have also been highlighted by recent innovations. Lee *et al*. (*103*) reported a patient who underwent total laparoscopic hepatectomy followed by robot-assisted graft implantation. The living donor right hemi-hepatectomy was performed laparoscopically. Laparoscopic LT was also performed (*104*). The right side donor hepatectomy and implantation were done laparoscopically.

Successful outcomes and a full recovery of graft function indicate the feasibility of combining robotic and/or laparoscopic LT for selected recipients.

4. Conclusions

Better perioperative care and advances in surgical techniques have allowed surgeons to use grafts with extended criteria. The field of LT will continue to evolve.

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Original Article

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Clinically constrained optical design of a high-numerical aperture miniature immersion objective for probe-based confocal laser endomicroscopy

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SUMMARY: Confocal laser endomicroscopy (CLE) is a critical modality for the early, minimally invasive diagnosis of intraluminal diseases. However, its clinical translation is constrained by the inherent optical-mechanical trade-offs between numerical aperture (NA), probe diameter, and clinical maneuverability. Achieving high-performance imaging within the strict dimensional limits of standard biopsy channels remains a significant technical bottleneck. To address these challenges, we propose a clinically constrained optical design strategy. This integrated design approach incorporates anatomical boundary constraints directly into the optical optimization process. Based on this method, the developed miniature immersion objective achieved a 0.78 μm lateral resolution across a 300 μm field of view, while the integrated pCLE probe maintained a 1.1 μm lateral resolution. This system realizes stable cellular-level imaging under constrained geometry. It is bending-compatible and clinically deployable. Animal experiments and representative histology-correlated clinical gastric images demonstrated the feasibility of resolving tissue microstructures and clinically relevant mucosal abnormalities, supporting the translational potential of the integrated pCLE probe.

Keywords: optical biopsy, gastric neoplasia, fluorescence microendoscopy, fiber-bundle imaging, translational validation

1. Introduction

Confocal laser endomicroscopy (CLE) has emerged as a pivotal modality for early, minimally invasive diagnosis of intraluminal diseases by enabling real-time, cellular-level optical biopsies. In clinical practice, probe-based CLE (pCLE) is the dominant implementation. Because this probe must simultaneously navigate narrow anatomical channels and acquire microscopic images, the diagnostic capability of pCLE is fundamentally limited by the optical and mechanical performance of the probe (*1,2*).

The clinical utility of pCLE is fundamentally governed by an inherent optical-mechanical trade-off. Specifically, there exists a persistent conflict between achieving a high numerical aperture (NA) for resolution, maintaining millimeter-scale miniaturization for channel compatibility, and ensuring clinical maneuverability for navigating tortuous anatomical paths. This inherent contradiction remains the primary barrier to achieving high fidelity imaging in deep or curved intraluminal environments. (*3-7*).

Existing miniaturization strategies generally fall into three compromised frameworks. First, designs prioritizing anatomical compatibility typically restrict the probe diameter to fit standard biopsy channels, which severely limits the NA (typically ≤ 0.5) and constrains fluorescence collection efficiency (*8-10*). Second, architectures maximizing optical performance (NA ≥ 0.6) often result in bulky outer diameters or extended rigid lengths, precluding safe navigation through tight bending radii (*11*). Third, efforts to mitigate rigidity through mechanically compliant designs, such as flexible gradient-index (GRIN) relays or distal scanning units, often introduce secondary trade-offs including optical path perturbations during bending or increased safety risks from distal actuation (*12-18*). Consequently, a systematic approach to decoupling clinical

maneuverability from optical degradation remains an unresolved challenge.

To address these translational challenges, we propose a clinically constrained optical co-design framework. Unlike traditional sequential design approaches, this method incorporates anatomical boundaries such as biopsy channel diameter, bending radius, and liquid-immersion conditions as practical boundary conditions from the early stage of optical design. By co-optimizing the optical power distribution and mechanical packaging limits, we developed a 5E4G (five-element, four-group) coaxial hybrid architecture. This design provides a practical route for developing high-performance micro-optical systems while preserving maneuverability and anatomical accessibility in clinical applications.

2. Materials and Methods

2.1. Integrated design approach

The core of our methodology is an integrated design approach. This approach maps clinical requirements directly into optical and mechanical design variables. It achieves a dynamic balance among physical laws, manufacturing tolerances, and biological application requirements (Supplementary Materials 1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=304*).

We first define a Requirement Vector (R_s) based on clinical benchmarks for cellular-level imaging, which incorporates spectral characteristics, target lateral resolution, working distance, and mechanical constraints dictated by the standard biopsy channel geometry and tissue immersion environments. Correspondingly, an Optical Design Vector (D_s) is established to represent the tunable parameters of the objective, linking R_s and D_s through a series of interconnected physical constraints rather than traditional sequential methods. Within this method, the object-side NA and system magnification are derived from the Nyquist sampling limit of the specific imaging fiber bundle, while the maximum clear aperture of the lens elements is explicitly limited by the barrel wall thickness and biopsy channel diameter to ensure mechanical navigability. Furthermore, high-efficiency fiber coupling is promoted by prioritizing the minimization of the image-side RMS spot radius ($R_{RMS} < d_{core}/2$, where $d_{core}/2$ is the fiber core diameter) over traditional Modulation Transfer Function (MTF) criteria, while the requirements of chromatic aberration and field curvature residuals are related to the system's depth of focus. Finally, these constraints were considered together during optimization to balance high-fidelity imaging with anatomical accessibility.

2.2. pCLE system and miniature objective design

The pCLE system mainly consists of a confocal scanning unit and a confocal imaging probe (Figure 1; detailed supplementary explanation is provided in Supplementary Materials 2, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=304*). Excitation laser (488 nm) is relayed through a dichroic mirror and optical scanner into a Fujikura FIGH-S series imaging fiber bundle (Fujikura Ltd., Tokyo, Japan). The distal end features a novel miniature fiber-coupled fluorescence microscope objective (hereinafter referred to as the miniature objective) designed to focus the light onto the tissue surface, collect the emitted fluorescence and guide the signal back through the coupling optics for subsequent detection. The optical characteristics are

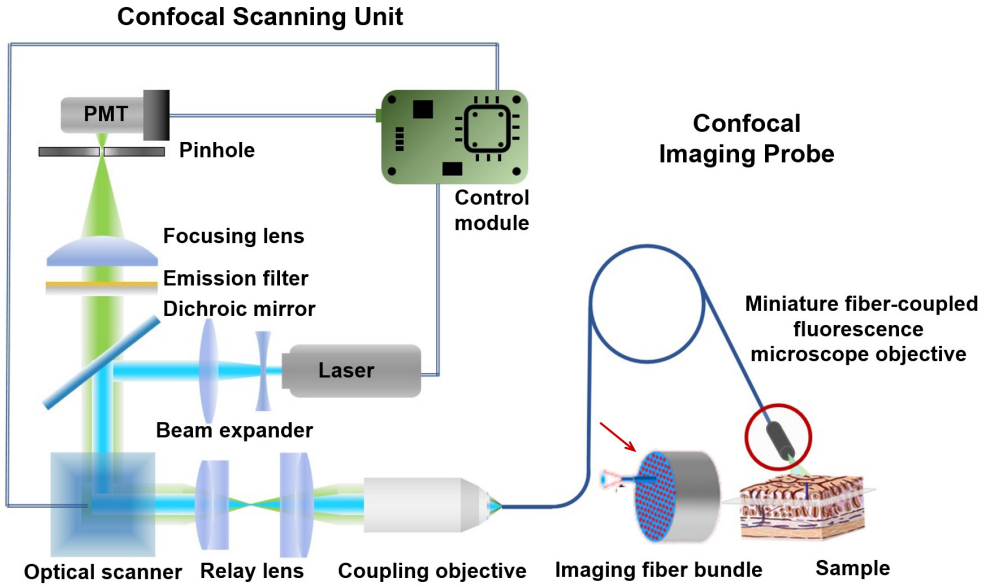

Figure 1. Schematic diagram of the pCLE System.

strictly matched to the properties of sodium fluorescein, a clinically prevalent contrast agent (*19*).

Considering that the probe needs to implement contact imaging, we take seawater to accurately characterize the biological tissue environment(*20*). For contact-mode pCLE imaging, the working distance defines the nominal focal plane beneath the distal optical window and is closely related to the effective imaging depth in superficial gastrointestinal mucosa. Reported pCLE systems using 488-nm excitation and intravenous fluorescein typically generate optical sections at approximately 55-70 μm, while comparable miniature confocal objectives have adopted working distances (WD) of approximately 60-80 μm. Therefore, a WD of 65 μm was selected to position the focal plane within the superficial mucosal layer, enabling visualization of epithelial architecture and cellular-level features while maintaining high-NA fluorescence collection efficiency and compact probe geometry (*3,11,14*) This selection also reflects the general trade-off in turbid biological tissues, where excessive imaging depth can increase scattering-induced degradation of contrast and signal-to-noise ratio (*21*). The miniature objective employs a custom five-element, four-group (5E4G) coaxial hybrid architecture (Figure 2; detailed supplementary explanation is provided in Supplementary Materials 3, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=304*), designed and optimized using Zemax OpticStudio. The lenses were fabricated using optical glasses sourced from Chengdu Guangming (CDGM Glass Co., Ltd., Chengdu, China). The object-side NA is 0.7, magnifying a 280 μm field of view (FOV) by 2.5× to match the fiber bundle's image circle (3.3 μm core pitch, ~2 μm core diameter). The mechanical outer diameter is strictly limited to 2.6 mm to ensure compatibility with standard 2.8 mm gastrointestinal endoscope working channels (*9,22,23*), with a final rigid mechanical length of 9.1 mm (Figure 2). Within reasonable machining and assembly tolerance ranges (such as sub-ten-micrometer axial errors and tilt errors of less than 0.5°), the system's primary imaging performance metrics remain stable, exerting no significant impact on fiber-coupled imaging. Optical simulations confirm that the objective achieves diffraction-limited performance, featuring an RMS spot radius below 1.0 μm, an MTF exceeding 0.5 at the 151 lp/mm Nyquist frequency, a maximum chromatic focal shift of 3.0 μm, and over 90% uniform relative illumination across the 280 μm field of view. Detailed optical comprehensive performance metrics such as spot diagrams (Supplementary Figure S1, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=304*), MTF (Supplementary Figure S2, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=304*), and various aberration curves (Supplementary Figure S3, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=304*), are provided in the Supplementary Materials.

2.3. Multi-level performance characterization

To verify the efficacy of the constraint-driven design, the fabricated objective underwent rigorous optical and mechanical evaluations. Physical dimensions of the fabricated objective were verified using a high-precision digital micrometer prior to assembly. Under deionized water immersion, lateral resolution and effective FOV were characterized using a standard USAF 1951 resolution test chart and an 80 lp/mm Ronchi grating, respectively. Distortion was analyzed *via* a 10 μm pitch grid distortion target. Furthermore, mechanical navigability and imaging stability were experimentally assessed under physical bending conditions. The integrated probe, with a distal length of 11.48 mm, underwent passability testing within the working channel of a standard electronic endoscope deflected to a maximum mechanical limit, corresponding to a bending radius of 30 mm. To evaluate imaging reliability under mechanical stress, a portion of the probe was coiled around a custom test fixture at a bending radius of 35 mm. This characterization serves to validate that the pre-defined clinical constraints were successfully translated into the final mechanical-optical assembly without

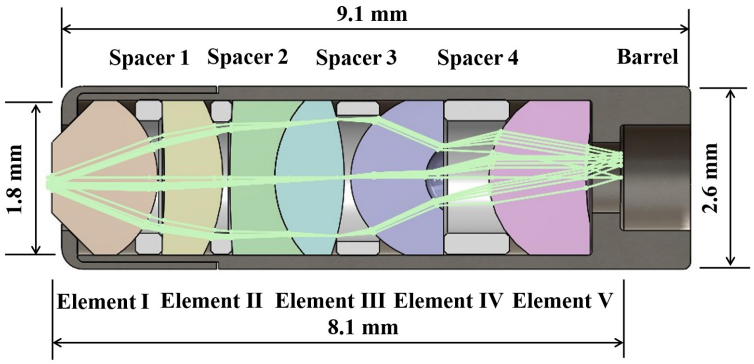

Figure 2. Optical and Mechanical Structure of the Miniature Fiber-Coupled Fluorescence Microscope Objective.

compromising clinical navigability.

2.4. Biological and clinical imaging protocols

To evaluate the biological imaging capability and translational feasibility of the integrated pCLE system, validation experiments were performed using SD rat tissues, an *in vivo* Bama miniature pig bladder model, and representative histology-correlated clinical gastric images. Sodium fluorescein was used as the fluorescence contrast agent. During imaging, the probe tip was gently placed in contact with the target tissue surface while avoiding excessive compression-induced deformation. pCLE images and dynamic video sequences were stored for subsequent comparison with histopathological findings.

For small-animal validation, SD rat colonic mucosa and tibialis anterior muscle/superficial fascia were examined. For colonic mucosal imaging, adult male SD rats were anesthetized by intraperitoneal injection of 10% chloral hydrate solution at 3 mL/kg. Sodium fluorescein solution was then administered *via* the tail vein at a dose of 30 mg/kg. After laparotomy, the colorectum was separated and exposed. An approximately 10-cm colorectal segment was excised, opened longitudinally, and flat-mounted on a glass slide with the mucosal surface facing upward. Intestinal contents were removed, and the mucosal surface was moistened with 0.9% sodium chloride solution. pCLE imaging was performed immediately, with particular attention to colonic crypt architecture and cellular-level mucosal structures.

For tibialis anterior muscle and fascia imaging, adult male SD rats were anesthetized by intramuscular ketamine at 0.3 mL/kg followed by intraperitoneal propofol at 10 mg/kg for continued sedation. The right lower limb was shaved, and the tibialis anterior region was dissected layer by layer to expose the skin, superficial fascia, deep fascia, and tibialis anterior muscle. Sodium fluorescein was locally applied to the exposed tissue surface. Based on preliminary optimization of the staining protocol, pCLE imaging was initiated approximately 30 s after local fluorescein application and completed within 20 min. Images and videos were acquired from the tibialis anterior muscle and superficial fascia, focusing on muscle fiber morphology, intermuscular microvessels, vascular perfusion, and fascia-associated microstructures. After imaging, tissue samples corresponding to the pCLE imaging sites were harvested for histological examination.

For large-animal validation, *in vivo* bladder imaging was performed in a Bama miniature pig model. The animal was fasted for 12-24 h before surgery. Atropine sulfate was administered intramuscularly at 0.05 mL/kg, followed by Zoletil 50 at 0.1 mL/kg for anesthesia induction. After loss of consciousness and attenuation of the corneal reflex, endotracheal intubation was performed, and anesthesia was maintained with isoflurane. An ear-vein catheter was established for intraoperative drug administration, fluid infusion, and sodium fluorescein injection. The bladder was surgically exposed through a midline abdominal incision. Approximately 1 min after intravenous injection of 10% sodium fluorescein, the pCLE probe was gently placed on the bladder mucosa and muscular layer to acquire real-time images and videos. After completion of imaging, the animal was euthanized under deep anesthesia by rapid intravenous injection of potassium chloride. Tissue samples were collected from the corresponding probe-contact sites for histological comparison.

Clinical gastric pCLE images were obtained from a prospective, single-center observational study conducted at the Digestive Endoscopy Center of Guangdong Second Provincial General Hospital. This prospective single-center study included a small patient cohort for feasibility evaluation. Eligible participants were patients aged 20-70 years who presented with digestive symptoms, were suitable for and willing to undergo gastric pCLE examination and provided written informed consent. Patients were excluded if they had a history of gastric surgery; severe cardiac, hepatic, or renal dysfunction that could preclude anesthesia, endoscopy, surgery, or sodium fluorescein metabolism; current anticoagulant or antiplatelet therapy or coagulation disorders that could preclude biopsy; radiological evidence of lymph-node metastasis; pregnancy or lactation; allergic constitution or known sodium fluorescein allergy; or psychiatric conditions preventing cooperation with the study procedures. Before examination, patients fasted for at least 12 h and abstained from water for at least 4 h. Anesthesia risk was evaluated, and an oral defoaming agent and lidocaine were administered 10 min before endoscopy. A sodium fluorescein allergy test was performed before pCLE imaging.

During the clinical procedure, a high-resolution upper gastrointestinal endoscope was first used to inspect the stomach and identify suspicious lesions. The pCLE probe was then advanced through the endoscopic biopsy channel. The probe tip was first placed perpendicular to the adjacent normal mucosa and subsequently moved to the suspicious lesion for pCLE image acquisition. Targeted biopsy, endoscopic resection, or surgical specimens were obtained from the corresponding sites when clinically indicated. The pCLE examination was performed by experienced endoscopists with at least 5 years of pCLE experience. In the present manuscript, the clinical images were used as representative histology-correlated examples of gastric antral high-grade intraepithelial neoplasia and adenocarcinoma rather than for independent diagnostic-accuracy analysis.

For both animal and clinical specimens, tissues corresponding to the pCLE imaging sites were fixed in formalin, embedded in paraffin, sectioned, and stained with hematoxylin and eosin. Histological

sections were reviewed by experienced pathologists and compared with the matched pCLE images to evaluate the correspondence between optical features and tissue microstructures. Representative pCLE images were analyzed descriptively using gray-value histograms and line-intensity profiles to assess image contrast, dynamic range, and structural visibility.

2.5. Ethical approval

All SD rat procedures were approved by the Ethics Committee of Beijing Institute of Technology (Ethics Approval No.: BIT-EC-SCXK2016-0006-M-2021067). The Bama miniature pig experiment was approved by the Institutional Animal Care and Use Committee of Hubei Tianqin Biotechnology Research Institute Co., Ltd. (Approval No.: IACUC-YJY-2024-025). The clinical study was approved by the Medical Ethics Committee of the Second People's Hospital of Guangdong Province (Ethics Approval No.: 2023-KY-KZ-296-02). Written informed consent was obtained from all participants before enrollment, and the clinical study was conducted in accordance with the Declaration of Helsinki.

3. Results

3.1. Optical performance of the miniature objective

The fabricated miniature objective achieves high structural compactness with a length of 9.08 mm and a maximum outer diameter of 2.59 mm (Supplementary Figure. S4, *https://www.biosciencetrends.com/action/getSupplementalData.php?ID=304*). These dimensions confirm that the design is fully compatible with the standard 2.8 mm biopsy channel while maintaining adequate clearance for the pCLE probe.

As shown in Figure 3 (A), in the resolution image obtained with the miniature objective, the finest distinguishable target in the entire imaging area was Group 9, Element 3, corresponding to a lateral resolution of 0.78 μm. This result is sufficient to resolve the detail of imaging fiber pitches for a pCLE probe. As shown in Figure 3 (B), approximately 24-line pairs are visible across the entire imaging area when observing the 80 lp/mm Ronchi grating, yielding an object-side FOV diameter of 300 μm. This measured FOV not only successfully fulfills the rigorous 280 μm design specification but also delivers an extended spatial margin for mechanical tolerance. Figure 3 (C) is the resolution image obtained with our resolution test system alone. By comparing the dimension of the same target (*e.g.*, Group 6, Element 2 in (A) and (C)), the imaging magnification of the miniature objective is calculated to be 2.5x, demonstrating perfect agreement with the theoretical optical design target. Figure 3 (D) shows the measured working distance of the miniature objective, averaging 64.6 ± 3.8 μm across five samples. This minor deviation remains strictly within the acceptable tolerance range and thoroughly satisfies practical application requirements. Finally, the measured MTF curve (Figure 3 (E)) demonstrates the miniature objective's contrast transfer capability. At the system's Nyquist frequency of 151 lp/mm, the miniature objective achieves an MTF value greater than 0.5 in the vertical orientation and 0.6 in horizontal orientation. As shown in Figures 3 (F) and (G), the relative illumination remains above 90% across the entire FOV, satisfying the design specifications. As shown in Figure 3 (H), negligible distortion was observed, which is consistent with theoretical design.

3.2 Probe integration and navigability in a bent endoscopic channel

3.2.1. Probe-level optical performance after integration

Following system integration, the distal rigid length of the complete pCLE probe is 11.48 mm (Figure 4 (A)). The mechanical length is reduced compared to that of the Mauna Kea Technologies (MKT) gastrointestinal probe, which is reported in the literature to be 14 mm (*12*). This miniaturization is a direct result of the integrated design approach that prioritizes distal rigid length as a primary design variable to enhance clinical passability in tortuous anatomical channels.

To evaluate the imaging efficacy of the proposed high-NA architecture, the USAF 1951 resolution target was used. Our probe resolved Group 8, Element 6, corresponding to a lateral resolution of 1.1 μm (Figure 4 (B)). Beyond the resolution target, the integrated probe provided clear visualization of cellular morphology during *ex vivo* rat colon imaging (Figure 4 (C)). Figure 4 (D) shows that approximately 19-line pairs were visible across the field, translating to an effective FOV diameter of ~240 μm. This enhancement is consistent with the high-NA (0.7) optical design employed in this work. It provides high luminal adaptability and effectively elevates the signal floor in biological tissues. These results validate that the integrated design approach achieves an optimal balance between high optical fidelity and the physical constraints inherent to fiber-coupled systems.

3.2.2. Clinical navigability and imaging stability under bending constraints

To validate the translational value of the clinically constrained design, we evaluated the mechanical passability and optical performance stability of the integrated probe under severe bending conditions. We assessed the navigability of the probes within the working channel of a standard electronic endoscope (Model: GIF-H180J, Olympus). The proposed probe, benefiting from its optimized distal rigid length, successfully navigated through the endoscopic

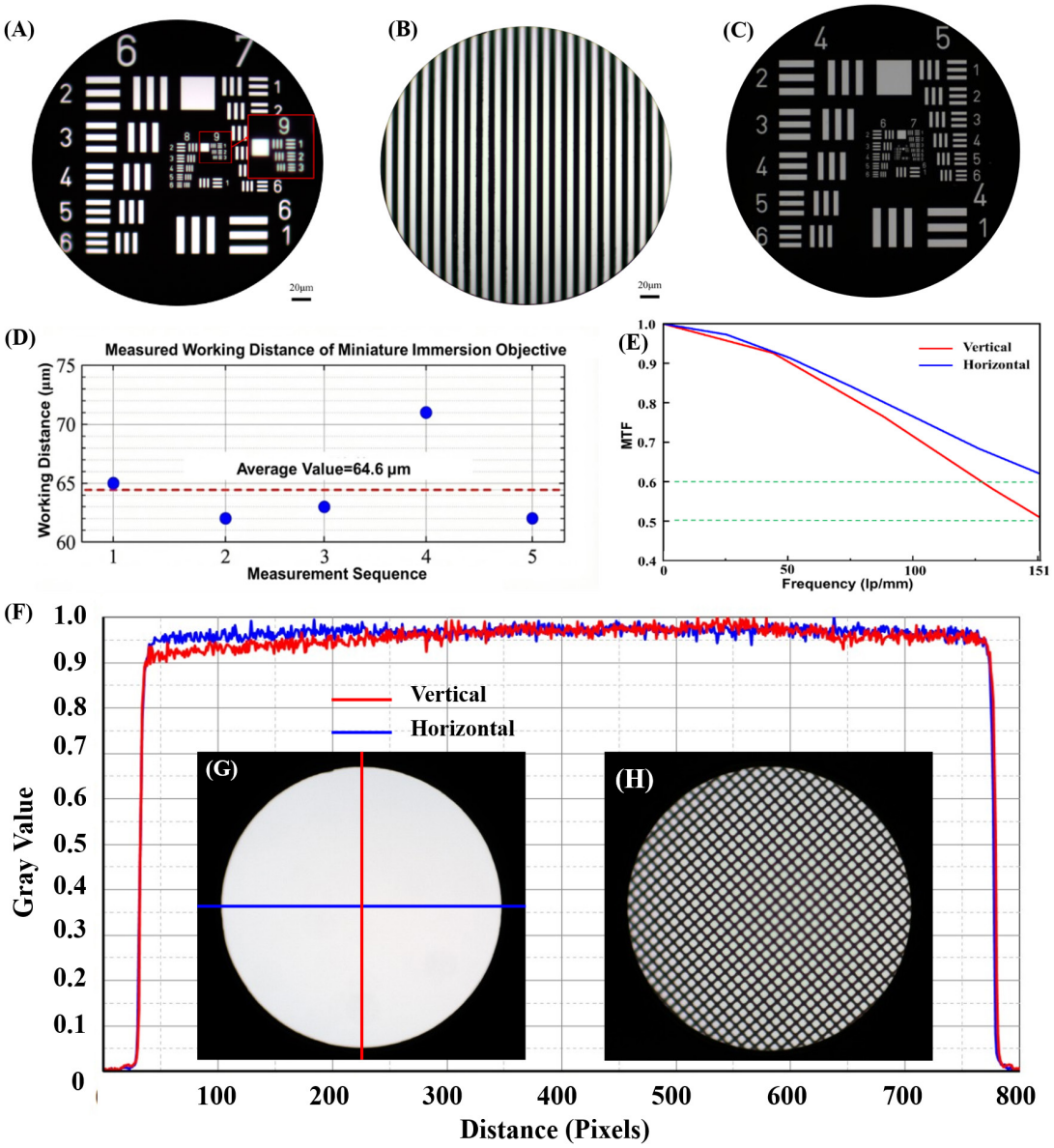

Figure 3. Optical Performance Characterization of the Miniature Fiber-Coupled Fluorescence Microscope Objective. (A) Image of the USAF 1951 Resolution Test Chart with miniature objective; **(B)** Image of the Ronchi Grating Test Plate; **(C)** Image of the USAF 1951 Resolution Test Chart with our resolution test system only; **(D)** Measured Working Distance of Miniature objective; **(E)** MTF Measurement Curve of the Miniature objective; **(F)** Relative illumination measurement results; **(G)** Original image of relative illuminance; **(H)** Distortion measurement results.

channel even when the endoscope tip was deflected to its maximum mechanical limit, corresponding to a limit bending radius of 30 mm (Figure 4 (E)). This passability test directly confirms that our design improves the probe maneuverability in complex luminal geometries.

Beyond physical passability, image degradation caused by probe deformation during clinical maneuvers represents a fundamental challenge in pCLE. Because conventional static evaluations may not fully reflect these conditions, we used a bending stress-test method to evaluate imaging stability under clinically relevant mechanical deformation. Imaging stability was evaluated with a portion of the probe coiled around a custom fixture with a rigorous bending radius of 35 mm (Figure 4 (F)). Under this condition, the resolution target imaging confirmed that the lateral resolution remained stable at 1.1 μm (Figure 4 (G)). Furthermore, *ex vivo* rat colon imaging acquired under the bending state revealed no discernible loss of cellular detail or architectural contrast compared with the unbent configuration (Figure 4 (H)). By aligning optical validation directly with clinical reality, this problem-driven methodology provides critical evidence for the probe's translational viability. These results confirm that the proposed probe successfully passed through the endoscope working channel at a bending radius of 30 mm. Under a bending radius of 35 mm, the proposed probe maintained a

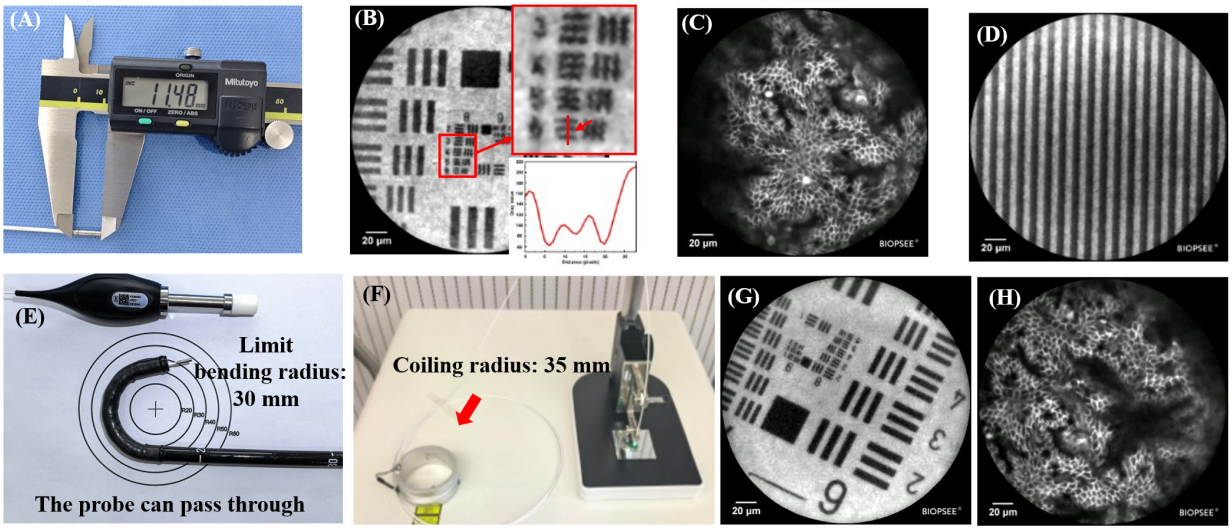

Figure 4. Probe-Level Optical Performance and Bending-Compatible Endoscopic Navigability of the Integrated pCLE System. (A) The distal rigid length of the complete pCLE probe; **(B)** Resolution test chart of the complete pCLE probe; **(C)** *Ex vivo* rat colon imaging of the complete pCLE probe; **(D)** Image of the Ronchi Grating Test Plate. **(E)** The proposed probe successfully passing through the endoscope channel bending at a radius of 30 mm; **(F)** Experimental setup for evaluating imaging stability with a portion of the probe coiled at a 35 mm radius; **(G)** Resolution Target image acquired under the 35 mm bending configuration; **(H)** *Ex vivo* Rat Colon image at the 35 mm bending configuration. (The limit bending radius is defined as the smallest radius of the electronic endoscope's distal bending section when the deflection control knob is rotated to its maximum extent).

Table 1. Parameter Comparison

Specification Items	Yang L (*9*)	Li H (*14*)	Lu T (*11*)	Rouse A R (*15*)	Kyrish M (*10*)	Ours
Object						
Wavelengths (nm)	488-550	488-550	488-550	480-660	452-623	488-600
Magnification	2	2.2	2	1.6	2	2.5
Object-side NA	0.5	0.52	0.6	0.46	0.55	0.7
Working distance (μm)	150	80	60	0-200	15	64.6 ± 3.8
Object-side FOV (μm)	360	570	600	450	360	300
RMS Radius (μm)	< 1.2	< 2	< 2	< 3	/	< 1.0
MTF@Nyquist Frequency (lp/mm)	> 0.5@167	> 0.5@132	>0.5@132	> 0.5@166	/	> 0.5@151
Clear Aperture (mm)	1.4	1.8	3	1.6	1.5	1.8
Mechanical Length (mm)	/	11.2	21	13	/	9.1
Outer Diameter (mm)	2.6	2.6	4.6	3	2.1	2.6
Number of Elements	4	6	5	6	6	5
Probe						
Lateral resolution (μm)	1.55	1.95	1.95	/	2.19	1.10
Distal rigid length (mm)	10.3	/	/	/	/	11.48
FOV	/	512.5μm	540 μm	/	/	240 μm
Dynamic bending validation	Not reported	Not reported	Not reported	Not reported	Not reported	Validated
Endoscopic channel compatibility under extreme bending	Not reported	Not reported	Not reported	Not reported	Not reported	Validated

/ Refers to the lack of information or detailed numerical values provided.

lateral resolution of 1.1 μm and preserved cellular-level imaging quality with no discernible degradation compared to the unbent configuration.

A comparative analysis of the specifications between our design and existing designs is presented in Table 1. A comprehensive assessment of critical metrics (including NA, Total Mechanical Length, Magnification, and RMS radius) demonstrates that our design achieves a favorable engineering balance among high NA, compact outer diameter, short distal rigid length, and cellular-level resolution, establishing it as a viable solution for pCLE applications that balances high imaging performance with clinical navigability.

3.3. Tissue imaging

3.3.1. Imaging of rat colon and tibialis anterior muscle

In rat colonic mucosa, the pCLE system clearly visualized crypt-like glandular architecture and

cellular-level epithelial structures (Figures 5 (A) and 5 (B)). The glandular openings, epithelial lining, and luminal boundaries were distinguishable, indicating sufficient contrast for resolving superficial mucosal microstructures. Line-intensity and gray-value analyses further showed clear signal differences between crypt structures and surrounding tissue without obvious signal saturation (Figures 5 (C) and 5 (D)).

In tibialis anterior muscle, pCLE images showed elongated hypointense muscle fibers separated by hyperintense intermuscular microvessels (Figures 6 (A) and 6 (B)). Dynamic imaging further allowed visualization of microvascular perfusion. The corresponding histological section confirmed the parallel arrangement of skeletal muscle fibers (Figure 6 (C)). In the superficial fascia, pCLE visualized elliptical adipocyte-like structures and interlacing vascular networks (Figures 6 (D) and 6 (E)), which were consistent with the adipose and fibrous components observed on histology (Figure 6 (F)). Gray-value histograms of representative images showed variable contrast among muscle, vascular, and fascial structures without obvious signal saturation (Figures 6 (G-J)).

3.3.2. Imaging of bama miniature pig bladder

In the Bama miniature pig bladder model, the integrated pCLE system visualized urothelial, vascular, and muscular structures *in vivo* (Figures 7 (A), 7 (C), 7(E), and 7 (G)). Capillary networks in the lamina propria and fiber-bundle-like structures in the muscular layer were distinguishable, and flowing blood cells could be observed during dynamic imaging. Matched histological sections confirmed the presence of urothelium, loose connective tissue, vascular structures, and smooth muscle layers corresponding to the pCLE findings (Figures 7 (B), 7 (D), 7 (F), and 7 (H)). Gray-value histograms of representative images showed tissue-dependent contrast patterns, supporting the ability of the probe to distinguish heterogeneous bladder microstructures (Figures 7 (I-L)).

3.3.3. Imaging of human antrum

Representative clinical pCLE images of gastric antral HGIN and adenocarcinoma showed histology-correlated abnormalities, including reduced glandular

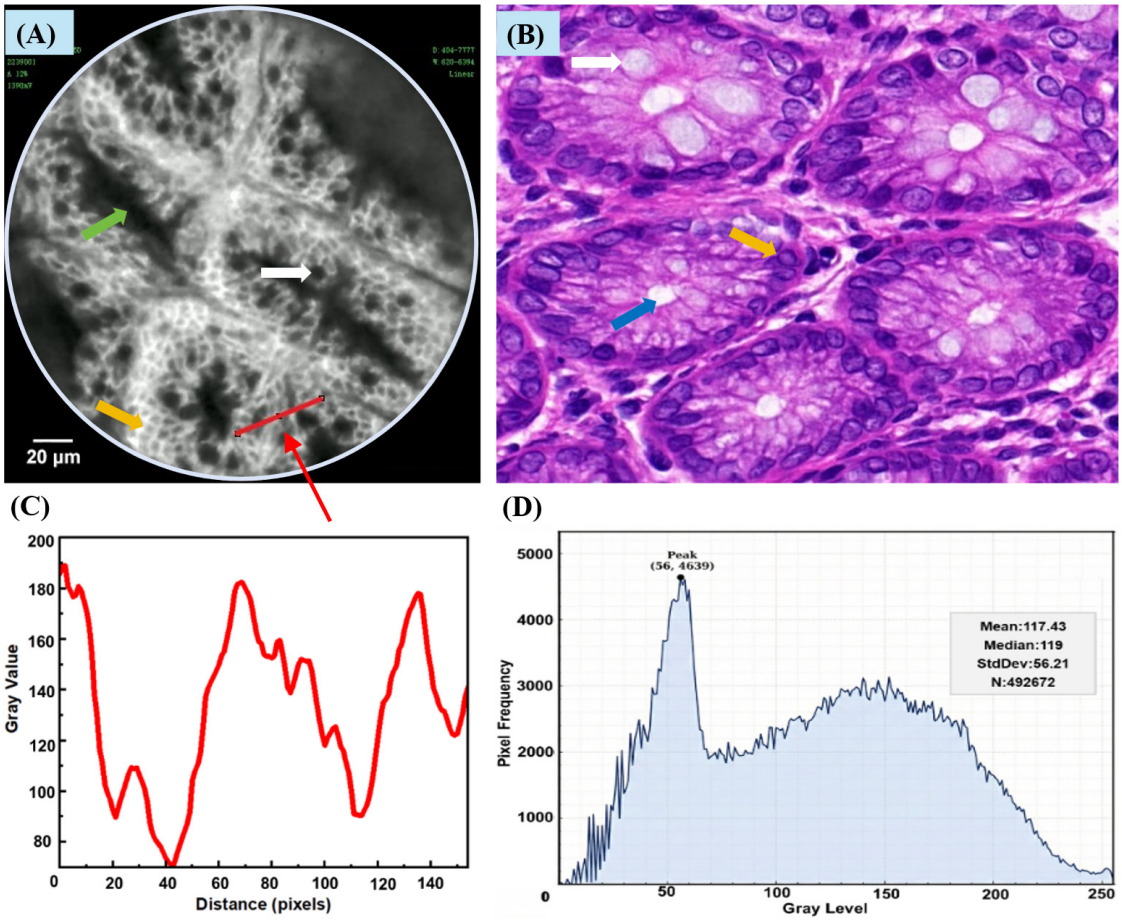

Figure 5. *Ex vivo* Imaging of Rat Colonic Mucosa. (A) Confocal Laser Endomicroscopic Image of Colonic Mucosa. This demonstrates the capability to resolve cellular level mucosal structures; **(B)** Histopathological Section of Colonic Mucosa. White arrows: Goblet cells arranged in a chrysanthemum-like pattern within the glands; Green arrows: Central openings of the glands; Yellow arrows: Columnar epithelial cells; Blue arrows: Glandular lumens; **(C)** The line profile of the area marked by the red line in the **(A)**; **(D)** Histograms of gray values in the **(A)**.

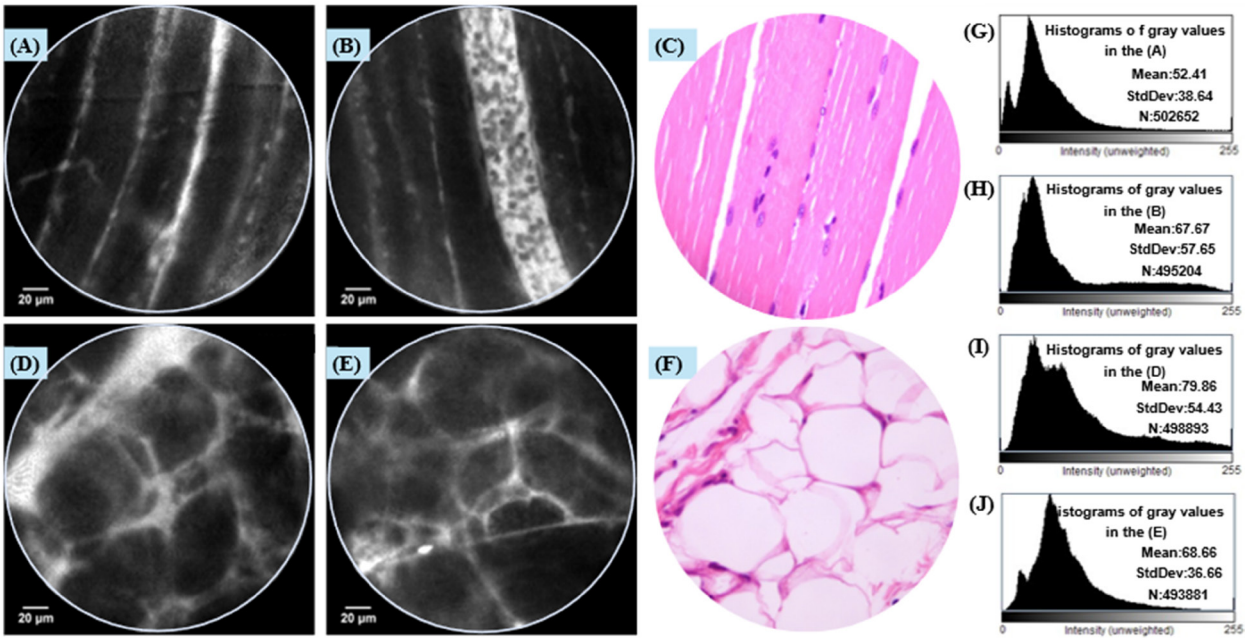

Figure 6. Imaging of the Muscular Layer and Superficial Fascia Layer of Rat Tibialis Anterior Muscle. (A) and **(B)** pCLE Image of the Muscular Layer. These images display excellent microvascular and fibrous structural contrast; **(C)** Histopathological Section of the Muscular Layer; **(D)** and **(E)** pCLE Image of the Superficial Fascia Layer. They exhibit distinct fascial architecture; **(F)** Histopathological Section of the Superficial Fascia Layer; **(G)**, **(H)**, **(I)** and **(J)** Gray-value histograms corresponding to **(A)**, **(B)**, **(D)** and **(E)**, respectively.

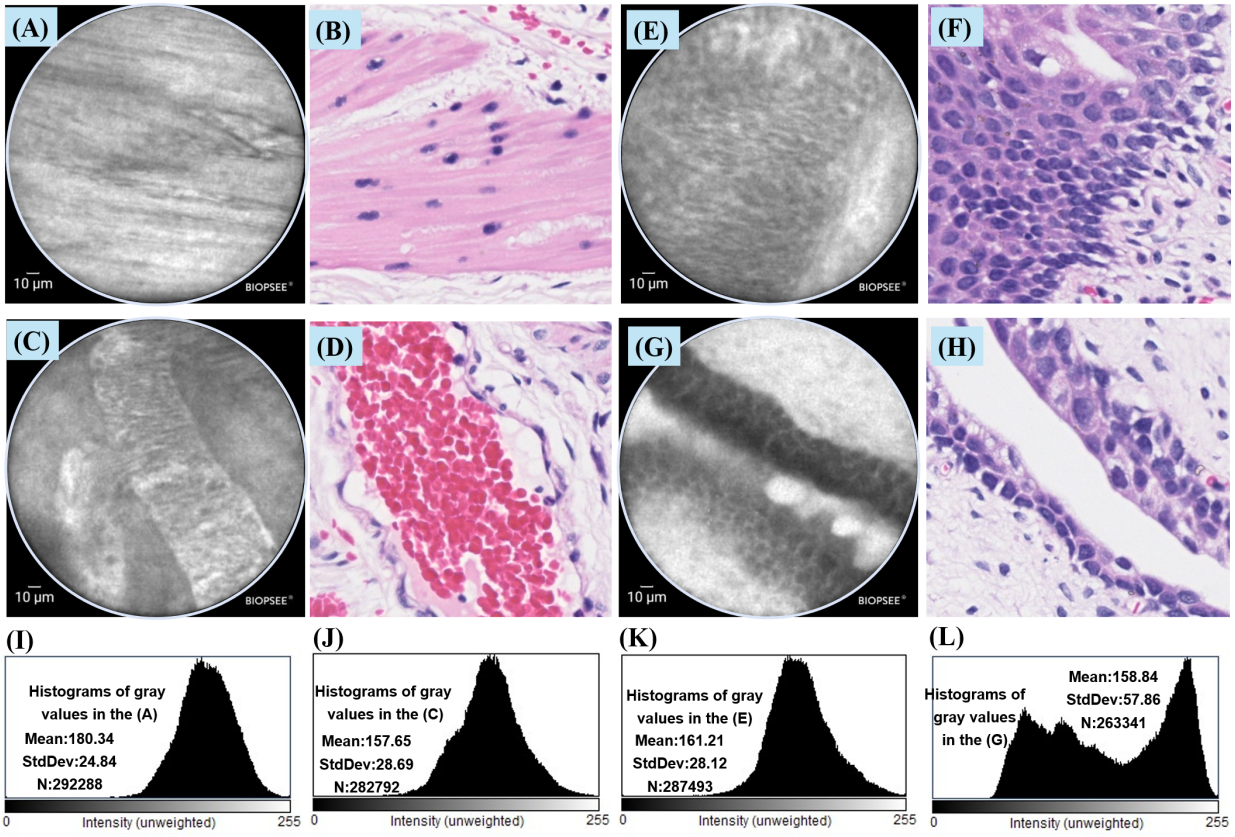

Figure 7. ***In vivo*** **Imaging of Bama Miniature Pig Bladder. (A)** pCLE Image of Muscle Fibers. This confirms the luminal adaptability of the probe in living tissue; **(B)** Histopathological Section of Muscle Fibers; **(C)** pCLE Image of Capillaries; **(D)** Histopathological Section of Capillaries; **(E)**, **(G)** pCLE Images of Epithelial Cells; **(F)**, **(H)** Histopathological Sections of Epithelial Cells; **(I)** **(J)**, **(K)** and **(L)** Gray-value histograms corresponding to **(A)**, **(C)**, **(E)** and **(G)**, respectively.

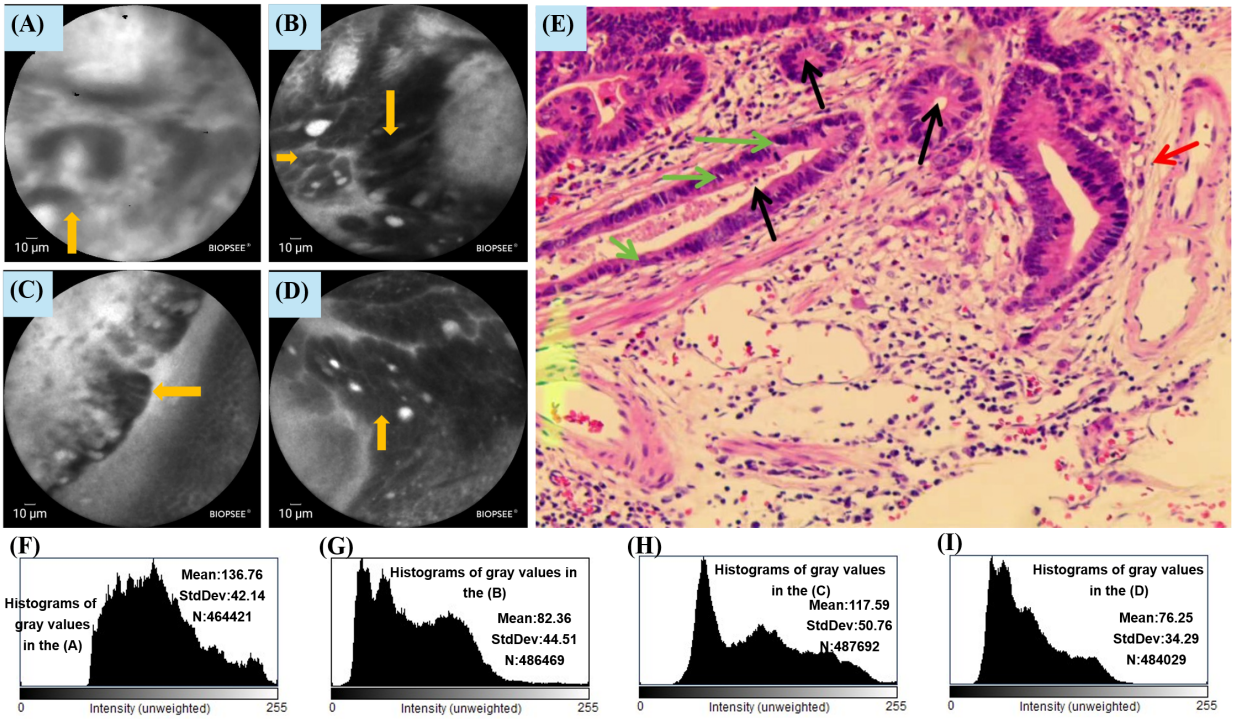

Figure 8. Imaging of Human Gastric Antrum. (A) (B) (C) and **(D)** pCLE Images of High-Grade Intraepithelial Neoplasia (HGIN)-Adenocarcinoma. These are representative histology correlated gastric lesion images. They demonstrate the preservation of glandular structural visibility under clinically constrained probe geometry; **(E)** Histopathological Section. (Yellow arrows: Sparse glandular structures. Green arrows: Epithelial cells. Red arrows: Glandular epithelial structures. Black arrows: Sparse glands); **(F) (G)**, **(H)** and **(I)** Gray-value histograms corresponding to **(A)**, **(B)**, **(C)** and **(D)**, respectively.

density, disrupted glandular architecture, epithelial disorganization, and focal fluorescein leakage (Figures 8 (A-D)). The matched histopathological section confirmed neoplastic epithelial proliferation with glandular architectural distortion and cellular atypia (Figure 8 (E)). Gray-value histograms showed heterogeneous contrast distributions among different fields, reflecting variable glandular architecture, mucus/surface scattering, and fluorescein distribution (Figures 8 (F-I)). These findings demonstrate the feasibility of visualizing clinically relevant gastric mucosal abnormalities with the integrated pCLE probe.

4. Discussion

This study developed and evaluated a clinically constrained miniature immersion objective for pCLE, with the goal of balancing high-NA fluorescence collection, cellular-level resolution, compact distal geometry, and endoscopic navigability. The major finding is that the proposed objective was not only optically feasible as an isolated component but could also be integrated into a probe that retained cellular-level imaging performance under clinically relevant bending conditions. The fabricated objective achieved an object-side NA of 0.7, a 2.6-mm outer diameter, and a 9.1-mm rigid length. After integration, the pCLE probe maintained a lateral resolution of 1.1 µm, an effective FOV of approximately 240 µm, and stable imaging performance during bent-channel testing. The compact distal architecture achieves both high optical performance and clinical accessibility.

These findings hold important translational significance. They address the limitations of existing technologies. Conventional pCLE systems may encounter limitations in anatomically tortuous or highly angulated luminal environments due to distal rigidity and maneuverability constraints. These limitations are particularly relevant in applications requiring stable imaging through sharply bent endoscopic channels. The present design was developed specifically to address this translational bottleneck while preserving cellular-level imaging capability.

The design strategy differs from conventional miniature optical design workflows in that clinical constraints were treated as initial boundary conditions rather than as post-design packaging requirements. For fiber-bundle-based pCLE, optical resolution, FOV, working distance, and magnification must be matched to the discrete sampling properties of the imaging fiber, while the distal optical assembly must remain compatible with standard endoscopic working channels and mechanical bending. In this context, the proposed clinically constrained co-design approach links fiber-bundle sampling, water-immersion contact imaging, endoscopic channel diameter, short rigid-

tip requirements, and bending navigability into a single clinically constrained design. Detailed optical optimization and engineering design procedures are provided in the Supplementary Materials (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=304*), while the main text focuses on the translational performance of the fabricated and integrated probe.

The present architecture helps mitigate a common trade-off in miniature pCLE probe development. GRIN-lens-based probes can provide favorable flexibility and compactness, but bending-related changes in the optical path may affect image quality in some configurations (*16*). Distal-scanning approaches based on MEMS or piezoelectric actuation can reduce fiber-bundle pixelation and provide continuous scanning images; however, the integration of actuators, driving components, and protective packaging may increase distal complexity, rigid length, and safety requirements (*13,24*). In contrast, the present design uses a passive high-NA distal objective coupled to an imaging fiber bundle. Although this architecture retains the intrinsic sampling limitation and pixelated pattern of fiber-bundle imaging, it provides a mechanically simple and compact solution that is compatible with standard endoscopic access and stable under bending. The 30-mm endoscopic passability test and 35-mm coiling test support the mechanical feasibility of this approach.

The biological imaging results further support the feasibility of the integrated pCLE probe in tissue environments. In freshly excised rat colonic mucosa after systemic sodium fluorescein administration, the system visualized crypt-like glandular architecture and cellular-level mucosal features. In rat tibialis anterior muscle and superficial fascia after local fluorescein application, the probe resolved muscle fiber organization, intermuscular microvascular structures, and fascia-associated adipose and vascular networks. In the Bama miniature pig bladder model, *in vivo* imaging demonstrated distinguishable urothelial, vascular, and muscular features with histological correspondence. These results indicate that the high-NA miniature objective can provide sufficient contrast and structural visibility across epithelial, muscular, vascular, and connective-tissue-rich structures.

The representative clinical gastric images provide preliminary evidence of translational relevance but should be interpreted as histology-correlated feasibility observations rather than diagnostic-accuracy validation. In gastric antral HGIN and adenocarcinoma, pCLE images showed abnormal glandular architecture, epithelial disorganization, reduced glandular regularity, and focal fluorescein leakage, with corresponding histopathological confirmation. These findings suggest that the integrated probe can visualize clinically relevant mucosal abnormalities during endoscopic imaging. However, the present clinical dataset is not sufficient to establish diagnostic sensitivity, specificity, interobserver agreement, or lesion-level diagnostic accuracy. Future clinical studies should therefore include larger patient cohorts, standardized image-quality criteria, blinded image interpretation, and predefined histopathological correlation protocols.

Previous clinical studies have shown that pCLE can provide microscopic information during endoscopy in a range of clinical settings, including pharyngeal neoplasia, Barrett esophagus-associated intestinal metaplasia, esophageal neoplasia, gastric cancer and precancerous lesions, small-bowel diseases, Crohn disease, and selected extra-gastrointestinal applications (*25-35*). These studies collectively support the clinical demand for real-time optical biopsy tools capable of resolving epithelial architecture, cellular atypia, vascular leakage, and glandular organization. Importantly, these prior reports should be viewed as evidence for the broader clinical need and potential utility of pCLE, rather than as direct validation of the miniature objective developed in the present study. The contribution of this work is to address a device-level bottleneck: achieving high-NA, cellular-level imaging while preserving compatibility with standard endoscopic working channels and bent intraluminal navigation.

Several limitations should be acknowledged. First, the ultimate spatial resolution of the integrated pCLE system remains constrained by the core-to-core pitch of the imaging fiber bundle, even though the 0.7-NA objective improves fluorescence collection efficiency. Second, effective FOV is limited by the need to maintain cellular-level resolution within a compact optical design, which may restrict wide-area screening. Third, the current biological and clinical experiments were primarily feasibility and histology-correlation studies. The animal experiments were not designed to evaluate disease-specific diagnostic performance, and the clinical images were not sufficient for formal statistical analysis. Because fluorescein administration routes and tissue environments differed among the animal models, gray-value histograms were used for descriptive image-quality assessment rather than direct quantitative comparison across tissues. Fourth, the present system was optimized for fluorescein-based visible-light imaging; therefore, its performance with other fluorophores, molecular probes, or near-infrared excitation requires further optical and biological validation.

Future work should focus on three directions. First, the integrated probe should be evaluated in larger prospective clinical studies with standardized acquisition protocols, quantitative image-quality metrics, and blind interpretation. Second, the optical design may be further adapted to expand FOV, reduce fiber-bundle artifacts, or improve compatibility with different endoscopic platforms. Third, molecularly targeted contrast agents and near-infrared pCLE may enhance lesion-specific contrast and improve the detection of early-stage disease

at the cellular level (*36*). Such extensions will require optimization of lens transmission, fiber compatibility, fluorescence collection efficiency, and clinical safety. Overall, this study supports the feasibility of a clinically constrained high-NA miniature objective for pCLE and may provide a compact platform for future real-time optical biopsy and molecular endomicroscopy studies.

5. Conclusion

This study developed and validated a clinically constrained high-NA miniature immersion objective for pCLE. The integrated probe achieved cellular-level imaging performance within compact distal geometry and maintained stable imaging under bent-channel conditions. Animal imaging and representative histology-correlated clinical gastric images further supported its feasibility for real-time optical biopsy. Larger prospective clinical studies are needed to determine diagnostic accuracy and clinical utility.

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Original Article

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Early post-reperfusion neutrophil dynamics after liver transplantation: Association with graft size

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SUMMARY: Patients with end-stage liver disease often exhibit impaired neutrophil function and have an elevated risk for perioperative infections. Liver transplantation (LT) restores hepatic function; however, perioperative neutrophil dynamics and their association with graft size remain unclear. We retrospectively analyzed 71 adult patients who underwent LT between January 2019 and June 2021. Leukocyte, neutrophil, and lymphocyte counts and the neutrophil-to-lymphocyte ratio were assessed at three intraoperative time points: beginning of surgery (BS), anhepatic phase (AP), and abdominal closure (AC), as well as on postoperative days (PODs) 1–3. The patients were stratified by graft-to-recipient weight ratio (GRWR < 1.0 *vs*. ≥ 1.0), and the correlations between GRWR and leukocyte parameters were evaluated. Neutrophil and leukocyte counts remained unchanged from the BS to AP and increased significantly after graft reperfusion (AC *vs*. BS: $p < 0.01$). Lymphocyte counts declined significantly during surgery. On POD 1, both neutrophil counts and their increases from BS correlated significantly with GRWR in the GRWR < 1.0 group (r_s = 0.424 and 0.442, respectively; both $p < 0.01$), although not in the GRWR ≥ 1.0 group. No postoperative infections were observed within 7 days. Graft reperfusion was associated with a robust increase in peripheral neutrophil counts, particularly in the recipients of smaller grafts. These findings suggest an association between graft size and early postoperative neutrophil dynamics, which may help interpret early immune responses after LT.

Keywords: end-stage liver disease, leukocyte kinetics, neutrophil mobilization, graft-to-recipient weight ratio, perioperative immunity

1. Introduction

Liver transplantation (LT) is a definitive and life-saving treatment for patients with end-stage liver disease (ESLD). However, ESLD is associated with profound alterations in host immunity, including quantitatively and qualitatively impaired neutrophil function, which increases the risk for perioperative infections (*1-3*). Understanding perioperative innate immune dynamics is clinically important for managing patients who undergo liver transplantation.

Neutrophils are critical first responders in innate immunity. In ESLD, circulating neutrophil counts are often reduced due to enhanced apoptosis and splenic sequestration (*4,5*). Their perioperative mobilization from bone marrow into peripheral circulation is influenced by inflammatory mediators, surgical stress, and organ function (*6–9*). Notably, clinical observations suggest that neutrophil counts frequently increase after graft reperfusion during LT. Whether the transplanted liver contributes to the modulation of systemic neutrophil mobilization is unclear. The mechanisms underlying perioperative neutrophil mobilization in LT remain poorly understood. Only limited studies have quantified intraoperative changes in circulating neutrophil counts at defined surgical phases. Furthermore, whether the magnitude of neutrophil mobilization varies with graft size, which is an important determinant of early graft performance, is undetermined.

In this retrospective cohort study, we evaluated perioperative changes in leukocyte and neutrophil counts in LT recipients and examined their associations with graft-to-recipient weight ratio (GRWR), a clinically relevant index of graft volume. We hypothesized that neutrophil mobilization would remain attenuated until graft reperfusion and increase thereafter, and that graft size would influence the magnitude of this response. By clarifying the relationship between graft size and early innate immune dynamics, we aimed to provide clinical insight into graft-size-dependent modulation of early

innate immune responses following LT.

2. Materials and Methods

2.1. Study design and ethical approval

This retrospective cohort study was approved by the Clinical Research Ethics Committee of the University of Tokyo (approval No. 2203-(7)). The requirement for individual written informed consent was waived due to the observational nature of the study; however, eligible patients were given the opportunity to opt out *via* public notification. The study adhered to the principles of the Declaration of Helsinki and followed institutional policies for patient data protection.

2.2. Patient selection

We identified all adult recipients of liver transplants from either living or brain-dead donors, between January 1, 2019 and June 30, 2021, using the institutional electronic anesthesia record system.

The exclusion criteria comprised preoperative use of immunosuppressive therapy such as for autoimmune disease or re-transplantation; ABO-incompatible LT; fulminant liver failure within 8 weeks of onset; preoperative sepsis or other infection-associated conditions; missing key laboratory data; and patient refusal *via* the opt-out process.

2.3. Anesthetic and perioperative management

All patients underwent general anesthesia with tracheal intubation and mechanical ventilation. The anesthetic technique was at the discretion of the attending anesthesiologist, and volatile-based general anesthesia was used in 69 patients (97.1%).

Perioperative management included:

• Intraoperative circulatory management: dopamine, dobutamine, norepinephrine, or phenylephrine were administered intraoperatively as needed.

• Steroid therapy: intravenous methylprednisolone (20 mg/kg) was administered at the time of patient transfer to the operating room and at graft reperfusion.

• Other intraoperative medications: nafamostat mesilate (1 mg/kg/h) and alprostadil alfadex (0.01 μg/kg/min) were routinely infused from the beginning of surgery.

• Postoperative immunosuppression: all patients received tacrolimus and corticosteroids based on a standardized protocol.

2.4. Graft selection, surgical procedure, and perioperative immunosuppressive regimen

Graft selection for living-donor liver transplantation (LDLT) procedures at our center has traditionally been based on the recipient's standard liver volume (SLV), with a minimum requirement of 35% of the estimated SLV to ensure sufficient functional graft mass, which is consistent with previously reported requirements (*10*). SLV-based criteria are used in a limited number of centers in Japan, and GRWR is the gold-standard index for assessing graft size in LDLT. In this study, GRWR was calculated using the actual graft weight measured at the time of preservation with University of Wisconsin solution and was used for all analyses regarding the impact of graft size. The surgical procedures, including live donor hepatectomy and graft implantation, adhered to standard institutional protocols for LT. The University of Wisconsin solution was used for cold static storage of the liver graft.

The immunosuppressive regimen comprised tacrolimus and methylprednisolone, with gradually tapered doses. The targeted tacrolimus trough level was increased to > 10 ng/mL within 5 days. Methylprednisolone (20 mg/kg) was administered before surgery and during the AP and then tapered to maintenance doses of 3–0.75 mg/kg during the first week after LDLT. Additionally, mycophenolate mofetil was administered to patients with acute or chronic kidney injury.

2.5. Data collection

Demographic and clinical variables were obtained from electronic medical and anesthesia records including age, sex, height, weight, underlying liver disease, Model for End-Stage Liver Disease score, and Child–Turcotte–Pugh score. Graft characteristics such as graft type and GRWR were also recorded. Laboratory data included leukocyte, neutrophil, and lymphocyte counts measured at the beginning of surgery (BS), at AP, after graft reperfusion, at the time of abdominal closure (AC), and at postoperative days (PODs) 1–3. Intraoperative information including anesthetic technique, surgical duration, blood loss, and transfusion volume (red blood cells, fresh frozen plasma, and platelet concentrate), and the intraoperative administrations of steroids, catecholamines, and other continuously infused medications were collected.

This perioperative window (BS–POD 3) was selected to capture innate immune responses expected to peak within 72 hours. In addition to leukocyte subsets, the neutrophil-to-lymphocyte ratio (NLR) was calculated as a composite index reflecting the balance between neutrophil mobilization and lymphocyte depletion, which has been reported as a clinically relevant marker of systemic inflammation in surgical and transplant settings (*11*).

2.6. Outcomes

The primary outcome was the change in leukocyte, neutrophil, and lymphocyte counts as well as the NLR across the perioperative period: BS, AP, AC, and POD 1–3.

The secondary outcomes were the correlations between GRWR and leukocyte or neutrophil counts on POD 1, as well as the correlations between GRWR and the perioperative increase in leukocyte or neutrophil counts from BS to POD 1.

The clinical outcomes, including infection and biopsy-proven acute rejection, were also monitored through POD 7 to document early complications. These outcomes were collected for descriptive purposes and not included in the leukocyte dynamics analysis. To evaluate the effect of graft size, patients were stratified into two groups: GRWR < 1.0 (small-for-size grafts) and GRWR ≥ 1.0.

2.7. Statistical analyses

Categorical variables are presented as absolute counts and percentages. Continuous variables are summarized as mean ± standard deviation or median with interquartile range (IQR), depending on normality assessed by histograms and quantile–quantile plots. Intraoperative changes across timepoints were analyzed using Friedman's test, with Bonferroni correction applied for multiple post hoc comparisons.

Associations between GRWR and leukocyte or neutrophil counts on POD 1, as well as their increases from BS to POD 1, were assessed using Spearman's rank correlation, with analyses conducted separately for GRWR < 1.0 and GRWR ≥ 1.0 groups. A two-sided p value < 0.05 was considered significant.

All statistical analyses were performed using SPSS version 25 (IBM Corp., Armonk, NY, USA). A post hoc power analysis for Friedman's test was additionally conducted using G*Power version 3.1.9.7 (Heinrich Heine University Düsseldorf, Düsseldorf, Germany).

3. Results

3.1. Patient enrollment and baseline characteristics

Between January 1, 2019, and June 30, 2021, a total of 26,780 surgical cases were recorded at our institution. Among them, 117 patients underwent LT. After excluding patients who received preoperative immunosuppressive therapy (n = 30), had fulminant hepatic failure within 8 weeks of onset (n = 15), or had missing laboratory data (n = 1), the remaining 71 patients (60 living-donor LT and 11 deceased-donor LT) were included in the final analyses (Figure 1).

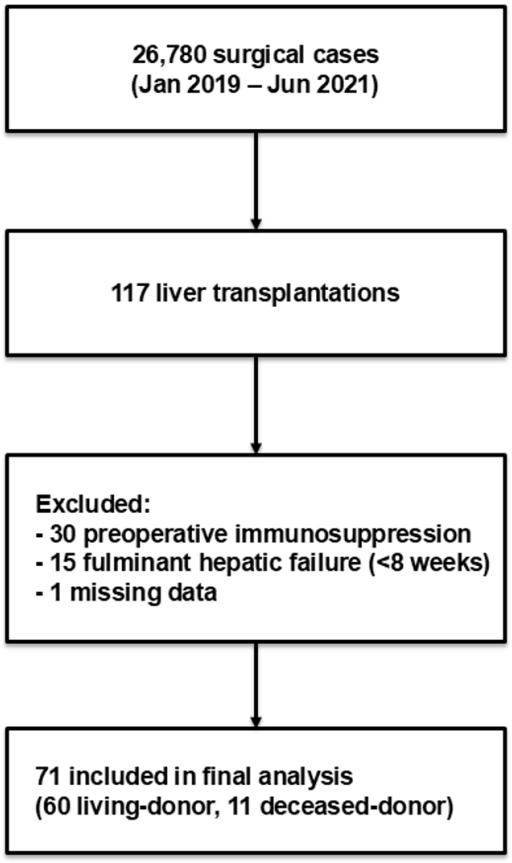

Figure 1. Flow diagram of patient enrollment.

Table 1. Patient characteristics

Factor	
Age (years)	50.5 ± 11.3
Sex (male)	39 (53.9%)
BMI (kg/m^2)	23.6 ± 4.7
MELD score	17.1 ± 8.3
CTP score	10.3 ± 2.3
Indication	
Viral hepatitis	12
Alcoholic liver disease	14
Nonalcoholic steatohepatitis	10
Cholestatic liver disease	19
Metabolic liver disease	6
Vascular disorders	6
Others	4
Graft	
Whole liver/right lobe/left lobe/posterior segment	11/30/24/6

Values are presented as the mean (± standard deviation) or median (interquartile) for continuous variables and n (%) for categorical variables. BMI, body mass index; MELD score, model for End-Stage Liver Disease score; CTP score, Child–Turcotte–Pugh score.

Table 1 presents a summary of patient baseline characteristics. The mean patient age was 50.5 ± 11.3 years, and 54% of patients were men. The mean Model for End-Stage Liver Disease score was 17.1 ± 8.3, and the mean Child–Turcotte–Pugh score was 10.3 ± 2.3. Etiologies of ESLD included viral hepatitis (n = 12), alcoholic liver disease (n = 14), nonalcoholic steatohepatitis (n = 10), cholestatic liver disease (n = 19), metabolic liver disease (n = 6), vascular disorders (n = 6), and other causes (n = 4). Graft types included whole liver (n = 11), right lobe (n = 30), left lobe (n = 24), and right posterior segment (n = 6).

3.2. Intraoperative and postoperative course

The intraoperative and postoperative variables are

summarized in Table 2. All the patients underwent general anesthesia with endotracheal intubation and mechanical ventilation. Inhalation-based anesthetic techniques were used in 69 patients (97.1%). The mean anesthesia time was 749 ± 79 minutes, and the mean surgical duration was 635 ± 78 minutes. The time from BS to AP was 209 ± 59 minutes and from AP to AC was 344 ± 70 minutes.

Median intraoperative blood loss was 5,135 mL (IQR 3100–9830). Median transfusion volumes were 1,680 mL red blood cells (IQR: 1,120–3,640), 2,640 mL fresh frozen plasma (IQR: 1,440–4,080), and 400 mL platelet concentrate (IQR: 0–600). Intraoperative vasoactive agents (dopamine, dobutamine, norepinephrine, or phenylephrine) were administered as required. Methylprednisolone (20 mg/kg) was administered preoperatively and during reperfusion in all patients. Continuous intraoperative infusions of nafamostat mesilate (1 mg/kg/hour) and alprostadil alfadex (0.01 μg/kg/minutes) were also used routinely.

All patients were admitted to the intensive care unit after surgery with planned mechanical ventilation. The median duration of postoperative mechanical ventilation was 1 day (IQR: 1–1). Three patients required reoperation within 3 days (two for postoperative hemorrhage and one for portal vein thrombosis). These patients were included in the overall leukocyte dynamics analysis. All patients received tacrolimus-based immunosuppression therapy postoperatively. No infectious complications occurred during the 7-day observation period. Six patients (8.5%) experienced biopsy-proven acute rejection after POD 6.

Table 2. Intraoperative and postoperative courses

Factors	
Intraoperative factors	
Anesthesia method (inhalation anesthesia)	69 (97.1%)
Anesthesia time (min)	749 ± 79
Surgical time (min)	635 ± 78
Blood loss (mL)	5,135 (3,100–9,830)
Volume of infusion (mL)	6,100 (4,850–7,802)
Blood transfusion (mL)	4,560 (2,400–8,680)
RBC transfusion (mL)	1,680 (1,120–3,640)
FFP transfusion (mL)	2,640 (1,440–4,080)
PC transfusion (mL)	400 (0–600)
GRWR (%)	0.81 (0.68–1.12)
CIT (min)	99 (77–137)
WIT (min)	35 (31–42)
From BS to AP (min)	209 ± 59
From AP to AC (min)	344 ± 70
Intraoperative steroid use	71 (100%)
Postoperative factors	
Postoperative immunosuppressant use	71 (100%)
Ventilator duration (days)	1 (1–1)
Reoperation within 3 days	3 (4.2%)
Infectious complications within 7 days	0 (0%)
Biopsy-proven acute rejection within 7 days	6 (8.5%)

Values are presented as the mean (± standard deviation) or median (interquartile range) for continuous variables and *n* (%) for categorical variables. RBC, red blood cell; FFP, fresh frozen plasma; PC, platelet concentrate; GRWR, graft-to-recipient weight ratio; CIT, cold ischemic time; WIT, warm ischemic time; BS, beginning of surgery; AP, anhepatic phase; AC, abdominal closure.

3.3. Perioperative leukocyte dynamics

Perioperative changes in leukocyte subsets are shown in Figure 2. Total leukocyte counts remained stable between the BS and AP (median: 3.3 → 3.8 × 10^3/μL; not significant), followed by a significant increase after reperfusion, peaking at AC (7.6 × 10^3/μL). The overall difference across the three intraoperative time points was significant (Friedman test, $p < 0.01$), with post hoc analysis confirming significant increases at AC compared with both BS and AP (both $p < 0.01$). Neutrophil counts demonstrated a similar trend: unchanged between BS and AP (2.4 → 3.1 × 10^3/μL; not significant) and then rising markedly after reperfusion to 6.8 × 10^3/μL at AC (AC *vs*. BS and AP, both $p < 0.01$).

In contrast, lymphocyte counts began to decline during AP ($p = 0.035$) and fell further to 3.2 × 10^2/μL at AC ($p = 0.035$), consistent with perioperative lymphopenia. Consequently, NLR increased significantly from BS (median 5.9) to AP (8.5, $p = 0.045$+) and further to AC (19.6, $p < 0.01$), reflecting the divergence between neutrophil mobilization and lymphocyte depletion.

These findings indicate that the perioperative leukocyte increase was predominantly neutrophil-driven, whereas lymphocytes decreased in parallel.

3.4. Postoperative course: PODs 1–3

As shown in Figure S1 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=305*), leukocyte and neutrophil counts increased further on POD 1 compared with those at AC (median leukocyte = 8.1 × 10^3/μL; neutrophils = 7.4 × 10^3/μL). On PODs 2 and 3, both parameters remained elevated at levels similar to those on POD 1 and did not return to baseline, indicating a sustained neutrophil-dominant leukocytosis during the early postoperative period. Contrastingly, lymphocyte counts remained suppressed throughout PODs 1–3. Consequently, NLR also remained elevated across PODs 1–3, reflecting the persistent predominance of neutrophils in the early postoperative phase.

3.5. Correlation with graft size

When the patients were stratified by GRWR, significant associations were observed only in the GRWR < 1.0 group ($n = 49$). In these recipients, both leukocyte and neutrophil counts on POD 1 correlated positively with graft size ($r_S = 0.413$, $p = 0.003$, and $r_S = 0.424$, $p = 0.002$, respectively). Similarly, increases from BS to POD 1 also showed significant correlations ($r_S = 0.444$, $p = 0.001$ for leukocytes; $r_S = 0.442$, $p = 0.001$ for neutrophils). In contrast, among the recipients with GRWR ≥ 1.0 (n =

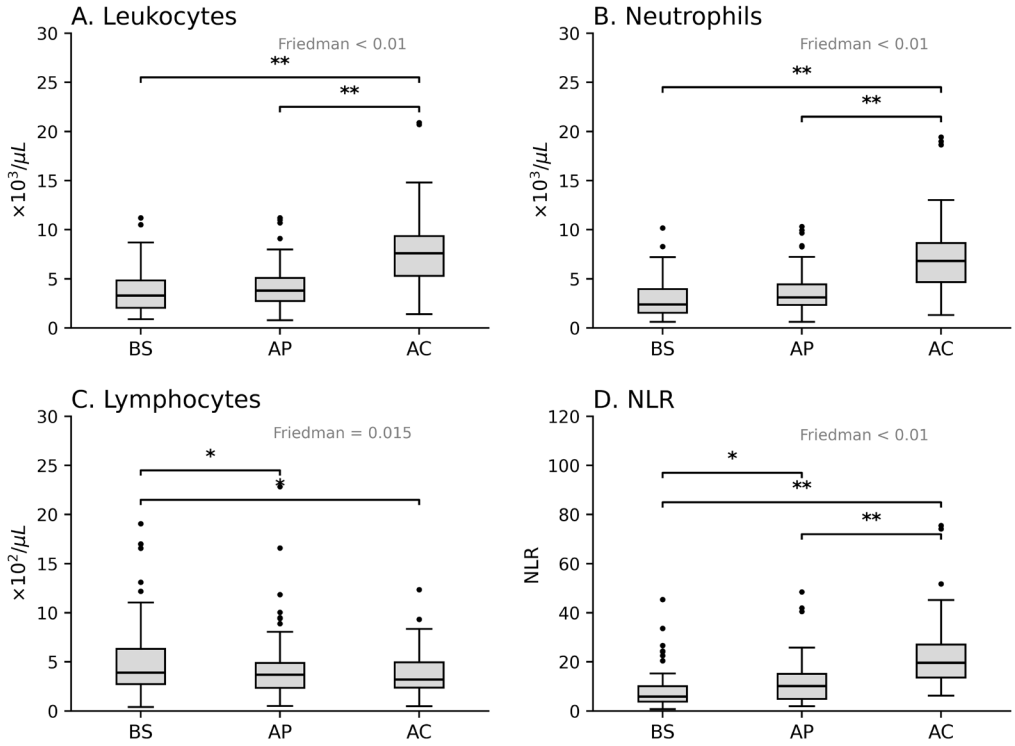

Figure 2. Temporal changes in leukocyte-related parameters. (A), Leukocyte count; **(B)**, neutrophil count; **(C)**, lymphocyte count; and **(D)**, NLR. The Friedman test was used to detect differences across the three intraoperative time points (BS, AP, and AC). Bonferroni-adjusted Wilcoxon signed-rank tests were used for post hoc analysis. Box plots show the median (horizontal line), interquartile range (box), 10–90 percentiles (whiskers), and outliers (dots). *$p < 0.05$, **$p < 0.01$. BS, beginning of surgery; AP, anhepatic phase; AC, abdominal closure; NLR, neutrophil-to-lymphocyte ratio.

21), no significant correlations were observed between graft size and POD 1 leukocyte or neutrophil counts, nor with their perioperative changes.

3.6. Post hoc power

The Friedman's test for neutrophil counts across intraoperative phases (BS–AP–AC) yielded $\chi^2 = 63.7$ (df = 2, $n = 71$); the post hoc analysis showed an effect size w = 0.45 and statistical power of 0.93, supporting the robustness of the primary findings.

4. Discussion

In this retrospective cohort study, we evaluated the perioperative dynamics of leukocyte subsets in patients with ESLD undergoing LT. We found that leukocyte and neutrophil counts remained unchanged from the BS to AP and then increased significantly after graft reperfusion, with maximal values observed at AC. This increase occurred in parallel with a decline in lymphocyte counts. In the recipients with GRWR <1.0, the magnitude of neutrophil increase on POD 1 correlated positively with graft size. These findings suggest graft-dependent modulation of early postoperative neutrophil mobilization.

In most surgical settings, neutrophil counts increase markedly within the first few hours after the start of surgery, usually within approximately 3 hours, driven by cortisol and granulocyte colony-stimulating factor (G-CSF) release (*12–15*). In contrast, neutrophil counts in the present study did not increase during the AP (>3 h after baseline) despite ongoing surgical stress. This pattern may reflect a relatively attenuated mobilization response in ESLD, possibly related to cirrhosis-associated immune alterations.

After reperfusion, leukocyte counts increased sharply, with a marked increase in neutrophils and a decrease in lymphocytes. This pattern may reflect enhanced neutrophil mobilization into the peripheral circulation, although redistribution cannot be excluded. Blood loss differed before and after reperfusion (median 645 *vs.* 497 mL/h); however, the abrupt increase in neutrophil counts immediately after reperfusion suggests that hemodilution alone is unlikely to fully explain this change. The postoperative lymphopenia is consistent with previous reports linking it to surgical stress and immune redistribution (*16–21*). The divergence between neutrophil mobilization and lymphocyte depletion may indicate that these leukocyte subsets are influenced by partially distinct regulatory pathways during LT.

The mobilization of neutrophils in response to surgical injury has been well described (*22–24*), and our findings suggest that this response may be relatively blunted in ESLD and increases substantially after reperfusion. From a mechanistic perspective, neutrophil

mobilization during liver transplantation is likely governed by a combination of cytokine-mediated bone marrow release and redistribution within the peripheral circulation. Surgical stress and reperfusion are known to induce rapid increases in circulating G-CSF and interleukin-8 (IL-8), which promote neutrophil release from the bone marrow and enhance chemotaxis (*6,25,26*). In addition, ischemia–reperfusion injury is associated with endothelial activation and increased expression of adhesion molecules, which can alter neutrophil margination and trafficking (*27*). The transplanted liver may contribute to this process as a potential source of inflammatory mediators after reperfusion (*26*), although systemic responses are also likely involved. In recipients with smaller grafts, altered cytokine production or clearance may partly contribute to the observed graft-size–dependent differences in neutrophil dynamics. In the present study, cytokine levels were not measured; however, these mechanisms may partly explain the marked increase in neutrophil counts after reperfusion. Notably, among recipients with a GRWR < 1.0, the magnitude of neutrophil increase up to POD 1 correlated with graft size, whereas no such correlation was observed in those with a GRWR ≥ 1.0. This finding may reflect differences in inflammatory responses in relatively small grafts, potentially related to susceptibility to ischemia–reperfusion injury. However, these interpretations remain speculative and warrant further investigation.

As our center uses SLV-based criteria (SLV ≥ 35%) for graft selection, the generalizability of graft-size–related findings may be questioned. To ensure comparability, all analyses in this study used GRWR based on actual graft weight.

From a perioperative management perspective, these results may be clinically relevant. Volatile anesthetics and perioperative steroids are known to modulate neutrophil and lymphocyte function (*8,13,20,28,29*); however, the absence of intraoperative neutrophil increase until reperfusion suggests that graft-related factors may contribute to perioperative neutrophil dynamics beyond pharmacologic influences. Nafamostat and alprostadil, both administered routinely, may influence inflammatory responses (*30,31*), although their specific contribution in this setting remains unclear. Although NLR increased during the perioperative period, this change primarily reflected neutrophil mobilization rather than an independent immunological process and should therefore be interpreted as a supportive marker rather than a primary indicator.

On POD 1, samples were obtained more than 9 hours after reperfusion. Neutrophils are known to survive longer when recruited locally to inflammatory sites (*27,32,33*); however, their half-life in systemic circulation is estimated to be 6–9 hours (*34,35*). More recent studies have suggested that circulating neutrophils may persist longer under certain conditions (*32,36*). Based on these kinetics, the increase observed on POD 1 is more consistent with mobilization of recipient-derived cells than with donor-derived neutrophils. Perfusion flushes of the graft further reduce the likelihood of donor cell spillover. Although neutrophil accumulation within grafts has been documented (*37–39*), our findings suggest that systemic mobilization may exceed sequestration within the graft when the graft size is adequate.

This study provides clinical insight into perioperative neutrophil dynamics during LT, an area that has not been extensively characterized. In Japan, where living-donor transplantation predominates, graft size varies widely, offering an opportunity to examine the immunologic consequences of limited graft mass. Such insights may be less accessible in regions dominated by deceased-donor transplantation and may therefore offer complementary perspectives on perioperative innate immune dynamics.

The absence of neutrophil mobilization during AP, followed by a marked increase after reperfusion, suggests that graft-related factors after reperfusion may contribute to systemic neutrophil mobilization. Although we did not measure mediators such as G-CSF or IL-8, these mediators may contribute to the observed changes, and future studies incorporating cytokine profiling are warranted. Importantly, all rejection episodes occurred after POD 6, outside the perioperative observation window, suggesting that leukocyte dynamics captured here primarily reflect early innate immune responses rather than alloimmune rejection.

4.1. Limitations

This was a single-center retrospective study and is therefore subject to residual confounding. Perioperative interventions, including corticosteroids, immunosuppressive therapy, blood transfusion, vasoactive agents, and anesthetic management, may have influenced leukocyte dynamics; however, these factors were not formally adjusted for in the present analysis. The relatively small sample size, particularly in the GRWR ≥1.0 group, may have limited statistical power and increased the possibility of false-negative findings. The distribution of GRWR values is shown in Figure S2 (*https://www.biosciencetrends.com/action/getSupplementalData.php?ID=305*). In addition, differences in group sizes may have resulted in differences in baseline characteristics between groups, which could influence the interpretation of the observed associations. Multivariable analysis was not performed due to the limited sample size, and residual confounding cannot be excluded.

Leukocyte dynamics were analyzed only through POD 3 to focus on the perioperative phase, whereas clinical outcomes were monitored through POD 7. The absence of early infections and the low number of events limited the ability to assess associations between neutrophil dynamics and clinical outcomes. Therefore, the prognostic significance of these findings remains uncertain.

Cytokine measurements were not available, which may limit mechanistic interpretation of the observed neutrophil dynamics. Finally, although subgroup analyses based on GRWR were performed, the relatively small number of patients in each group may limit the robustness of these findings.

4.2. Clinical implications

Perioperative neutrophil dynamics, particularly in recipients with small grafts, may provide additional context for interpreting early postoperative immune changes. Routine leukocyte monitoring may complement conventional parameters in anesthetic practice when interpreted alongside clinical findings.

Beyond descriptive interpretation, these findings may inform future approaches to risk assessment. Integration of perioperative neutrophil dynamics with inflammatory mediators, such as cytokine profiles, may facilitate early identification of immune-related complications following LT. Although such applications remain speculative, they warrant further investigation in prospective studies to evaluate their clinical utility.

4.3. Conclusion

In patients with ESLD undergoing LT, neutrophil counts did not increase until after graft reperfusion, at which point they increased markedly. In recipients with small grafts (GRWR < 1.0), the magnitude of this increase was associated with graft size, suggesting graft-size-dependent differences in early postoperative neutrophil dynamics.

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Perspective

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Imported Ebola as a stress test of hospital resilience in an era of global connectivity

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SUMMARY: In May 2026, an outbreak of Ebola virus disease caused by Bundibugyo ebolavirus emerged in the Democratic Republic of the Congo and spread to Uganda, prompting a WHO Public Health Emergency of International Concern. With no approved vaccine or specific antiviral treatment, Bundibugyo virus poses an acute importation risk in an era of dense global air travel. This perspective frames imported Ebola as a hospital resilience stress test and proposes the Hospital Resilience 4P Framework, organizing preparedness around Prediction, Preparedness, Protection, and Partnership. We critically analyze the drivers of nosocomial amplification, including diagnostic delay, healthcare worker undertraining, and insufficient infection prevention and control. For China, whose aviation hubs in Guangzhou and Shenzhen sustain dense air links with Africa under the Belt and Road Initiative, this risk is particularly urgent. We further examine the vulnerabilities of East Asian healthcare systems - aging workforces, emergency department overcrowding, and skewed PPE stockpiles - and evaluate emerging technologies (deep-ultraviolet laser disinfection, AI-driven surveillance, differential serology) with explicit evidence grading. A full-chain, multi-layered system from the aircraft cabin to isolation ward, guided by the 4P Framework, can ensure imported cases remain contained clinical events rather than triggers of hospital-based outbreaks.

Keywords: Ebola virus disease, importation risk, infection prevention and control, multi-sectoral coordination, future technologies

1. Introduction

1.1. A vaccine-free outbreak with broader implications

In May 2026, an outbreak of Ebola virus disease (EVD) caused by the Bundibugyo ebolavirus emerged in the Democratic Republic of the Congo (DRC) and rapidly spread to Uganda, leading the World Health Organization (WHO) to declare a Public Health Emergency of International Concern (PHEIC) (*1*). This represents the 17th Ebola outbreak in the DRC, and it is distinguished by a critical gap: unlike Zaire ebolavirus, Bundibugyo virus has no approved vaccine or specific antiviral treatment, and the case fatality rates in the previous two Bundibugyo outbreaks ranged from approximately 30 to 50% (*2,3*). The 2026 event was characterized by nosocomial amplification and a four-week delay between the onset of symptoms in the index case and laboratory confirmation, highlighting persistent flaws in infection prevention and control (IPC) even in endemic settings. Although the 2026 Bundibugyo outbreak provides the immediate context for this analysis, the framework and preparedness principles discussed here are applicable to other high-consequence pathogens, including Marburg virus, Lassa fever virus, and future emerging infections with pandemic potential.

1.2. Hospital-centered defense in an era of global mobility

Global air connectivity has shifted the primary barrier against imported filovirus disease from border screening to the hospital. The incubation period of up to 21 days permits an asymptomatic traveler to cross international borders, present to an emergency department far from the point of entry, and initiate nosocomial transmission before the infection is recognized (*4,5*). In the absence of approved vaccines or specific antiviral treatments for Bundibugyo virus, and with limited cross-protection from existing vaccines based only on non-human primate data, containment depends entirely on non-pharmaceutical interventions (*6,7*). For China, the

high density of direct flights from Africa to aviation hubs such as Guangzhou and Shenzhen, combined with extensive population mobility under the Belt and Road Initiative, makes importation a predictable long-term risk and reinforces the urgency of hospital-based preparedness (*8,9*).

1.3. A structured framework for hospital resilience

To guide this hospital-centered preparedness, we propose the Hospital Resilience 4P Framework, which organizes the required measures into four interdependent pillars: Prediction (early warning through tiered screening and a graded response activation), Preparedness (institutionalized, simulation-based healthcare worker training), Protection (comprehensive IPC, including environmental decontamination and personal protective equipment (PPE) systems), and Partnership (multisectoral integration linking port health, public health agencies, hospitals, and communities through a shared digital platform) (Figure 1). This article synthesizes the importation risk of EVD from the perspective of hospital system resilience. We critically examine the epidemiological drivers of healthcare-based amplification, detail each pillar of the 4P Framework with supporting evidence, highlight the neglected preparedness challenges facing East Asian healthcare systems, and evaluate emerging technologies with explicit evidence grading. Establishing an integrated, multi-layered system that extends from the aircraft cabin to the isolation ward is essential to ensuring that an imported case remains a contained clinical event rather than triggering a hospital-based outbreak.

2. Importation risk and healthcare facilities as amplifiers

2.1. Nosocomial transmission as a persistent pattern

Healthcare facilities are repeatedly identified as principal sites of Ebola amplification. Among 31 documented EVD outbreaks with human-to-human spread, 80.6% involved nosocomial transmission (*10*). During the 2018-2020 DRC epidemic, healthcare-associated infections accounted for 579 of 3,481 confirmed cases (16.6%), and the case fatality rate among infected healthcare workers reached 41.3% (*11*). The 2026 Bundibugyo virus outbreak reproduced this pattern and further demonstrated how local conditions facilitate international spread. A four-week detection gap elapsed between symptom onset in the presumed index case and

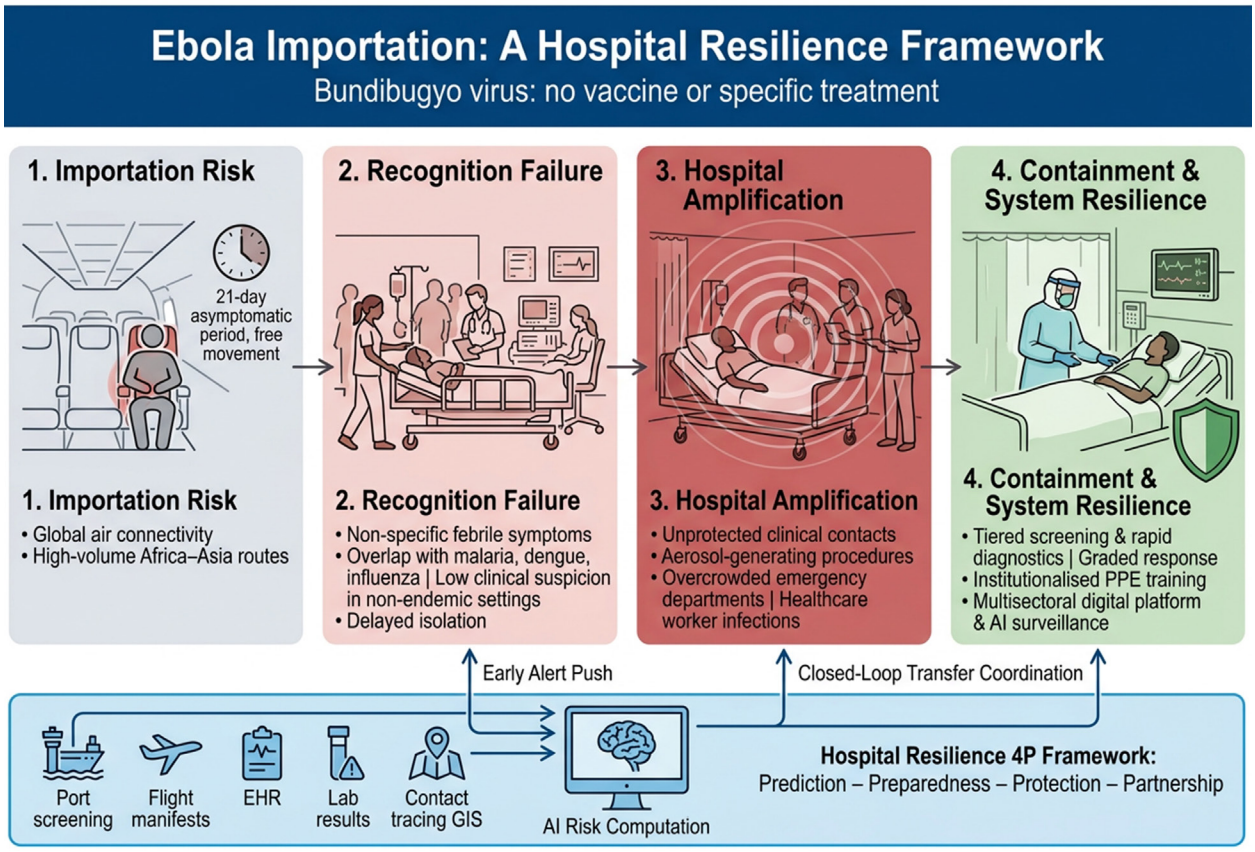

Figure 1. Mechanistic chain of hospital resilience against imported Ebola virus disease. This schematic shows the full-chain mechanism from importation to containment and the pillars of hospital resilience. An infected traveler enters via an international flight, undergoes an asymptomatic incubation period, and presents to the emergency department, where overlapping symptoms cause diagnostic delay. Placement in a general ward before diagnosis triggers hospital amplification, which is ultimately contained through a graded response, isolation, and a digital platform providing AI-driven early alerts and closed-loop transfer coordination.

laboratory confirmation, four health workers died within four days at Mongbwalu General Referral Hospital, and cross-border exportation was confirmed within days of the outbreak declaration, with two imported cases identified in Kampala, the second having no apparent epidemiological link to the first (*1*).

2.2. Drivers of hospital amplification in non-endemic settings

In non-endemic settings, the risk of hospital amplification is driven by several interlocking factors. First, the initial clinical presentation of EVD, which includes a fever, headaches, myalgia, and pharyngitis, is nonspecific and overlaps extensively with common febrile illnesses such as malaria, dengue, typhoid, and influenza (*4*). This syndromic overlap routinely delays diagnosis, and during this period patients are managed with standard rather than enhanced barrier precautions. The 2026 outbreak demonstrated this effect even in an endemic setting with prior outbreak experience, where a four-week gap occurred between symptom onset and laboratory confirmation. Second, emergency department overcrowding, a near-universal condition in urban hospitals globally, increases the probability of unrecognized exposure during the early symptomatic phase when viral loads may be rising. Third, high-risk bedside procedures, including venous catheterization and endotracheal intubation, are often performed before a definitive diagnosis is established, generating aerosols and posing significant occupational exposure risks (*12*). Fourth, Ebola virus can persist in immune-privileged sites, including the testes, ocular fluid, and central nervous system, and cause recrudescence months or years after recovery. The genomic link between the 2021 Guinea outbreak and the 2013-2016 West African epidemic strongly supports this mechanism of late reactivation as a source of new transmission chains (*10*).

2.3. Cross-border spread and the first point of healthcare contact

The 2026 outbreak also illustrates how local epidemiological conditions enable international dissemination. Ituri Province functions as a commercial and migratory hub that direct borders South Sudan and Uganda, with the Bunia Health Zone located less than 500 km from the Ugandan border. Cross-border exportation was confirmed within days of the declared outbreak, and the second imported case in Kampala had no apparent epidemiological link to the first, indicating that multiple exportation events can occur before an outbreak is officially recognized. This sequence, in which regional spread precedes official notification, defines the preparedness scenario that non-endemic countries must anticipate. For receiving countries, the first point of healthcare contact determines whether an imported case is contained or amplified into a nosocomial cluster.

3. The Hospital Resilience 4P framework

The Hospital Resilience 4P Framework organizes hospital preparedness around four interdependent pillars: Prediction, Preparedness, Protection, and Partnership. Unlike conventional preparedness models that focus predominantly on infection prevention and control protocols, this framework integrates anticipatory surveillance, workforce capacity building, environmental protection, and cross-sector governance into a unified resilience architecture. Each pillar was developed through structured engagement with stakeholders across clinical, administrative, and public health domains and was designed to address specific vulnerabilities identified through analysis of prior filovirus outbreak responses. Although the four pillars are presented sequentially here, their application in practice is neither linear nor strictly chronological. The components operate concurrently, and the relative emphasis on each pillar shifts in response to the evolving epidemiological context.

3.1. The recognition deficit in frontline settings

A recurring failure across filovirus outbreaks is the delayed recognition of cases at the point of first clinical contact. In settings where viral hemorrhagic fevers are not endemic, the non-specific early symptoms are frequently attributed to more common febrile illnesses, and transmission proceeds before any enhanced precautions are implemented. The 2026 Bundibugyo virus outbreak illustrated this pattern, with a four-week interval between symptom onset in the index case and laboratory confirmation occurring in a country with prior Ebola experience.

This diagnostic delay is compounded by persistent gaps in healthcare worker preparedness. A 2023 nationwide survey in Uganda found that fewer than 35% of emergency healthcare workers had received Ebola-related training in the preceding year (*13*). During the 2018-2020 DRC epidemic, only 16% of healthcare workers had completed formal Ebola training, and their awareness of key transmission pathways, including risks associated with traditional burial practices, ranged from 28 to 34% (*14,15*). These figures point to a structural deficit in training that has permitted nosocomial transmission to recur across multiple outbreak settings. The WHO's assessment of the 2026 event further underscored this concern, noting critical breaches in infection prevention and control protocols.

3.2. Pillar 1: Prediction through tiered screening and a graded response

Shortening the interval between presentation and isolation requires a systematic approach to case

identification. The Prediction pillar establishes a three-tier screening pathway for emergency departments and fever clinics: first, ascertainment of epidemiological risk factors, defined as travel to or residence in an affected area within the preceding 21 days; second, use of a clinical risk prediction score; and third, deployment of rapid diagnostic testing for individuals meeting the clinical or epidemiological case definition. The evidence supporting each of these tiers has grown substantially. A pediatric Ebola risk score validated in West Africa resulted in an area under the curve (AUC) of 0.87, significantly exceeding the performance of the standard WHO case definition, which has an AUC of 0.56 (*16*). When embedded within a screening algorithm, such scores, combined with rapid diagnostic tests, have been shown to reduce unnecessary isolation while accelerating the identification of true cases in a cost-effective manner (*17*). Although rapid diagnostic tests for EVD have a pooled sensitivity of 86.1% and specificity of 97% (*18*), their value lies in enabling immediate risk stratification: patients testing positive are transferred directly to negative-pressure isolation, while those testing negative but presenting with a high-risk epidemiological or clinical profile enter a structured observation pathway. This approach limits the duration of potential exposure in general clinical areas.

Screening tools alone are insufficient in the absence of clear activation thresholds. A three-level response structure, aligned with the Alert, Suspect, and Confirmed categories recommended by the WHO, allows for graduated escalation. At the Alert Level, identification of an asymptomatic traveler from an affected area prompts health monitoring and verification of PPE stocks, without requiring immediate isolation. At the Suspect Level, a patient meeting the clinical case definition or whose rapid test result is positive triggers activation of the hospital incident command structure, preparation of the negative-pressure unit, enhancement of IPC measures across the facility, and initiation of contact tracing. At the Confirmed Level, laboratory confirmation of infection escalates the response to full emergency status: isolation zones are instituted, non-essential visits are suspended, all staff in affected areas transition to high-risk PPE, and the broader multisectoral coordination mechanism is activated. The value of this graduated structure lies in its proportionality; it avoids both the costs of over-reaction to low-risk events and the delays associated with indecision during genuine threats.

3.3. Pillar 2: Protection through environmental decontamination and healthcare worker safety

Environmental decontamination is a fundamental component of outbreak response, but the predominant modality - chlorine-based disinfection - has well-documented limitations. Organic matter rapidly inactivates chlorine, the compounds are corrosive to medical equipment, and prolonged exposure poses respiratory risks to staff, particularly in tropical environments where ventilation may be limited. Standard chlorine-based disinfectants have demonstrated virucidal activity against Ebola virus in complex matrices such as tripartite soil and whole blood (*19*), confirming their utility when correctly applied. However, the observation that Ebola virus can remain infectious on dry surfaces for up to 28 days (*20*) underscores the importance of thorough terminal decontamination and prompts the exploration of complementary methods of physical inactivation.

The protection of healthcare workers requires attention to factors that extend beyond the content of written protocols. Despite the existence of a well-established tiered PPE framework, breaches in PPE use are consistently implicated in healthcare worker infections. The deaths of health workers early in the 2026 Bundibugyo outbreak illustrate that protocol documentation alone does not ensure safe practice (*20*). Investigations of PPE failures consistently point to human-factor issues as the predominant cause: heat stress and fatigue degrade concentration during doffing, competency-based training is often inadequate, and supervision during high-risk procedures is frequently insufficient. Evidence from a study involving a simulated Ebola treatment unit demonstrated that performing clinical tasks in full PPE at an ambient temperature of 35°C significantly prolonged task completion times and increased physiological heat stress, with a quarter of participants reaching predefined health trigger thresholds (*21*). These data support the implementation of strict limits on shift duration, the adoption of active cooling strategies, and the design of training programs that replicate the thermal and psychological conditions of actual clinical work.

3.4. Pillar 3: Preparedness through institutionalized training

Transitioning from episodic training to sustained institutional competence requires a systems-level approach. Simulation-based training improves both safety awareness and willingness to work, but the relationship between training and performance is not linear. Excessive repetition can induce training fatigue and erode psychological readiness (*21*), suggesting that the frequency and intensity of training must be carefully calibrated. The East Africa Infection Prevention and Control Learning Network offers an instructive model. This collaborative initiative, spanning 20 tertiary hospitals across four countries, employed a combination of virtual and in-person training, structured mentorship, and collaborative quality-improvement projects to raise average hospital IPC compliance from 65 to 92% (*22*). Those results indicate that durable competence is built through sustained, networked capacity-building rather than through isolated instructional events. Extending this

principle, the recognition and initial management of viral hemorrhagic fevers should be integrated into mandatory annual continuing education for all emergency, infectious disease, and critical care physicians, with competence verified through simulation-based assessment rather than passive knowledge tests.

3.5. Pillar 4: Partnership through multisectoral integration

The fourth pillar addresses the coordination deficit that has characterized many outbreak responses. Effective containment requires that port health authorities, public health agencies, and designated treatment hospitals operate as components of a single functional system rather than as independent entities. The operational mechanism for this integration is a shared digital platform that consolidates real-time data from customs declarations, flight manifests, electronic health records, laboratory information systems, and geospatial contact tracing. The 2026 outbreak response provided a clear demonstration of this need: the WHO's operational framework called for strengthened Point of Entry screening and cross-border coordination, with rapid response teams positioned at formal and informal border crossings, major transit routes, and pilgrimage corridors. The concurrent armed conflict, population displacement, and insecurity in Ituri Province further underscored the necessity of coordination structures that extend beyond governmental agencies.

However, technological infrastructure cannot substitute for social infrastructure. A cross-national analysis of the 2014-2016 West African epidemic demonstrated that regions characterized by higher levels of voluntary association participation and stronger social trust networks experienced significantly shorter outbreak durations (*23*). During the 2018-2020 DRC epidemic, the circulation of conspiracy theories, mistrust of public authorities, and perceptions that the Ebola response constituted a commercial enterprise drove patients away from formal healthcare facilities towards private or informal care, with measurable consequences for transmission dynamics and diagnostic delays (*24*). Effective multisectoral coordination therefore depends on the active involvement of community leaders and trusted local organizations, supported by transparent risk communication strategies.

For China, the Partnership pillar can draw on existing infrastructure established under the Belt and Road Initiative. Health-related cooperation within this framework already encompasses medical assistance, joint laboratory construction, and infectious disease surveillance activities in multiple African countries. These established channels could be adapted to support real-time sharing of outbreak signals between African health ministries and Chinese port health authorities, with the potential to reduce the interval between detection and cross-border notification. In parallel, large Chinese enterprises operating in Africa, and particularly in the construction, mining, and telecommunications sectors, manage substantial workforces that regularly rotate through aviation hubs in Guangzhou and Shenzhen. Integrating the health management systems of these enterprises with national public health surveillance architecture would address a critical information gap in the current preparedness framework.

Operationally, the Partnership pillar includes the closed-loop transfer of suspected cases *via* dedicated negative-pressure ambulances along predetermined routes to pre-alerted receiving hospitals, with escort personnel in full PPE. This is complemented by internationally recommended restrictions on international travel for confirmed cases and contacts, with exceptions only for medical evacuation, and by exit screening at international airports, seaports, and major land crossings for all individuals presenting with unexplained febrile illness consistent with potential Bundibugyo virus disease. The entire multisectoral system requires annual stress-testing through full-scale simulated exercises that cover the complete operational chain, from initial port detection through to terminal disinfection of the isolation facility. Structured after-action reviews following each exercise serve as the mechanism for turning identified gaps into systemic improvements (*22*).

4. Preparedness challenges in East Asian healthcare systems

Current EVD preparedness discourse has devoted limited attention to the specific vulnerabilities of East Asian healthcare systems. This gap is both analytically unwarranted and operationally consequential, given the region's deep economic ties with Africa, extreme airport density, and distinctive demographic profile. The rapid cross-border spread observed during the 2026 outbreak demonstrates how quickly an outbreak can generate multiple exportation events before containment measures are fully activated.

4.1. China's increased exposure through aviation and economic corridors

Within East Asia, China faces a uniquely increased exposure profile. The country is Africa's largest trading partner, and population mobility between the two regions has intensified substantially over the past two decades. Guangzhou Baiyun International Airport and Shenzhen Bao'an International Airport serve as the primary aviation gateways, operating direct flights to multiple African cities including Addis Ababa, Nairobi, Lagos, and Johannesburg. This high-volume, multi-directional mobility means that an individual infected during an Ebola outbreak in Central or West Africa could arrive in southern China within 24 to 36 hours of exposure. Unlike historical importation events in North America or Europe, which were sporadic and originated from a

limited set of destinations, China's connectivity to Africa is both geographically broader and quantitatively more extensive, making repeated importation statistically probable over the long term.

4.2. Healthcare system vulnerabilities at the receiving end

Once an imported case arrives, the healthcare environment in Chinese megacities introduces additional challenges. Emergency departments in Guangzhou and Shenzhen, like those in other major East Asian cities, routinely operate at over 100% bed occupancy, leaving minimal surge capacity for the isolation and management of a high-consequence pathogen. The clinical workload, combined with limited familiarity with viral hemorrhagic fevers, which are not systematically covered in routine medical education or continuing professional development in China, creates a substantial recognition gap. Moreover, the healthcare-seeking behavior of returning Chinese workers and African residents in cities such as Guangzhou may differ from that of the general population. Studies on African migrants in Guangzhou have documented low healthcare utilization rates and significant barriers including language difficulties, fear of deportation, and cultural differences in health beliefs, all of which may contribute to delayed care-seeking for febrile illnesses (*25,26*). Hospital-based surveillance data also indicate that this population carries a high burden of infectious diseases and yet testing uptake remains suboptimal, creating conditions for imported pathogens to remain undetected (*27*).

Beyond China, several structural factors affect East Asian healthcare systems collectively. The healthcare workforce in Japan, South Korea, and China is aging rapidly; older healthcare workers face disproportionately higher risks of severe outcomes from EVD, while a shrinking workforce reduces surge capacity. PPE stockpiling, although substantially improved after the COVID-19 pandemic, remains oriented toward dealing with respiratory pathogens rather than the full-barrier ensembles required for filovirus care. Moreover, the density of intra-regional travel means that a single imported case can rapidly generate multi-country contact tracing requirements that challenge the interoperability of separate national surveillance systems.

4.3. Training and regional strategies as priority investments

For China, the institutionalization of healthcare worker training in EVD recognition is a more urgent priority than further material stockpiling. We recommend that EVD and other high-consequence infectious diseases be incorporated into the mandatory annual continuing medical education credit system for all emergency, fever clinic, and intensive care unit physicians and that regional simulation centers be established to provide standardized, high-fidelity training. Region-specific strategies, including pre-positioned isolation facilities at key hub airports, joint cross-border simulated exercises, and harmonized digital contact-tracing protocols, would substantially strengthen the regional preparedness architecture.

5. Future technologies: Promise, evidence gaps, and implementation realities

Emerging technologies can strengthen the preparedness chain, but rigorous evidence grading is essential to preventing overstatement.

5.1. Deep-ultraviolet laser air disinfection

A novel 266-nm deep-ultraviolet laser technology offers a potential shift from chemical to physical disinfection. Unlike chlorine-based agents with their documented toxicity and corrosion risks, this system operates through a purely physical process, achieving high single-pass inactivation efficiencies against surrogate viruses while presenting zero airflow resistance—a critical advantage over HEPA filters and conventional UV lamps that trade airflow rate for efficiency (*20*). The core module can be integrated into central ventilation systems, field hospitals, and mobile platforms. However, validation against aerosolized Bundibugyo ebolavirus under tropical conditions still needs to be done. Until such data are available, this technology is graded as conceptually and experimentally promising but not validated for an Ebola outbreak. Low-cost photodynamic approaches such as methylene blue photoinactivation, effective against coronaviruses for PPE reuse, also warrant investigation for Ebolavirus in resource-limited settings (*28*).

5.2. AI-driven risk surveillance

Deep learning models have been applied to social media sentiment analysis during Ebola outbreaks to guide risk communication (*29*), and machine learning has accelerated the screening of potential Ebola virus inhibitors (*30*). Computer vision algorithms can detect high-risk IPC events—breaches of safe distances, incorrect doffing, mask removal—and issue real-time alerts. Multi-source data fusion platforms integrating customs declarations, electronic health records, syndromic surveillance, and Internet-based health monitoring can compute spatiotemporal risk indices and trigger hospital alerts within minutes. These tools represent a shift from reactive IPC to algorithmically augmented safety, but none has been rigorously evaluated during an active, multi-country Ebola outbreak. They should be regarded as experimentally demonstrated but not outbreak-proven.

5.3. Differential serology for surveillance in a vaccine era

As ring vaccination with rVSV-ZEBOV expands, distinguishing natural infection from vaccine-induced antibody responses becomes essential. The "Ebola-Detect" assay targets conserved peptides from internal viral proteins absent from current vaccines, achieving a specificity > 94% and sensitivity > 96% (*31*). Although its immediate relevance to Bundibugyo virus is limited, this capability is critical for surveillance in co-endemic regions where ring vaccination is deployed and for avoiding misclassification of vaccine recipients. Integration into routine confirmatory algorithms is an achievable near-term priority.

5.4. Humanized PPE and ergonomic innovation

Future PPE designs incorporating active cooling, breathable membranes, augmented-reality face shields, and simplified doffing mechanisms promise to reduce heat stress, cognitive load, and error rates (*21*). Prototypes have demonstrated improved comfort and protocol adherence in simulations, but field data in high-consequence pathogen settings remain absent. These innovations are classified as the conceptual development stage and require end-user evaluation in endemic settings before operational deployment.

6. Limitations

Several limitations should be noted. First, the evidence base derives largely from previous Ebola outbreaks, predominantly Zaire ebolavirus, and Bundibugyo-specific data remain limited. Second, the 4P Framework has not been prospectively validated as a bundled intervention. Third, some emerging technologies discussed, including deep-ultraviolet laser disinfection and AI-driven surveillance, have not been tested under active outbreak conditions. Finally, this is a perspective article, and the selection and interpretation of evidence may reflect the authors' judgment. Despite these limitations, the framework offers a structured basis for preparedness planning that can be refined as new evidence emerges.

7. Conclusion

The 2026 Bundibugyo virus outbreak exposes a systemic vulnerability: global connectivity ensures that high-consequence pathogens will repeatedly test the preparedness of non-endemic countries. For China, which has direct flights from Africa to Guangzhou and Shenzhen that sustain high-volume population movement, repeated importation is a statistical certainty rather than a remote possibility. The Hospital Resilience 4P Framework - Prediction, Preparedness, Protection, and Partnership - offers a structured model for turning this exposure into operational readiness. The framework integrates tiered early warning and a graded response (Prediction), comprehensive infection prevention and human-factors - informed safety (Protection), simulation-based workforce training (Preparedness), and cross-sectoral coordination that capitalizes on existing Belt and Road health-related cooperation channels and corporate health management networks (Partnership). For Bundibugyo virus, for which no vaccine or antiviral exists, this non-pharmaceutical foundation constitutes the entire available defense, and the same logic applies to Marburg virus, Lassa fever, and future emerging pathogens for which medical countermeasures may also be unavailable. Emerging technologies can augment each pillar, but their integration must be governed by rigorous evidence. Embedding the 4P Framework into routine hospital preparedness, and particularly in cities at the terminus of high-volume Africa air corridors, would help ensure that imported cases are contained as clinical events rather than developing into outbreaks.

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From organ replacement to functional restoration: A paradigm shift in liver failure therapy

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SUMMARY: Liver transplantation has long been the definitive treatment for end-stage liver diseases, and yet its clinical use remains constrained by donor shortages, surgical risks, and the burden of lifelong immunosuppression. Emerging regenerative strategies, and particularly chemically induced liver progenitors (CLiPs), are reshaping this paradigm by enabling functional restoration rather than organ replacement. CLiP technology utilizes small-molecule-mediated partial reprogramming of mature hepatocytes into proliferative progenitor-like cells, which can be expanded and re-differentiated into functional hepatic lineages. This commentary discusses the conceptual shift from replacement to regeneration, it evaluates the clinical positioning of CLiP-based therapies, and it highlights key translational challenges. Rather than serving as a complete substitute for liver transplantation, such approaches may significantly reduce transplant demand by restoring critical hepatic function in selected patients.

Keywords: liver transplantation, chemically induced liver progenitors, regeneration

1. Introduction

Liver transplantation represents one of the most successful therapeutic interventions for end-stage liver diseases in modern medicine. Nevertheless, its clinical efficacy is inherently restricted by structural limitations, most notably the global shortage of donor organs and the risks associated with major surgery and lifelong immunosuppression. Despite advances in surgical techniques and perioperative care, a substantial proportion of patients with end-stage liver disease remain ineligible for transplantation or die while on waiting lists (*1,2*). These challenges have prompted a growing interest in alternative strategies that can restore liver function without requiring whole-organ replacement.

The liver possesses a remarkable intrinsic regenerative capacity, capable of recovering mass and function following injury (*3*). In chronic liver diseases such as cirrhosis or non-alcoholic steatohepatitis (NASH), however, this regenerative potential becomes impaired (*4*). Therapeutic approaches that can reactivate or augment endogenous repair mechanisms may therefore offer a viable alternative to transplantation. Among recent advances in regenerative medicine, chemically induced liver progenitors (CLiPs) have emerged as a promising candidate, suggesting that the future of end-stage liver disease treatment may lie not in replacing the organ, but in restoring its residual function. A historical overview of the evolving treatment strategies for liver failure is summarized in Table 1.

2. Current development of CLiP technology

The development of CLiPs stems from in-depth investigations into hepatocyte plasticity. This technology is based on the partial reprogramming of mature hepatocytes using defined small-molecule cocktails, converting them into proliferative progenitor-like cells with bipotent differentiation capacity (Figure 1) (*5,6*). Unlike induced pluripotent stem cells (iPSCs), which require complete dedifferentiation into a pluripotent state (*7*), CLiPs retain lineage restriction, thereby reducing the risk of tumorigenicity and improving differentiation fidelity (*8*). This lineage-constrained plasticity represents a key conceptual advance in regenerative biology. Although small-molecule cocktails inherently carry the potential risk of inducing genomic instability during cellular reprogramming (*9*), recent studies have yielded experimental data supporting the long-term safety of chemically induced hepatic cells. In a murine model, transplantation of chemically induced hepatocyte-like cells (ciHeps) exhibited no tumorigenic potential in either *in vitro* or *in vivo* settings, substantiated by comprehensive safety evaluations throughout the

Table 1. Historical stages and core characteristics of liver failure treatment paradigms

Stage	Timeframe	Representative Technologies/Strategies
Stage I: Symptomatic support and conservative management	1950s-1970s	Hepatoprotective drugs, nutritional support, ascites drainage
Stage II: Organ replacement and liver transplantation era	1980s-present	Orthotopic liver transplantation, living donor liver transplantation, split liver transplantation
Stage III: Cell therapy and regenerative medicine exploration	2000s-2010s	Hepatocyte transplantation, bone marrow stem cells, mesenchymal stem cells
Stage IV: Functional restoration and chemically induced reprogramming	2017-present	Chemically induced liver progenitors (CLiPs), chemically induced hepatic-like cells (ciHeps), hepatocyte-derived liver progenitor-like cells (HepLPCs)

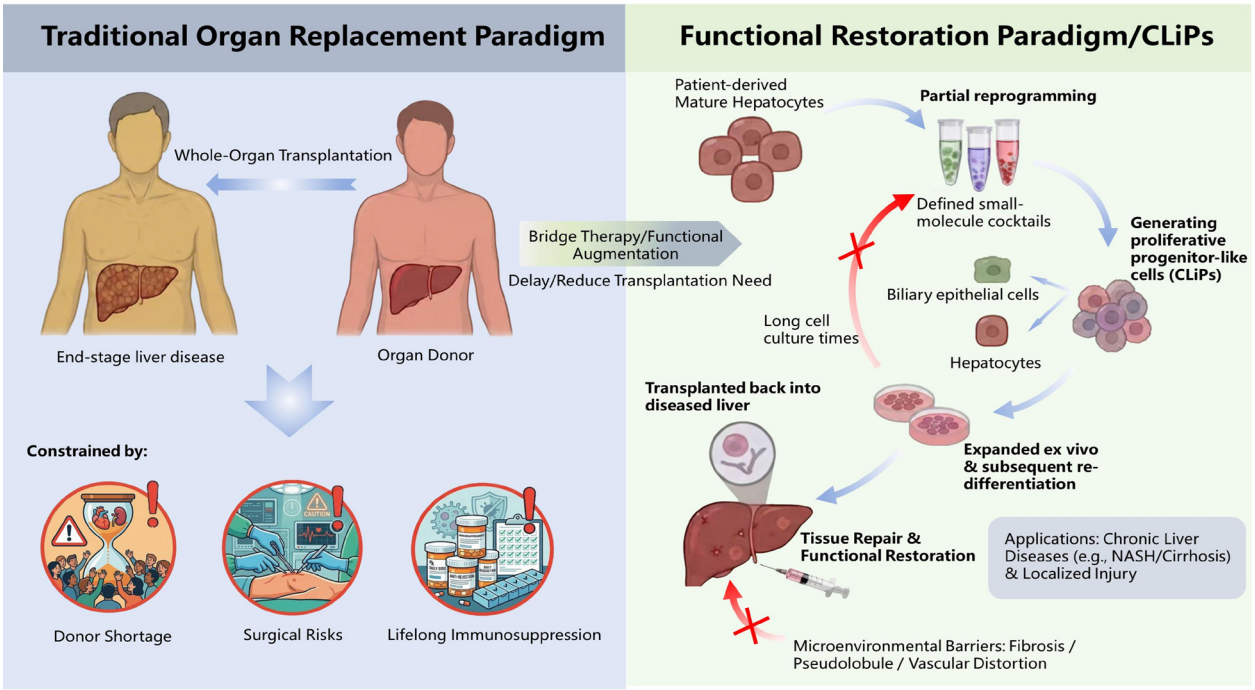

Figure 1. Schematic illustration of the paradigm shift from conventional liver transplantation to CLiP-based functional liver regeneration. *Abbreviations*: CLiPs, chemically induced liver progenitors; NASH, non-alcoholic steatohepatitis; ex vivo, outside the organism.

experimental period (*10*). Moreover, human chemically derived hepatic progenitors (hCdHs) retained a normal karyotype following at least 10 passages of self-renewal, thereby confirming their genomic stability (*11*). Although direct long-term (>1 year) tumorigenicity data specifically for CLiPs remain limited (*12*), these findings from chemically induced hepatic lineage cells offer persuasive empirical evidence regarding the safety advantages of lineage-constrained reprogramming over pluripotent approaches. However, recent evidence from a rat model of CLiP transplantation suggests that CLiPs may be susceptible to innate immune attack *in vivo*, raising additional safety considerations regarding immunogenicity (*13*).

In clinical practice, the critical threshold for meaningful hepatic recovery is highly dependent on the baseline quality of the liver parenchyma. While classic partial hepatectomy models establish that a healthy liver remnant of 20-25% is sufficient to sustain metabolic homeostasis and survival, this volumetric safety margin increases significantly in the presence of chronic liver disease (*14*). For patients with cirrhosis, surgical and radiological consensuses mandate a minimum retained liver volume of 40-50% to prevent post-procedural hepatic failure (*15*). This elevated requirement reflects a profound disconnect between macroscopic liver volume and actual functional capacity, driven by extensive fibrosis, pseudolobule formation, and microvascular distortion. Consequently, the therapeutic advantage of CLiPs lies in their capacity to deliver high-quality, functional hepatic mass. By directly replenishing the functional cellular pool rather than relying on the regeneration of compromised tissue, CLiP-based therapies have the potential to bypass the prohibitive

volumetric thresholds inherent to end-stage liver disease, achieving clinical stabilization without the need for massive structural regeneration.

Preclinical studies have demonstrated that CLiP-derived cells can engraft into injured liver tissue and contribute to functional recovery. In animal models, these cells have shown the capacity to repopulate damaged liver parenchyma and improve survival outcomes, with their functions mainly reflected in the following three aspects. First, CLiPs possess potent regenerative and repopulation capacity. A study by Katsuda *et al*. (*16*) demonstrated that rat CLiPs achieved a liver repopulation efficiency of 75-90% in cDNA-uPA/SCID mice, which was significantly higher than that of conventional hepatocyte transplantation. Second, CLiPs exhibit bipotent differentiation potential. *In vitro* 3D culture studies have confirmed that rat CLiPs can spontaneously form cystic structures containing both hepatocyte lineage and cholangiocyte lineage cells, suggesting a cellular basis for reconstructing complex hepatic tissue architecture (*17*). Third, CLiPs also possess important paracrine functions. Fukumoto *et al*. (*18*) successfully induced CLiPs from steatotic livers using a miniature pig model and further demonstrated that although the number of extracellular vesicles (EVs) derived from CLiPs in the disease group was lower than that in the normal group, their *in vivo* proliferative capacity was higher. In addition, these secreted factors may play an important role in the anti-fibrotic effects of CLiPs (*19*). Moreover, CLiPs can be generated from autologous hepatocytes, potentially eliminating the need for immunosuppressive therapy and overcoming one of the major limitations of liver transplantation (*20*). These findings support the feasibility of CLiP-based approaches as a form of cell-based liver regeneration.

Rather than positioning CLiPs as a direct replacement for liver transplantation, a more appropriate stance may be to consider this technology within a complementary therapeutic framework. This is particularly relevant for end-stage liver disease accompanied by severe structural disruption, including hepatic fibrosis, pseudolobule formation, and distortion of the vascular architecture (*21*). Despite demonstrated benefits in hepatic functional recovery and fibrosis resolution, the capacity of CLiPs to achieve definitive structural reconstruction remains unproven; specifically, direct evidence demonstrating the restoration of normal vascular architecture and the reversal of pseudolobules has yet to be established. Therefore, for liver diseases characterized by severe structural disorganization, such as portal hypertension, CLiP-based therapeutic strategies are best regarded as a form of functional augmentation, helping patients maintain essential liver function while serving as a bridge between medical management and organ transplantation.

For different types of liver disease, the use of CLiPs should focus on different therapeutic priorities (*22*). Several potential clinical applications for CLiP technology can be envisioned. First, the regenerative and differentiation capacity of CLiP therapy may function as a bridge to transplantation, maintaining hepatic function in patients with end-stage liver disease who are awaiting donor organs. It may also provide a therapeutic option for those who are not candidates for transplantation due to age or comorbidities. Second, CLiPs may be particularly relevant in earlier stages of chronic liver disease, including NASH and fibrosis, where disease progression may still be modifiable (*23*). In such cases, CLiPs have anti-fibrotic effects and improve liver function through their paracrine activity, which could delay or even obviate the need for transplantation. Occurring in approximately 10% of patients, post-hepatectomy liver dysfunction (LD) is a serious complication following liver resection and is associated with increased postoperative mortality and morbidity (*24*). Currently, no effective treatments are available to support postoperative liver regeneration. The dual action of CLiPs, which combines rapid paracrine support with direct cell engraftment, may offer a novel therapeutic approach for this condition. Unlike in chronic fibrosis, the remnant liver tissue in LD retains a relatively intact structure, providing favorable conditions for CLiP homing and integration. Moreover, a study by Viswanathan *et al*. (*25*) demonstrated that in an APAP-induced acute liver failure model, hepatocyte transplantation rescued mice without the need for hepatic repopulation, relying solely on paracrine factors. This finding suggests that in acute settings, CLiPs may similarly have rapid anti-apoptotic and anti-inflammatory effects through paracrine pathways, even before cell integration occurs.

3. Challenges in CLiP technology

Despite its promise, significant translational challenges remain. A 2025 review in *Nature Reviews Clinical Oncology* noted that autologous products require individualized manufacturing processes that are time-consuming and costly, with each product usable in only one patient (*26*). Similarly, a 2024 article in *The Journal of Immunology* pointed to challenges in patient applicability, safety, and efficacy consistency (*27*). These limitations of autologous cell therapies are equally pertinent to CLiPs.

One of the primary obstacles is scalability. Autologous cell therapies require individualized manufacturing processes, which are complex, time-consuming, and costly (*28*). Standardizing production while ensuring safety, potency, and reproducibility will be critical for clinical adoption. In addition, the long-term safety of partially reprogrammed cells must be carefully evaluated, particularly with regard to genomic stability and oncogenic risk (*29*).

Another critical challenge is the temporal disparity in therapeutic application. For chronic liver diseases, the hepatic microenvironment is relatively stable with

progressive yet slow injury, making autologous CLiPs derived from the patient's own hepatocytes a feasible approach. For acute liver injury or post-hepatectomy liver dysfunction, however, the processes of autologous cell procurement, reprogramming, and *in vitro* expansion are time-consuming (*30*), rendering the manufacturing timeline severely mismatched with the narrow therapeutic window. In such urgent settings, allogeneic CLiPs banks or "off-the-shelf" universal products are urgently needed, although these would raise additional issues regarding immune compatibility and long-term safety.

Economic considerations also represent a major barrier. The high cost of personalized cell therapies raises important questions regarding reimbursement and healthcare system integration. Without innovative funding models, the accessibility of such treatments may remain limited. Moreover, rigorous clinical trials need to be conducted to establish comparative effectiveness relative to existing therapies, including transplantation and pharmacological interventions (*31*).

In addition, regulatory and standardization challenges further complicate the clinical translation of CLiP-based therapies. The classification of CLiPs as advanced therapy medicinal products (ATMPs) imposes stringent regulatory requirements that vary considerably across jurisdictions. Establishing unified guidelines for good manufacturing practice (GMP) compliance, batch release criteria, and quality control metrics remains an urgent but unresolved issue (*32*).

At a broader level, the development of CLiPs reflects a fundamental shift in the conceptual framework of organ failure treatment. Traditional approaches have focused on replacing damaged organs, whereas emerging strategies aim to restore function by leveraging the plasticity of differentiated cells. This shift from organ replacement to functional restoration may have far-reaching implications not only for liver disease but for regenerative medicine as a whole.

In summary, CLiP technology presents a landscape of both promise and challenge. Its primary strengths, including a lower oncogenic profile relative to iPSCs, robust bipotent differentiation, and the potential for autologous application, position it as a frontrunner in regenerative hepatology. However, significant caveats remain: its capacity for structural reconstruction within severely distorted cirrhotic microenvironments is still unverified, framing its current role more as a functional augmentation than a definitive structural cure. Moreover, the logistical hurdles of autologous manufacturing—characterized by prolonged timelines and high costs—restrict its utility in acute settings where the therapeutic window is minimal. Coupled with emerging concerns regarding immunogenicity and the scarcity of long-term safety data, CLiPs are best integrated into a complementary therapeutic framework alongside liver transplantation. Future clinical success will hinge upon precise patient stratification, stage-specific application, and the successful maturation of universal, off-the-shelf products.

4. Conclusion

CLiPs exemplify a new generation of regenerative therapies that prioritize functional restoration over organ replacement. While liver transplantation will remain indispensable for patients with irreversible organ failure, CLiP-based approaches may significantly reduce transplant demand by enabling partial recovery of hepatic function. As clinical translation progresses, the success of this paradigm will depend on its ability to deliver safe, effective, and scalable therapies. Ultimately, the future of liver disease treatment may lie not in replacing the liver, but in repairing it.

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BST
BioScience Trends

Guide for Authors

1. Scope of Articles

BioScience Trends (Print ISSN 1881-7815, Online ISSN 1881-7823) is an international peer-reviewed journal. *BioScience Trends* devotes to publishing the latest and most exciting advances in scientific research. Articles cover fields of life science such as biochemistry, molecular biology, clinical research, public health, medical care system, and social science in order to encourage cooperation and exchange among scientists and clinical researchers.

2. Submission Types

Original Articles should be well-documented, novel, and significant to the field as a whole. An Original Article should be arranged into the following sections: Title page, Abstract, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, and References. Original articles should not exceed 5,000 words in length (excluding references) and should be limited to a maximum of 50 references. Articles may contain a maximum of 10 figures and/or tables. Supplementary Data are permitted but should be limited to information that is not essential to the general understanding of the research presented in the main text, such as unaltered blots and source data as well as other file types.

Brief Reports definitively documenting either experimental results or informative clinical observations will be considered for publication in this category. Brief Reports are not intended for publication of incomplete or preliminary findings. Brief Reports should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 4 figures and/or tables and 30 references. A Brief Report contains the same sections as an Original Article, but the Results and Discussion sections should be combined.

Reviews should present a full and up-to-date account of recent developments within an area of research. Normally, reviews should not exceed 8,000 words in length (excluding references) and should be limited to a maximum of 10 figures and/or tables and 100 references. Mini reviews are also accepted, which should not exceed 4,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 50 references.

Policy Forum articles discuss research and policy issues in areas related to life science such as public health, the medical care system, and social science and may address governmental issues at district, national, and international levels of discourse. Policy Forum articles should not exceed 3,000 words in length (excluding references) and should be limited to a maximum of 5 figures and/or tables and 30 references.

Communications are short, timely pieces that spotlight new research findings or policy issues of interest to the field of global health and medical practice that are of immediate importance. Depending on their content, Communications will be published as "Comments" or "Correspondence". Communications should not exceed 1,500 words in length (excluding references) and should be limited to a maximum of 2 figures and/or tables and 20 references.

Editorials are short, invited opinion pieces that discuss an issue of immediate importance to the fields of global health, medical practice, and basic science oriented for clinical application. Editorials should not exceed 1,000 words in length (excluding references) and should be limited to a maximum of 10 references. Editorials may contain one figure or table.

News articles should report the latest events in health sciences and medical research from around the world. News should not exceed 500 words in length.

Letters should present considered opinions in response to articles published in *BioScience Trends* in the last 6 months or issues of general interest. Letters should not exceed 800 words in length and may contain a maximum of 10 references. Letters may contain one figure or table.

3. Editorial Policies

For publishing and ethical standards, *BioScience Trends* follows the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals issued by the International Committee of Medical Journal Editors (ICMJE, *https://icmje.org/recommendations*), and the Principles of Transparency and Best Practice in Scholarly Publishing jointly issued by the Committee on Publication Ethics (COPE, *https://publicationethics.org/resources/guidelines-new/principles-transparency-and-best-practice-scholarly-publishing*), the Directory of Open Access Journals (DOAJ, *https://doaj.org/apply/transparency*), the Open Access Scholarly Publishers Association (OASPA, *https://oaspa.org/principles-of-transparency-and-best-practice-in-scholarly-publishing-4*), and the World Association of Medical Editors (WAME, *https://wame.org/principles-of-transparency-and-best-practice-in-scholarly-publishing*).

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Ethical Approval of Studies and Informed Consent: For all manuscripts reporting data from studies involving human participants or animals, formal review and approval, or formal review and waiver, by an appropriate institutional review board or ethics committee is required and should be described in the Methods section. When your manuscript contains any case details, personal information and/or images of patients or other individuals, authors must obtain appropriate written consent, permission and release in order to comply with all applicable laws and regulations concerning privacy and/or security of personal information. The consent form needs to comply with the relevant legal requirements of your particular jurisdiction, and please do not send signed consent form to *BioScience Trends* to respect your patient's and any other individual's privacy. Please instead describe the information clearly in the Methods (patient consent) section of your manuscript while retaining copies of the signed forms in the event they should be needed. Authors should also state that the study conformed to the provisions of the Declaration of Helsinki (as revised in 2013, *https://wma.net/what-we-do/medical-ethics/declaration-of-helsinki*). When reporting experiments on animals, authors should indicate whether the institutional and national guide for the care and use of laboratory animals was followed.

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Darby S, Hill D, Auvinen A, *et al*. Radon in homes and risk of lung cancer: Collaborative analysis of individual data from 13 European case-control studies. BMJ. 2005; 330:223.

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