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Beyond the "Prevention Paradox": Prioritizing adherence-weighted effectiveness in China's colorectal cancer screening strategy

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Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide, yet the global screening faces a critical tension between traditional endoscopy and emerging non-invasive technologies. The recent editorial by Dominitz et al. in *JAMA* introduced the concept of the "Cancer Prevention Paradox," which has garnered significant attention. Grounded in data from the PREEMPT CRC study—where a blood-based cell-free DNA (cfDNA) test demonstrated a sensitivity of only 12.5% for advanced precancerous lesions (APL)—the authors warned that blindly substituting colonoscopy with blood testing could undermine cancer prevention efforts by missing a substantial number of adenomas.[1,2] While this argument holds high public health value in Western healthcare systems characterized by ample endoscopic resources and high screening adherence, applying this logic directly to developing nations like China requires a critical "*epidemiological localization*." In China, the primary contradiction in colorectal cancer (CRC) control is not the performance degradation of screening modalities, but rather the stark reality of insufficient population coverage and critically low endoscopic compliance. Therefore, evaluating the clinical utility of liquid biopsy necessitates the introduction of a new dimension: "Adherence-Weighted Population Benefit."

THE EPIDEMIOLOGICAL REALITY: FROM "PREVENTION PARADOX" TO *"COVERAGE PARADOX"*

Distinct screening baselines between China and the US dictate different priorities. The US maintains a CRC screening coverage nearing 60%, focusing its strategy on interrupting carcinogenesis through adenoma resection. While the "Prevention Paradox" highlights missed adenomas in high-compliance settings, it assumes patients willingly undergo colonoscopy. In China, applying this logic ignores a more pressing reality: the *"Coverage Paradox."* Indeed, China's screening coverage remains approximately 3.0%.[3] Even within organized screening programs, compliance among high-risk populations remains suboptimal. A study involving 2.12 million participants in China revealed that even within the *"dual-high"* subgroup—individuals who were both positive for the Fecal Immunochemical Test (FIT) and identified as high-risk by questionnaire-based risk assessment (QRA)—colonoscopy compliance reached only 41.4%.[4] This challenge is further compounded by the shifting demographic profile of CRC in China. There is a perceptible rise in early-onset colorectal cancer (EOCRC) among individuals aged 45–49, a *"sandwich generation"* that bears the brunt of socio-economic activity. For this demographic, the high time-cost and invasiveness of colonoscopy are significant deterrents. Consequently, a convenient, non-invasive entry point is urgently needed to capture this emerging high-risk cohort that is currently slipping through the cracks of traditional screening programs.

In this context, enforcing a "gold standard" regimen that mandates colonoscopy often results in mass non-participation. Analytical superiority fails to translate into clinical utility if the target population remains persistently non-compliant. Accordingly, the value of liquid biopsy cannot be assessed solely by absolute technical parameters but must be weighed against its potential to deliver adherence-weighted population benefits (Figure 1A).

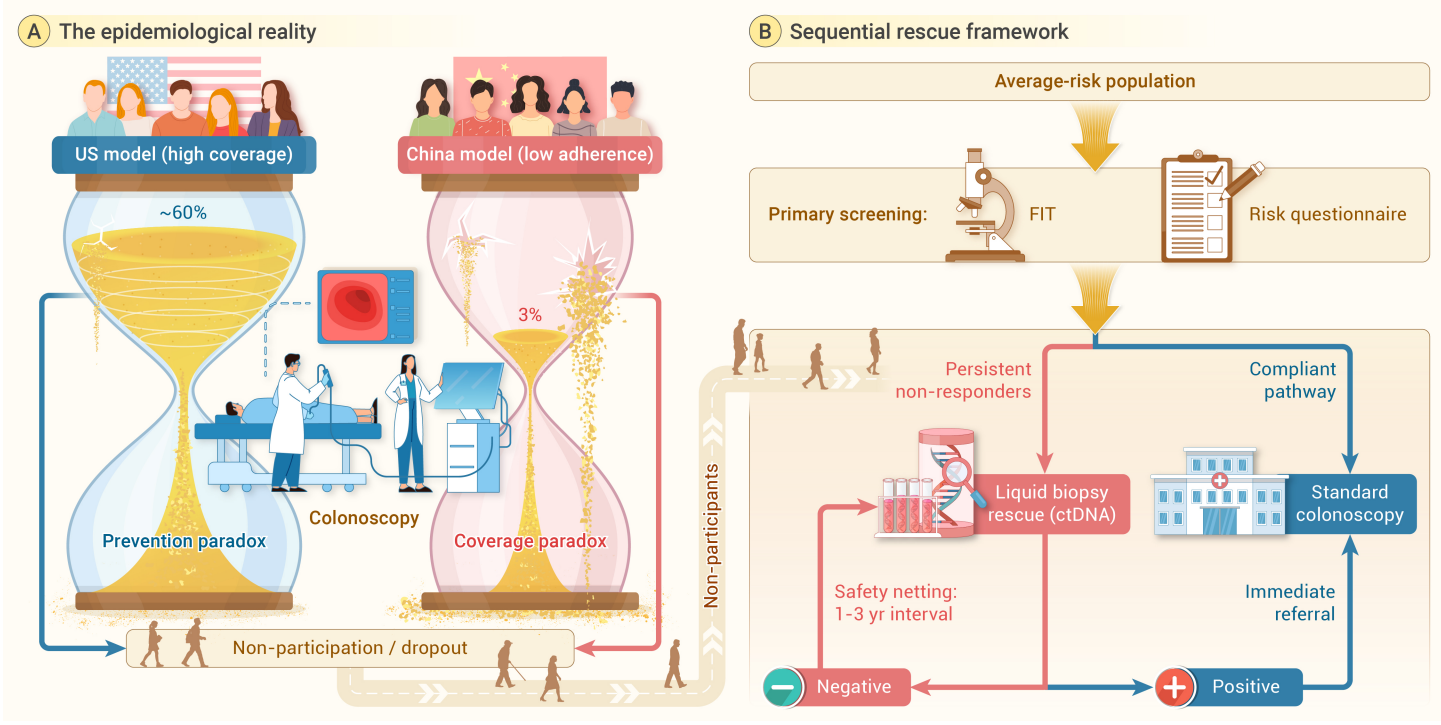

Figure 1. Strategic positioning of liquid biopsy in China's CRC screening (A) The epidemiological dilemma comparing high-coverage settings (US Model), which face the "Prevention Paradox," with the critical *"Coverage Paradox"* in China caused by low adherence to colonoscopy. (B) The proposed rescue regimen: FIT plus risk questionnaire remains first-line for mass screening; liquid biopsy (ctDNA) is reserved for persistent non-responders. Positive results trigger immediate referral to standard colonoscopy, while negative results require safety-netting with repeat testing at 1–3-year intervals. FIT, fecal immunochemical test; ctDNA, circulating tumor DNA.

STRATEGIC POSITIONING: A COMPLEMENTARY MODALITY FOR NON-RESPONDERS

Although the sensitivity of liquid biopsy for APL (12.5%) is significantly inferior to FIT and multitarget stool DNA tests, its non-invasive nature and convenience can substantially enhance participation rates and offer a critical advantage in expanding the screened population denominator.[2] For populations that remain unresponsive to health education and refuse colonoscopy or FIT (i.e., "persistent non-responders"), a blood test offering 79.2% sensitivity for CRC should be viewed as a necessary secondary line of defense rather than a simplistic replacement for primary screening methods. However, translating this potential into practice requires navigating formidable resource and economic barriers. Clinically, the PREEMPT CRC data indicated a positive predictive value (PPV) of only 15.5% for advanced colorectal neoplasia, meaning most positive blood tests will trigger low-yield confirmatory colonoscopy—an unsustainable trade-off under China's limited endoscopic capacity.[2] Given the relative shortage of endoscopists in China, indiscriminately using blood testing as a primary mass screening tool could precipitate a "resource displacement" effect, where limited endoscopic capacity is consumed by low-yield verifications, crowding out symptomatic patients or high-risk individuals. Economically, population-based models suggest that biomarker-based alternatives are not cost-effective under equal uptake compared to FIT and would require substantially lower prices and optimized follow-up to become competitive.[5] Thus, the clinical value of liquid biopsy is contingent upon a strategy that balances adherence benefits against these rigid efficiency constraints.

THE ECONOMIC RATIONALE FOR A "RESCUE" ROLE

While inefficient for mass screening, the economic calculus shifts fundamentally when targeting persistent non-responders. For this specific subgroup, the counterfactual is often the complete absence of screening until symptom onset. In China's first province-wide program, the programmatic cost per CRC detected was reported to be approximately US$16,684.[3] By converting these avoiders to earlier detection, a targeted liquid biopsy strategy may reduce a portion of the downstream treatment costs associated with advanced disease, helping justify the higher upfront testing cost. Conversely, broad first-line deployment risks combining high unit costs with a low PPV, exacerbating the budget impact through a surge in low-yield colonoscopies. Therefore, the financial viability of liquid biopsy is inextricably linked to its restriction as a "rescue" modality rather than a primary screening tool.

A "RESCUE" REGIMEN WITH STRUCTURED IMPLEMENTATION

We propose a stratified sequential strategy that preserves FIT-based efficiency while using liquid biopsy only to rescue persistent non-responders (Figure 1B).

Stratified positioning and sequential rescue

To preserve cost-effectiveness and sustain broad coverage, the FIT and risk-assessment questionnaires must remain the primary, first-line modalities for mass screening. Liquid biopsy could be strategically positioned as a targeted sequential rescue regimen, reserved for persistent non-responders who decline both colonoscopy and FIT. This focused application restricts the overall volume of high-cost testing and concentrates colonoscopy demand on higher-risk populations, thereby ensuring more predictable program expenditures.

Comprehensive practical implementation playbook

The theoretical "adherence-weighted" benefits of screening only translate into actual mortality reductions when downstream compliance is actively managed. Organized screening programs must embed rigorous safety and follow-up mechanisms. First, a robust informed consent process is critical; clinicians must frame liquid biopsy as an intermediate step rather than a definitive "all-clear," explicitly clarifying that a negative result does not rule out the presence of adenomas. Furthermore, to mitigate the risk of interval cancers, the screening interval for individuals with negative blood tests should be proactively shortened (e.g., to every 1–3 years) to compensate for the test's lower sensitivity. Finally, any positive result must trigger an immediate referral pathway (ideally providing a pre-scheduled colonoscopy appointment) to ensure timely diagnostic closure.

CONCLUSION

In the context of uneven medical resource distribution and insufficient screening adherence in China, there is no need to become trapped in a binary debate over the "Prevention Paradox." Liquid biopsy represents a critical component for closing the "adherence gap," provided it is deployed within a strictly stratified management framework. By precisely targeting persistent non-responders and leveraging the high specificity (91.5%) validated in the PREEMPT study, China can find an optimal balance between imperfect sensitivity and achievable coverage. Future research should also explore the utility of this modality in the emerging early-onset CRC cohort, whose adherence patterns and screening pathways warrant specific investigation. Finally, the integration of multi-omics platforms may further extend this utility from early screening to Minimal Residual Disease (MRD) monitoring, enhancing the public health value of liquid biopsy in China's cancer control landscape.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the authors used ChatGPT in order to improve language fluency and structural readability. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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AUTHOR CONTRIBUTIONS

All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.