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EDITORIAL

NEITHER WITH NOR WITHOUT: ARTIFICIAL INTELLIGENCE VERSUS SUSTAINABILITY IN SCIENTIFIC PUBLISHING

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In the contemporary era, wherein virtually all human activities are converted into digital footprints, the influence of information systems and artificial intelligence (AI) within production and daily life domains has become increasingly pronounced. While the primary objectives of digital transformation are framed around achieving time efficiency, cost-effectiveness, and sustainability, one of its most salient unintended outcomes has been the emergence of digital pollution. Key contributors to this phenomenon include the substantial energy consumption of electronic devices, the carbon footprint and water usage associated with data centers, and the escalating issue of electronic waste. Furthermore, the accelerated computing resources required for AI applications exacerbate this environmental burden (1). At present, digital technologies are estimated to account for approximately 10% of global electricity consumption and nearly 4% of worldwide carbon emissions (2). Although digitalization has often been associated with an era of convenience, it is evident that the phenomenon also gives rise to significant sustainability challenges.

In evaluating the sustainability implications of digital transformation, it is crucial to consider the expanding role of AI in scientific publishing. A survey conducted on nearly 5,000 researchers from approximately 70 different countries shows that these tools will become even more prominent in the following years (3). 62% of participants think that AI surpasses human ability in writing assistance and error detection, and 72% want to use AI for academic papers in the following two years, next to the 57% who already have (3).

Initially employed for relatively limited tasks such as language editing and translation, AI has now been integrated into more complex stages of the publication process, including editorial decision-making, peer review, detection of ethical misconduct, and the acceleration of publication workflows. However, this transformation not only increases scientific productivity but also brings with it critical sustainability issues by affecting digital pollution, such as energy consumption, carbon emissions, and hardware waste.

In recognition of the importance of AI as a key driver of scientific productivity, we propose the concept of "environmentally sensitive editorial and authorship" to promote sustainability. This concept aims to encourage sensitivity in the use of AI and digital technologies, as well as promote ethical considerations in academic research. We believe that the fundamental "principles of environmentally sensitive editorial/authorship" can be: researchers should consider the carbon footprint and environmental impacts of experimental studies designed with advanced technological devices, chemicals, and so on; they should be mindful of responsible technology use and should employ AI applications only at necessary points rather than at every stage of research writing; they should avoid repetitive data analysis and text writing when using AI during research writing; and they should raise awareness by defining the framework of a "sustainable scientific publishing" culture by national and international publishing associations. Previous publishing guidelines, frameworks, and checklists on sustainability issues should be revisited to include sustainable AI strategies designed for authors, journals, and publishers alike.

Through deliberate policy development and intentional individual choices, the academic world can guide this technological shift toward outcomes that are not only innovative and efficient but also ethical, inclusive, and environmentally responsible.

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REVIEW

IMMUNE ACTIVATION IN METASTATIC CANCERS: THE STING PATHWAY AND NANOPARTICLE-BASED THERAPEUTIC APPROACHES

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ABSTRACT

Cancer immunotherapy represents a significant treatment approach aimed at enhancing patient survival by targeting the tumor microenvironment and immune system. In recent years, considerable interest has been shown in novel therapeutic strategies that activate the immune system, particularly in patients with metastatic cancer. The stimulator of interferon genes pathway has been identified as a critical target due to its ability to enhance immune responses against malignancies. The stimulator of interferon genes adaptor protein plays a central role in cellular immune signaling and is an essential component of the deoxyribonucleic acid sensing machinery. Upon activation, the stimulator of interferon genes pathway induces the production of various cytokines, mainly type I interferons, to trigger an immune response in the tumor microenvironment. However, direct administration of stimulator of interferon genes agonists poses significant challenges due to systemic toxicity and off-target effects. To overcome these limitations, nanoparticle-based drug delivery systems have been developed to enhance therapeutic efficacy and minimize side effects. These systems enhance stimulator of interferon genes activation, ensure targeted distribution, and amplify immune stimulation. This review discusses the role of the stimulator of interferon genes pathway in metastatic tumors, the mechanisms underlying nanoparticle-based stimulator of interferon genes agonists, and recent findings from preclinical studies and clinical trials. Additionally, it discusses the advantages, challenges, and potential directions for future research on this approach.

Keywords: Immune activation, immunotherapy, metastatic cancers

INTRODUCTION

Cancer remains one of the leading causes of death worldwide (1). Metastatic cancers pose additional challenges as they frequently develop resistance to therapeutic agents (2). While the immune system can recognize and eliminate cancer cells, the tumor microenvironment (TME) typically employs immunosuppressive mechanisms that inhibit immune responses and allow tumors to evade immune surveillance (3). Consequently, there is a growing need for immunotherapeutic approaches that specifically target the innate immune system, a concept that has gained significant interest in recent years (4). Among these approaches, the stimulator of the interferon genes (STING) pathway has emerged as a valuable therapeutic target due to its ability to increase antitumor immune reactions (5). STING, an adaptor protein, is activated by cytosolic deoxyribonucleic acid (DNA), leading to the production of various cytokines, predominantly type I interferons (IFN-I) (6). This response initiates a strong immune response in the TME, thereby enhancing antitumor activity (7). STING activation not only triggers innate immunity but also enhances adaptive immune responses by priming cluster of differentiation 8^+ ($CD8^+$) T-cells for activation, which facilitates tumor-specific immunity (8). However, several tumor types suppress the STING signaling pathway, thereby limiting the effectiveness of immune activation (9). The development of pharmacological STING agonists has emerged as a strategy to overcome this limitation and enhance immune system function in cancer treatment (10). However, the direct application of STING agonists is limited by systemic toxicity and unexpected

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side effects (11). The use of nanoparticle-based drug delivery systems has emerged as a potential solution to overcome these limitations and improve treatment outcomes while minimizing unwanted effects (12). These nanoparticles are designed to increase STING activation, promote targeted delivery, and increase immune stimulation (13). Recent preclinical and clinical research has demonstrated promising findings regarding the use of nanoparticle-based STING agonists to treat metastatic cancers (14). This review will explore the involvement of the STING pathway in metastatic cancers, the development of nanoparticle-based STING agonists, their mechanisms of action, and their effects on immune responses, along with an examination of their advantages and disadvantages and future opportunities for nanoparticle-based STING activation.

1. STING Pathway and Immune Evasion Mechanisms in Metastatic Cancers

a) Escape mechanisms of metastatic cancers from the immune system

In metastatic cancers, immune evasion mechanisms are primarily triggered by acquired immune responses (15). The most significant mutations and genetic changes that contribute to this process occur during the early stages of tumor development (16). These include loss of heterozygosity, somatic mutations, and epigenetic changes that impair the presentation of neoantigens, programmed cell death ligand 1 (PD-L1) expression, and other immunosuppressive mechanisms (17, 18) (Figure 1).

b) The potential of STING to modulate the immune response

Stimulator of interferon genes activation has been shown to enhance the immune system's ability to recognize and eliminate metastatic tumor cells (19). This process involves a sequential five-stage cascade. Initially, the enzyme cyclic guanosine monophosphate (GMP)-adenosine monophosphate (AMP) synthase (cGAS) detects the accumulation of abnormal cytoplasmic DNA. cGAS then catalyzes the production of cyclic GMP-AMP (cGAMP), which acts as a second messenger activating STING. Once STING is activated, it triggers the release of damage-associated molecular patterns and tumor-specific antigens. These molecular signals are then recognized by dendritic cells, which are activated and subsequently prime T-cells. Finally, T-cells are activated to launch an immune response against cancer cells, thereby increasing the immune system's capacity to detect and destroy metastatic tumors (Figure 2) (20).

Within this immune-activating cascade, a sound rationale for combining STING agonists and immune checkpoint inhibitors (ICIs), particularly anti-programmed cell death protein 1 (anti-PD-1)/PD-L1 such as pembrolizumab or nivolumab, has been developed. While STING activation promotes dendritic cell maturation, enhances cross-presentation of tumor-derived antigens, and promotes T-cell priming and infiltration into the TME, ICIs operate at a later stage by maintaining T-cell effector function and preventing T-cell exhaustion (21). The STING agonists activate and amplify antitumor immune responses, whereas the ICIs act to sustain and maintain the immune response.

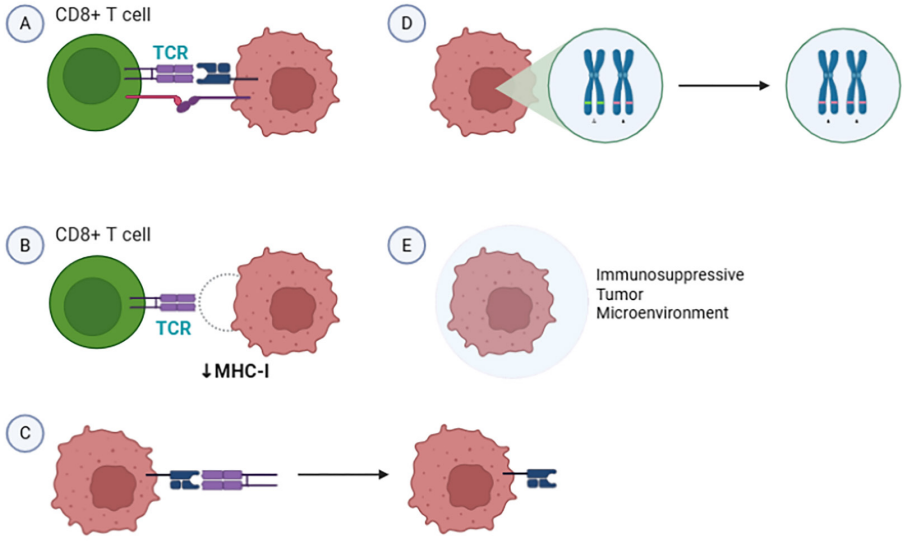

Figure 1: Mechanisms of immune evasion by metastatic cancers (created with BioRender.com).
Metastatic cancer cells employ various strategies to escape recognition and elimination by the immune system, often driven by acquired genetic and epigenetic changes during tumor development. A) Interaction between PD-1 on $CD8^+$ T-cells and PD-L1 on tumor cells inhibits T-cell activation and cytotoxic function, leading to immune evasion. B) Downregulation or loss of MHC class I molecules on tumor cells prevents antigen presentation, reducing $CD8^+$ T-cell recognition. C) Tumor cells may lose expression of immunogenic neoantigens due to selective pressure or mutations, hindering T-cell targeting. D) Genetic or epigenetic alterations in tumor cells can further impair antigen processing and presentation pathways. E) An immunosuppressive TME (e.g., presence of regulatory cells, cytokines, and metabolic factors) suppresses effective anti-tumor immune responses.
$CD8^+$: Cluster of differentiation 8^+, MHC: Major histocompatibility complex, PD-1: Programmed cell death protein 1, PD-L1: Programmed cell death ligand 1, TME: Tumor microenvironment, TCR: T-cell receptor

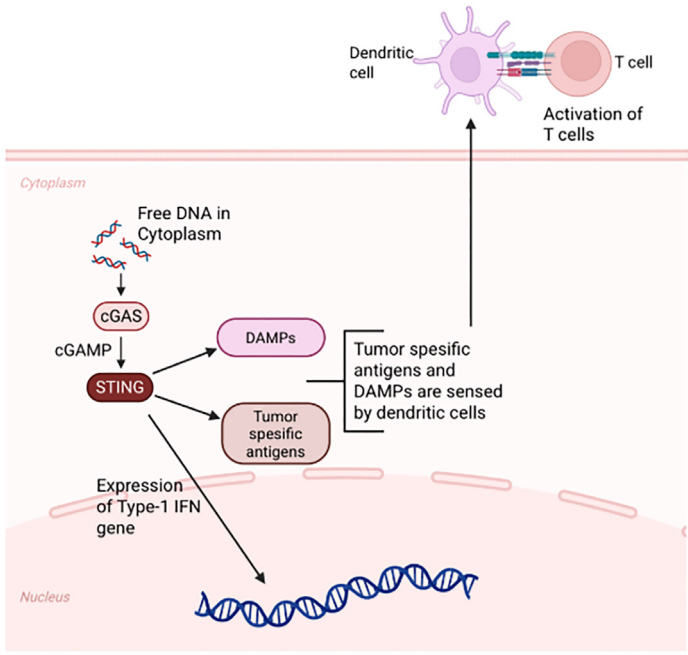

Figure 2: The cGAS-STING pathway and its role in anti-tumor immunity (created with BioRender.com).
This diagram illustrates the cGAS-STING pathway, a critical innate immune signaling cascade that detects cytosolic DNA and initiates anti-tumor immune responses.
cGAS-STING: Cyclic guanosine monophosphate-adenosine monophosphate synthase-stimulator of interferon genes, DNA: Deoxyribonucleic acid, IFN: Interferon, DAMPs: Damage-associated molecular patterns

Preclinical models have demonstrated that this dual approach can successfully "reprogram" immune "cold" tumors with poor T-cell infiltration that are resistant to checkpoint blockade into immune "hot" tumors in which immune cell trafficking, IFN signaling, and major histocompatibility complex-I expression are enhanced. These STING agonist-ICI combinations promote both the generation and persistence of effector T-cells, which lead to synergistic tumor regression with durable survival benefit (21).

Yet, this synergy may incur risks. The potentiated immune stimulation may result in a higher risk of immune-related adverse events (irAEs; e.g., colitis, hepatitis, pneumonitis, and systemic inflammatory syndromes). In addition, it is feasible that robust or continuous STING activation may trigger immune tolerance or cytokine storm-like effects that would counteract the anti-tumor effect (22). Therefore, additional focus on dose optimization, scheduling, and the integration of biomarkers for patient selection will be critical for safe or effective clinical translatability of combinations.

c) General evaluation of preclinical and clinical studies

The MIV-815 (ADU-S100) study, a clinical investigation conducted on the use of STING agonists in cancer immunotherapy, demonstrated that the immune system can be activated by injecting STING agonists directly into the TME (23). The study showed that MIV-815 was safe and able to trigger a systemic immune response. However, its clinical effectiveness was limited when used alone (23). This limitation highlights the difficulty of using a single treatment to overcome the immunosuppressive environment of a tumor and emphasizes the need for rationally designed combination regimens (24). Alternative methods of activating the STING pathway have also been explored. A preclinical study on Cadherin-11 (CDH11) inhibition found that this pathway indirectly activates STING signaling and enhances the immune system's response to tumor cells in metastatic cancers (24). The suppression of CDH11 has been shown to contribute to reducing tumor burden by increasing the activity of immune cells in the TME (25). However, this mechanism has only been validated in preclinical models, and further studies are required to assess its relevance in human cancers. A preclinical study also demonstrated that combining STING agonists with programmed cell death protein 1 (PD-1) inhibitors elicited a more robust immune response in metastatic tumors (26). This synergy potentiates T-cell responses by promoting dendritic cell activation within the TME. Although promising, the safety, timing, and dosage of such combination strategies require comprehensive clinical evaluation, particularly considering the risk of immune-related adverse events (26). These findings suggest that STING agonists can be activated not only through direct administration but also via alternative mechanisms. Furthermore, their combination with other immunotherapeutic agents, such as PD-1 inhibitors, holds significant promise for cancer treatment by enhancing immune responses in metastatic cancers (27). However, further investigations are essential to optimize delivery systems, clarify mechanistic interactions, and validate these strategies in large-scale clinical trials. An overview of selected STING agonists used in cancer therapy is presented in Table 1.

Table 1: Overview of selected STING agonists in cancer therapy.

STING agonist	Molecular class	Mechanism of action	Development phase	Types of metastatic cancer	Side effects
Cyclic dinucleotides (CDNs) (28)	Nucleotide derivatives (cGAMP, c-di-GMP, c-di-AMP)	Activate STING pathways, stimulating interferon production.	Preclinical and some clinical	Colorectal, breast, and lung cancer	Inflammation, fatigue, headache
Microsphere-based STING agonist (MBOP) (29)	Polymer structures	Activates STING pathways, activating the immune system.	Preclinical	Liver cancer	Immune side effects, injection site reactions
Elumusertib (BAY1895344) (30)	Chemical synthesis	Effectively activates STING pathways.	Phase 1	Prostate cancer	Inflammation, muscle pain
ADU-S100 (22)	Synthesized small molecules	Activates STING, stimulating IFN-I response.	Phase 1/2	Melanoma, lung cancer	High-dose fever, fatigue

This table summarizes key characteristics of various STING agonists currently under investigation for their potential in cancer treatment. It includes information on their molecular class, mechanism of action, current development phase, types of metastatic cancers they are being explored for, and reported side effects.
cGAMP: Cyclic guanosine monophosphate-adenosine monophosphate, c-di-GMP: Cyclic di-guanosine monophosphate , c-di-AMP: Cyclic di-adenosine monophosphate, IFN-I: Interferon type I, STING: Stimulator of interferon genes

Nanoparticle Technology and STING Activation: Structures, Mechanisms, and Clinical Potential

Stimulator of interferon genes agonists have emerged as powerful agents in cancer immunotherapy, particularly in the context of metastatic cancers, where conventional treatments often fall short. However, the clinical utility of these agonists is hindered by pharmacokinetic challenges such as low bioavailability, rapid systemic clearance, and immune-related adverse effects (31). To overcome these limitations, nanoparticle-based drug delivery systems have gained significant attention for their ability to deliver STING agonists effectively to the TME, including metastatic sites (31).

Lipid-Based Nanoparticles and STING Activation in Metastatic Cancer

Lipid-based nanoparticles, particularly liposomes, have been extensively studied for their capacity to enhance the delivery of both hydrophilic and hydrophobic drugs, including STING agonists (32). These nanoparticles are composed of phospholipid bilayers, which can encapsulate a wide range of therapeutic agents, offering protection from degradation and improving stability during circulation (Figure 3) (Supplementary Video 1). In the context of metastatic cancer, where tumor heterogeneity and the presence of distant secondary tumors complicate treatment, the ability of liposomes to deliver STING agonists directly to immune cells within the TME has significant therapeutic implications (32).

The acidic environment characteristic of metastatic tumors, particularly at distant metastatic sites, makes lipid nanoparticles (LNPs) particularly suitable for controlled release (33). These nanoparticles are pH-sensitive, allowing them to release their cargo efficiently within the TME, where the pH (~6.5-6.8) is lower than that of normal tissues (~7.4) (33).

This ensures the STING agonists are released where they are needed the most, potentially enhancing the activation of immune responses at metastatic sites (34).

Lipid-based nanoparticles also have the added benefit of modifying immune responses through their interaction with immune cells (35). These nanoparticles not only deliver STING agonists but also enhance the uptake of the agonists by immune cells, such as dendritic cells and macrophages (36). By triggering the STING pathway, they promote the activation of $CD8^+$ T-cells and the release of pro-inflammatory cytokines, which can lead to a robust anti-tumor immune response (37). In metastatic cancers, where immune evasion is a major hurdle, the ability of lipid-based nanoparticles to stimulate the immune system offers a promising strategy for overcoming this challenge (38).

In addition, surface modifications, such as polyethylene glycol conjugation or antibody conjugation, can improve the specificity of LNPs, enabling them to target specific metastatic tumor cells more effectively (39). These modifications help minimize off-target effects and enhance the accumulation of the nanoparticles at metastatic sites, ensuring that the therapeutic agent is delivered precisely where it is most needed (40).

Studies have demonstrated that lipid-based nanoparticles can successfully deliver STING agonists to immune cells, leading to enhanced antitumor responses in metastatic cancers. For instance, in mouse models of metastatic melanoma and breast cancer, LNPs loaded with STING agonists have been shown to suppress tumor growth and promote the activation of $CD8^+$ T-cells (41). These findings suggest that lipid-based nanoparticles not only act as carriers but also play an active role in modulating immune responses, making them highly suitable for the treatment of metastatic cancers (41).

In conclusion, lipid-based nanoparticles offer a promising approach to overcome the pharmacokinetic challenges associated with STING agonists in the treatment of metastatic cancers. By enhancing the targeted delivery, controlled release, and immune modulation of STING agonists, these nanoparticles hold the potential to improve the efficacy of cancer immunotherapy, particularly in the context of metastatic disease.

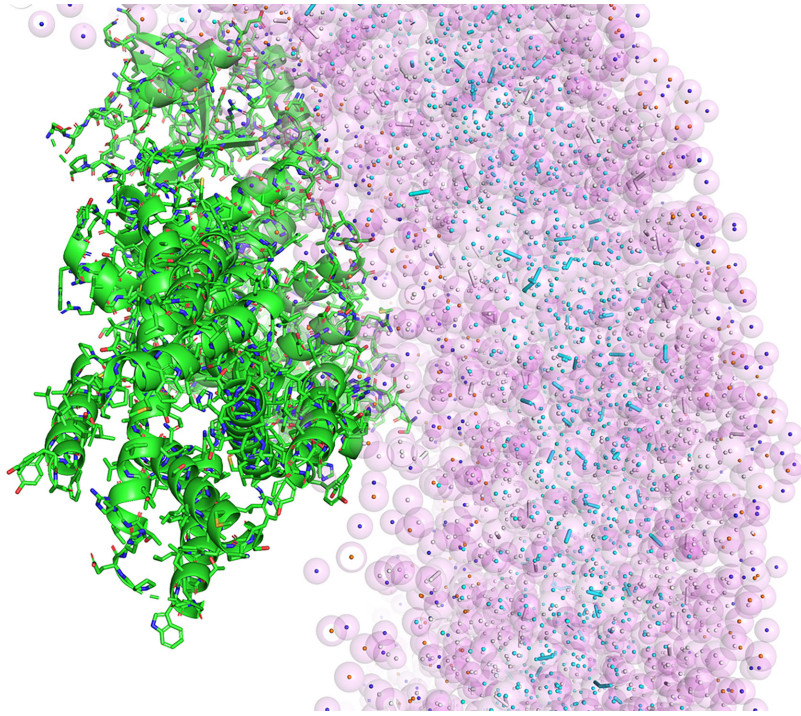

Figure 3: Molecular representation of a liposomal nanoparticle interacting with the STING agonist (with PyMol). The agonist (green) is located at the bilayer interface, demonstrating potential interaction with the synthetic lipid-based nanoparticle model (pink spheres).
STING: Stimulator of interferon genes

Polymer-Based Nanoparticles and STING Activation in Metastatic Cancer Immunotherapy

Polymeric nanoparticles, typically composed of biodegradable polymers such as polylactic-co-glycolic acid (PLGA), are emerging as promising carriers for the delivery of STING agonists in cancer immunotherapy, particularly for metastatic cancers (42). These nanoparticles are well-known for their high drug-loading capacity, controlled release properties, and biocompatibility, making them ideal candidates for overcoming the pharmacokinetic challenges associated with STING agonists (43). When engineered to carry STING agonists, polymer-based nanoparticles ensure that the agonists are efficiently delivered to immune cells, particularly within the TME, where they activate STING receptors and initiate a robust immune response (43).

In the context of metastatic cancer, where tumors are often dispersed across distant sites, the targeted delivery of STING agonists becomes crucial. Polymer nanoparticles can be functionalized with specific ligands or antibodies, enabling them to target particular cells or tissues, including metastatic tumor sites (44). This targeted approach minimizes off-target effects and maximizes the accumulation of the agonists at the site of action, which is especially important for tumors that are hard to treat with conventional therapies (44).

The biodegradable nature of polymer-based nanoparticles allows for the sustained release of STING agonists over an extended period, providing continuous and prolonged activation of immune cells (45). This feature is particularly valuable in metastatic cancers, where immune evasion and immune suppression often hinder the effectiveness of therapies. By ensuring prolonged immune activation, polymer nanoparticles help maintain a strong and persistent antitumor immune response, potentially preventing the re-emergence of metastases (45).

Some studies have demonstrated that polymer-based nanoparticles effectively facilitate the controlled release of STING agonists to immune cells such as dendritic cells, thereby enhancing the activation of $CD8^+$ T-cells and promoting systemic antitumor immunity (46, 47). In metastatic models, this sustained activation has been shown to suppress tumor growth and inhibit the spread of metastatic cells. These characteristics make polymer-based nanoparticles a promising strategy for the long-term, effective modulation of STING activation, offering hope for treating metastatic cancer more effectively than current treatments allow (46, 47).

Inorganic Nanoparticles and STING Activation in Metastatic Cancer Immunotherapy

Inorganic nanoparticles, such as gold (Au), iron oxide (Fe_3O_4), and silica, offer distinct advantages for the treatment of metastatic cancers, including high stability, ease of functionalization, and precise targeting capabilities (48). When STING agonists are incorporated into these nanoparticles, they not only serve as carriers but also enhance antigen transport, facilitate cellular uptake, and modulate immune responses-key factors in overcoming the challenges posed by metastatic tumor dissemination (48).

Magnetic Fe_3O_4 nanoparticles are particularly advantageous for targeting metastatic tumors due to their ability to be guided to specific tumor sites via external magnetic fields (49). This method ensures targeted delivery of STING agonists to distant metastases, improving therapeutic precision and reducing systemic toxicity (49).

Gold nanoparticles, with their photoresponsive properties, can further enhance the therapeutic effect of STING agonists by enabling localized activation upon light exposure (50). This is particularly beneficial for treating deep-seated metastatic tumors, where other methods of delivery may be less effective (50).

Silica nanoparticles, known for their high drug-loading capacity, facilitate the controlled release of STING agonists, ensuring sustained delivery to immune cells such as dendritic cells within the metastatic TME (51). This controlled release is critical in maintaining prolonged immune activation and preventing immune evasion, a common obstacle in metastatic cancers (51).

Recent studies have demonstrated that magnetic Fe_3O_4 nanoparticles can improve STING activation and promote robust antitumor immune responses within metastatic tumors (52). Additionally, Au nanoparticles can optimize the effects of STING agonists through their photoactivatable properties, enhancing their therapeutic potential in the treatment of metastatic cancers (53).

In conclusion, inorganic nanoparticles offer a powerful approach for enhancing the delivery and efficacy of STING agonists in metastatic cancer immunotherapy. With their unique targeting mechanisms, such as magnetic guidance and light activation, these nanoparticles hold great promise for improving the precision and effectiveness of treatment in metastatic disease.

Next-Generation Nanoparticles and STING Activation in Metastatic Cancer Immunotherapy

Innovative smart nanoparticle systems have emerged that involve light-responsive, pH-sensitive, and ligand-targeted nanocarriers, which are promising new modalities to improve STING agonist delivery specificity and efficacy. Much like light-sensitive drugs, light-responsive nanoparticles offer spatiotemporal control for drug release, as they can be activated by illumination either in the TME or even intratumorally, while keeping systemic exposure and the potential for off-target toxicity minimal (54). Photoactivatable nanoparticle platforms are also advantageous for deep-seated tumors or leadership tumors, since controlled and specific activation can be administered chronologically or spatially (55).

pH-sensitive carriers can leverage the acidic environment of the TME or pH sensitivity of endosomes and lysosomes to limit release of STING agonists. This limited release improves the concentration of the drug at the tumor site while avoiding excessive systemic side effects, which are considerable obstacles for clinical translation (56).

Lastly, ligand-targeted nanoparticles, where the nanoparticle scaffold can specifically recognize receptors that are overexpressed on tumor cells or antigen-presenting cells, can direct STING agonists to antigen presenting cells through receptor-mediated uptake and improve biodistribution of the drug. These smart systems can deliver STING agonists to dendritic cells or other immune subsets while improving antigen presentation, T-cell priming, and the overall anti-tumor immune response (57).

Emerging research illustrates the translational potential of these platforms and reports that smart nanocarriers can enhance pharmacokinetic profiles, maintain immune activation, and overcome resistance mechanisms in immunologically "cold" tumors (58). Taken together, these next-generation nanoparticle technologies have considerable clinical development prospects, opening doors for more precise, safer, and more effective STING-based cancer immunotherapies.

2. Evidence from Nanoparticle-Based Preclinical and Clinical Studies

Preclinical and clinical studies have revealed important findings in the evaluation of the potential of nanoparticle-based STING agonist delivery systems in metastatic cancers. For example, in a preclinical study using metal complex lipid-based nanoparticles, targeted delivery of STING agonists to lung cancer cells resulted in significant increases in $CD8^+$ T-cell activity by increasing the release of proinflammatory cytokines such as IFN in the TME. This study demonstrated that nanoparticle-mediated STING activation has the potential to suppress tumor growth by triggering immunogenic cell death mechanisms. However, the lack of long-term in vivo studies and survival data limits the extent to which these findings can be generalized to human applications (59).

Another preclinical study revealed that STING agonist-loaded LNPs can overcome anti-PD-1 resistance through natural killer cell activation. Experiments conducted in a B16-F10 melanoma lung metastasis model demonstrated that STING-LNP treatment induced PD-L1 expression by increasing IFN-γ production, thereby exerting a synergistic antitumor effect with anti-PD-1. These findings indicate that STING-LNPs represent promising candidates for combination therapy in metastatic tumors resistant to anti-PD-1 treatment. Despite these promising results, the translational relevance remains uncertain due to interspecies differences in immune responses and TME factors (38).

In addition, a preclinical study using polymer-based nanoparticles revealed that PLGA nanoparticles provide long-term and controlled release of STING agonists, thus strengthening antitumor immunity by supporting sustainable IFN production in metastatic melanoma (41). Nevertheless, the immunomodulatory capacity of PLGA-based delivery systems requires further optimization, particularly regarding their pharmacokinetics and tumor-targeting specificity in heterogeneous tumor models (43).

Early-stage clinical studies suggest that delivery of STING agonists via lipid-based nanoparticles may enhance immune

response and reduce tumor burden (38). Phase I clinical trials have reported increased IFN-β-mediated immune activation in metastatic lung cancer patients treated with STING agonist-containing nanoparticles but limited treatment responses (36). While some patients have exhibited disease stabilization or partial response, the necessity for further investigation is evident (38).

While these studies support the potential of STING agonist-loaded nanoparticles in the treatment of metastatic cancer, they also demonstrate the need for further research into their clinical efficacy and safety.

3. Challenges and Future Perspectives

While nanoparticle-based delivery of STING agonists holds great promise in preclinical models, tumor-intrinsic resistance mechanisms, along with barriers to clinical translation, interfere with success. Tumors use a variety of mechanisms to inhibit activation of the STING pathway. One well-defined mechanism is hydrolysis of extracellular cGAMP by ectonucleotide pyrophosphatase/phosphodiesterase 1 (ENPP1), which limits paracrine immune signaling and dampens anti-tumor immunity via the STING pathway (59). In addition to hydrolysis, TME-mediated epigenetic silencing by transcriptional regulators (e.g., FOXM1) can downregulate cGAS-STING components, reducing cytosolic DNA sensing and IFN-I production (60, 61). Likewise, findings demonstrate that cGAS and STING are often mutated, muscles are missed, or, like TANK-binding kinase 1 and interferon regulatory factor 3 signaling downstream of STING, are deleted or mutated. Furthermore, even non-mutated STING has been shown to lead to immune tolerance with sustained STING activation, which could have a counterproductive effect of impairing antitumor immunity and thus low long-term efficacy of immune pathways (62).

The strong immunostimulatory effects of STING agonists can raise concerns at the clinical level of systemic inflammation, cytokine storm, autoimmunity, and other potential systemic toxicities of prolonged activation. STING agonists, as well as their nanocarrier formulations, could also potentially induce undesired immunogenicity that could activate the innate or adaptive immune pathways differently than intended and result in a decreased therapeutic benefit. There are also challenges that stem from manufacturing issues associated with Good Manufacturing Practice processes, which create additional barriers for reproducibility, scalability, and regulatory approval (58). Treatment is further complicated by the pharmacokinetics of STING agonists and interpatient variation associated with biodistribution of nanoparticles and overall clearance, or circulation half-life, which could create significant variability in therapeutic window and dosing requirements (13). Further concerns include biocompatibility of the nanoparticle formulation, stability, and continued post-marketing biodegradability that require extensive safety assessment in preclinical models and initiating some form of rapid escalating dosing through phase 1 studies (62, 63).

In consideration of such issues, future nanoparticle formulations will aim to provide controlled and local release of STING agonists, limiting systemic side effects while providing better specificity. Smart drug carrier formulations, biodegradable polymers, and multimodal therapeutic formulations with chemotherapy/radiotherapy or checkpoint blockade immunotherapy are some potential strategies to enhance the duration of therapy and overcome resistance (58).

Thus, future research needs to combine approaches for overcoming tumor-intrinsic resistance (i.e., ENPP1 inhibition, epigenetic modulators, or synthetic agonists that could circumvent the inherent signaling deficiencies) with appropriate delivery platforms designed with an eye towards safety, reproducibility, and regulatory approval. Together, they may provide the opportunity for widespread clinical application of STING-based nanomedicines in anti-cancer immunotherapy.

Table 2 highlights important biological and translational obstacles, in addition to potential solutions, for the therapeutic targeting of the STING pathway.

Table 2: Challenges and potential solutions in therapeutic targeting of the STING pathway.

Challenges	Impact	Potential solutions
STING pathway inhibition (development of resistance)	Tumor cells can block STING activation by epigenetic changes or immunosuppressive mechanisms	New generation STING agonists, combination therapy with epigenetic modulators
Development of immune tolerance	Continuous STING activation may lead to tolerance formation and suppression of the immune response	Controlled release nanoparticle systems and dose optimization
Risk of systemic inflammation and autoimmune response	A strong immunostimulatory effect may increase the risk of treatment-related toxicity	Targeted STING activation and biocompatible carrier systems
Biocompatibility, stability, and biodegradability issues of nanoparticles	Needs to be evaluated for long-term safety and efficacy	Smart drug delivery systems, biodegradable polymers
Multimodal treatment requirement	STING activation alone may not be sufficient, combined approaches may be required	Combined treatment strategies with chemotherapy, immunotherapy, and radiotherapy

This table outlines key challenges encountered in developing and applying STING pathway modulators for cancer therapy, along with potential strategies to overcome these obstacles.
STING: Stimulator of interferon genes

CONCLUSION

The STING pathway has emerged as a pivotal target in cancer immunotherapy, particularly in addressing the complex immunosuppressive microenvironment characteristic of metastatic cancers. Despite its therapeutic promise, the clinical application of STING agonists remains hindered by challenges such as low bioavailability, systemic toxicity, and limited tumor specificity when administered directly. To overcome these limitations, nanoparticle-based drug delivery systems have been developed to enable localized, controlled, and sustained activation of the STING pathway within metastatic lesions.

Preclinical and early-phase clinical studies demonstrate that nanoparticle-mediated STING agonist delivery not only amplifies innate and adaptive immune responses but also contributes to the suppression of metastatic tumor growth. Nevertheless, critical challenges persist, including the fine-tuning of dosage, long-term immune regulation, and minimizing off-target immune-related toxicity. Future research should prioritize the engineering of next-generation, biocompatible, and tumor-targeted nanoparticle systems that maximize immunotherapeutic efficacy while minimizing adverse effects.

In this context, STING-targeted nanoparticle platforms hold substantial translational potential for the treatment of metastatic cancers. Advancing these technologies through rigorous preclinical validation and well-designed clinical trials will be essential for their integration into standard oncologic practice.

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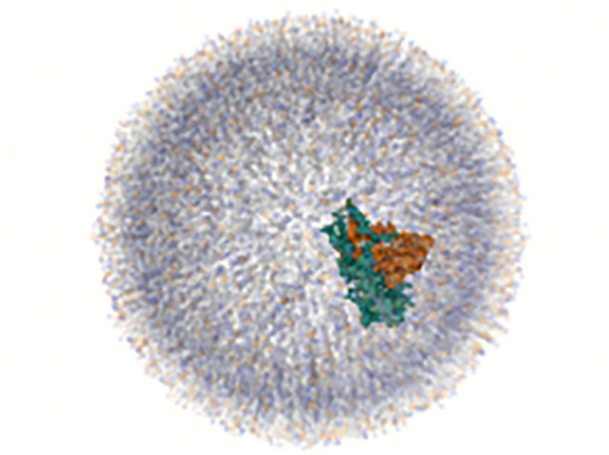

Supplementary Video 1: 3D animation showing the docking of a STING agonist with a liposomal nanoparticle. The animation demonstrates the spatial orientation and interaction interface between the STING agonist and the liposome surface. The molecular structures were visualized using Mol* after molecular docking (with HDOCK), and the dynamic rotation highlights the predicted binding region.
3D: Three-dimentional, STING: Stimulator of interferon genes

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REVIEW

THE IMPACT OF GENETIC AND EPIGENETIC FACTORS ON MAJOR DEPRESSIVE DISORDER

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ABSTRACT

Major depressive disorder is a serious and highly common mental illness that has negative effects on public health. Side effects of antidepressant medications and the cost of long-term treatments become a huge burden to both individuals and the healthcare system. Studying the genetic and epigenetic foundations of this disorder is essential for understanding how it develops and for creating personalized treatment strategies. This review aims to investigate the positive association of genetic and epigenetic factors with major depressive disorder. Our hypothesis posits that genetic and epigenetic alterations play a crucial role in the pathogenesis of depression. The findings derived from this review are expected to contribute to the advancement of more effective management strategies for depression and the development of personalized therapeutic interventions, thereby informing the formulation of comprehensive public health policies aimed at prevention and improvement.

Keywords: Epigenetics, gene expression, major depressive disorder

INTRODUCTION

Major depressive disorder (MDD) is a highly prevalent psychiatric illness that significantly impairs an individual's functioning and represents a significant global public health concern (1, 2). It is estimated that approximately 280 million people worldwide are affected by MDD, leading not only to a marked reduction in quality of life but also to substantial economic burdens on healthcare systems (3).

From an etiological perspective, MDD is a multifactorial disorder that cannot be attributed to a single cause (2, 4, 5). Instead, it emerges from the complex interplay between genetic predispositions, environmental stressors, neurobiological dysregulation, and epigenetic modifications (4, 6, 7).

Conrad Waddington defined epigenetics as "the branch of biology which studies the causal interactions between genes and their products which bring the phenotype into being" in the early 1940's. Over the years, the term has come to mean "the study of heritable changes in gene function that do not involve changes in the deoxyribonucleic acid (DNA) sequence. "These changes, influenced by environmental factors such as stress and early-life experiences, can alter gene expression and affect susceptibility to disorders like depression (8).

Recent studies have emphasized the critical role of genetic polymorphisms and epigenetic mechanisms in determining individual vulnerability to depression (6-10). Genes associated with neurotransmitter systems, regulation of the hypothalamic-pituitary-adrenal (HPA) axis, neurotrophic signaling pathways, and neuroinflammatory processes have been identified as key components in the pathogenesis of the disorder (11-15).

Studies reveal that molecular candidates such as solute carrier family 6 member 4 (*SLC6A4*), monoamine oxidase A (*MAOA*), nuclear receptor subfamily 3 group C member 1 (*NR3C1*), brainderived neurotrophic factor (*BDNF*), and FK506 binding protein 5 (FKBP5) are frequently reported to be associated with MDD. Both structural variations and epigenetic modifications in these genes are believed to influence the onset, progression, and treatment response of depression (10, 12, 16, 17). Notably, early-life stressors have been shown to induce methylation changes in

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these genes, which may lead to dysregulation of the HPA axis and increased susceptibility to depressive disorders (7, 9, 18, 19).

This review aims to provide a comprehensive analysis of the genetic and epigenetic mechanisms associated with MDD, based on systematic reviews published over the past five years. The findings are expected to contribute to a deeper understanding of the molecular underpinnings of MDD and to support the development of more personalized therapeutic approaches.

The Solute Carrier Family 6 Member 4

Solute carrier family 6 member 4 gene, which encodes the serotonin transporter protein, plays a central role in depression's neurobiology by regulating serotonin reuptake in the synaptic cleft (20). Genetic polymorphisms and epigenetic alterations in *SLC6A4* have been implicated not only in modulating individual vulnerability to depression but also in determining disease severity (21). The serotonin transporter long promoter region (5-HTTLPR) polymorphism located in the promoter region of the *SLC6A4* gene influences depression development by altering serotonin transport. Moreover, this polymorphism has been shown to affect the response to selective serotonin reuptake inhibitors (SSRIs) (21). Increased methylation levels of *SLC6A4* suppress gene expression, disrupt serotonin transport, and elevate the risk of depression (22). However, the definitive relationship between *SLC6A4* methylation and SSRI treatment response remains unclear. Therefore, the potential of methylation as a reliable biomarker for depression therapy is still under investigation (23). Additionally, microRNAs (miRNAs) have been demonstrated to play a significant role in the pathophysiology of depression. Elevated levels of miR-17 and miR-92, along with decreased levels of miR-4775, have been observed in patients with depression. These miRNAs are reported to target the *SLC6A4* gene, influencing stress responses and hippocampal neurogenesis processes (24). Furthermore, the pronounced expression of miR-17 in individuals with a history of physical neglect and miR-92 in those with a history of sexual abuse suggests that childhood trauma may increase depression risk through epigenetic mechanisms (24).

The Monoamine Oxidase A

Monoamine oxidase A gene plays a critical role in the pathophysiology of depression. *MAOA* is responsible for metabolizing serotonin, dopamine, and norepinephrine, thereby regulating their levels and contributing to the maintenance of neural system homeostasis (25). Specific variations in the *MAOA* gene have been shown to influence the metabolism of serotonin and norepinephrine, thereby increasing individual susceptibility to depression. Elevated *MAOA* activity may accelerate the breakdown of these neurotransmitters, potentially triggering the onset of depression (22). Additionally, dysregulation of the HPA axis and increased cortisol levels have been linked to *MAOA* activity. Chronic stress has been reported to elevate *MAOA* levels, accelerating the degradation of serotonin, dopamine, and norepinephrine. Studies conducted on animal models have demonstrated increased activity of both *MAOA* and monoamine oxidase B in subjects under stress, which has been linked to depression-like behaviors (26). Pharmacological studies have demonstrated that *MAOA* inhibitors can suppress enzyme activity, thereby increasing serotonin and dopamine levels (11). Specifically, certain pharmacological agents are believed to inhibit the *MAOA* enzyme, thereby enhancing neurotransmitter concentrations, making this mechanism a potential target for depression treatment (26). In addition to genetic variations, environmental stressors appear to regulate *MAOA* activity through mechanisms that are likely epigenetic in nature. For instance, chronic stress has been shown to increase *MAOA* levels and accelerate serotonin, dopamine, and norepinephrine degradation, contributing to depressive symptoms (11, 27). Such stress-related increases in *MAOA* activity suggest possible epigenetic modifications, including DNA methylation changes in promoter regions or histone alterations, which may sustain higher enzyme expression. Furthermore, *MAOA* has been identified among reliable risk genes for MDD (28), reinforcing the idea that genetic predisposition interacts with environmentally induced epigenetic regulation to shape individual vulnerability to depression. Overall, the *MAOA* gene is considered a significant risk factor in the genetic basis of major depression. While hundreds of genes associated with depression risk have been investigated, the critical role of *MAOA* in the biology of depression is particularly emphasized (27).

The Nuclear Receptor Subfamily 3 Group C Member 1

Nuclear receptor subfamily 3 group C member 1 gene encodes the glucocorticoid receptor (GR), which is sensitive to stress hormones and is critical for regulating the HPA axis (20). Hyperactivation of the HPA axis and elevated cortisol levels are considered key biological mechanisms that increase the risk of depression. Chronic stress can disrupt an individual's stress response by affecting GRs via *NR3C1*, thereby enhancing susceptibility to depression (20). Studies have found that individuals exposed to prolonged stress during childhood exhibit increased expression levels of the *NR3C1* gene. This upregulation may alter GR sensitivity, thereby disrupting normal stress responses (18). Epigenetic modifications in the *NR3C1* gene have been shown to influence an individual's ability to cope with stress, with methylation levels at specific cytosine-phosphate-guanine (CpG) sites correlating with psychological resilience. For instance, lower methylation at the CpG 2 site is associated with greater resilience, whereas higher methylation at the CpG 4 site has been linked to prenatal depressive symptoms. It has been suggested that interpersonal traumas experienced during childhood can induce methylation changes in *NR3C1* CpG regions, potentially contributing to the development of depression (29). Beyond its role in the HPA axis, the *NR3C1* gene has also been implicated in depression through its influence on brain cholesterol metabolism and synaptic plasticity (14). Recent studies have indicated a potential link between the *NR3C1* gene and neuroinflammatory processes. It has been reported that class II transactivator interacts with depression-associated genes such as *NR3C1*, prostaglandin-endoperoxide synthase

2, and glycogen synthase kinase-3 beta, suggesting that these interactions may contribute to depression development via immune system pathways (13). Overall, the *NR3C1* gene plays a critical role in depression development through multiple biological processes, including HPA axis regulation (12), epigenetic modifications (30), neuroinflammation, and synaptic plasticity (14). Alterations in its expression status can affect an individual's ability to cope with stress and their susceptibility to depression (12).

Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor is a key neurotrophic protein that supports the survival, growth, and differentiation of neurons. By regulating synaptic plasticity, it plays a crucial role in cognitive functions and mood regulation (31, 32). Findings indicate that *BDNF* levels are significantly decreased in patients with MDD, and this reduction contributes to the pathophysiology of depression through various neurological and molecular mechanisms. In the presence of elevated blood glucose alongside stress, *BDNF* levels remain suppressed for a prolonged period, which may impair neuronal growth and plasticity. Furthermore, this condition can exacerbate neuroinflammation, potentially leading to brain volume reduction (33). Animal studies have demonstrated significantly lower *BDNF* levels in the group exposed to both stress and high blood glucose compared to control subjects (33). A reduction in *BDNF* levels in MDD patients has been associated with decreased CAMP responsive element binding protein 1 (CREB) expression and phosphorylation. CREB, a key transcription factor involved in the pathogenesis of depression and mechanisms of treatment response, has been shown to have increased phosphorylation at the Ser133 site following chronic antidepressant treatment, which in turn elevates *BDNF* and Tropomyosin Receptor Kinase B levels (30). However, studies on depression models have reported variable *BDNF* alterations across different brain regions. While the decrease in *BDNF* is more pronounced in the hippocampus, changes in the frontal cortex have been less consistent (34). Postmortem studies have also demonstrated significantly reduced *BDNF* levels in individuals who died by suicide, with this reduction being associated with increased suicide risk. Patients with a history of suicide attempts exhibited lower *BDNF* concentrations compared to those diagnosed with MDD who had not attempted suicide (31, 35). Following repetitive transcranial magnetic stimulation treatment in depressed patients, notable increases in *BDNF* levels alongside reductions in oxidative stress markers have been observed (35). Moreover, depressed individuals not receiving antidepressant therapy showed significantly lower *BDNF* levels compared to those undergoing treatment (35). Changes in miRNA expression have been found to modulate *BDNF* expression, potentially triggering depressive symptoms. These findings suggest that miR-182 and other related miRNAs could serve as biomarkers for the diagnosis and treatment of depression.

Epigenetic mechanisms play a crucial role in regulating *BDNF* expression in depression. DNA methylation and histone modifications at the *BDNF* gene locus can suppress its transcription, linking early-life stress and environmental exposures to reduced *BDNF* levels (24, 31, 32). Additionally, specific miRNAs, such as mir-17 and mir-92, modulate *BDNF* expression post-transcriptionally, with dysregulation contributing to stress susceptibility and depressive phenotypes (24). Notably, interventions including antidepressant treatments and physical exercise may partially reverse these stress-induced epigenetic alterations, restoring *BDNF* expression and promoting synaptic plasticity (30, 36).

Brain-derived neurotrophic factor is initially synthesized as precursor-pro *BDNF* and subsequently processed into precursor *BDNF* (proBDNF) and mature *BDNF* (mBDNF) forms. While proBDNF has been shown to exert detrimental effects on neuronal cells, mBDNF supports neuronal survival and plasticity. In patients with MDD, elevated proBDNF levels alongside decreased mBDNF levels and a reduced mBDNF/proBDNF ratio have been observed. It is suggested that SSRI antidepressant treatments help restore this balance (37). Additionally, natural interventions such as physical exercise have been shown to increase *BDNF* levels, producing antidepressant-like effects (36).

Fk506 Binding Protein 5

FK506 binding protein 5 is a key regulator of GR sensitivity and stress response (12). Due to its role in modulating the HPA axis, *FKBP5* has been implicated in MDD across multiple studies. Epigenetic modifications and expression levels of *FKBP5* may critically influence an individual's susceptibility to depression and stress reactivity (16).

Childhood trauma has been associated with epigenetic modifications of *FKBP5*, with differential CpG methylation levels observed in intron 7 of the *FKBP5* gene during this process. Notably, individuals carrying the risk allele rs1360780 of *FKBP5* exhibit demethylation in this region following exposure to childhood trauma (38). Chronic stress and early-life adversity can induce persistent epigenetic modifications in *FKBP5*, including DNA methylation changes in regulatory regions, which influence GR sensitivity and HPA axis reactivity (38, 16). Epigenetic regulation of *FKBP5* may also interact with other stress-related genes, such as *NR3C1*, modulating both neuroendocrine and neuroinflammatory pathways implicated in depression (12, 13). However, some studies have failed to establish a clear relationship between *FKBP5* methylation and depression susceptibility (16). Hyperactivation of the HPA axis has been identified as a key mechanism in the pathogenesis of depression (18, 12). It has been demonstrated that GR function is regulated by a molecular chaperone associated with Heat Shock Protein 90, and *FKBP5* negatively impacts this process by inhibiting ligand binding and nuclear translocation of GR (12). Elevated levels of *FKBP5* may suppress the negative feedback mechanism mediated by GR, thereby contributing to the development of depression (18). *FKBP5* expression has been found to positively correlate with cortisol levels. In patients with depression, *FKBP5* levels were significantly lower compared to

control groups. Furthermore, the increase in GR levels alongside the decrease in *FKBP5* levels has been proposed as a characteristic biological marker in individuals with depression (18). In youths with depressed mothers, *FKBP5* expression was significantly lower compared to those without depressed mothers (18). *FKBP5*, together with *NR3C1*, encodes key proteins that regulate the stress response via the HPA axis, and *FKBP5* is a determinant of stress sensitivity (9, 12). Due to *FKBP5*'s role in the HPA axis and stress response, it is considered an important target for understanding the genetic basis of depression (9, 12). Some evidence suggests that *FKBP5*-targeted interventions, including pharmacological treatments or lifestyle modifications, could potentially reverse stress-induced epigenetic dysregulation, thereby normalizing HPA axis function (30, 38).

CONCLUSION

Each gene examined in this review points to different but interconnected biological processes involved in the pathogenesis of depression. While genetic make-up determines an individual's susceptibility to depression, environmental factors -particularly stress- play a decisive role in the manifestation of this susceptibility (29). Evidence suggests that adverse experiences during childhood leave lasting marks on the epigenetic regulation of certain genes, and these changes can alter an individual's stress response later in life (9, 18, 19). For example, epigenetic modifications in *NR3C1* and *FKBP5* have been shown to mediate gene-environment interactions, linking early-life trauma to altered HPA axis function and increased vulnerability to depression (16, 18, 38). Similarly, changes in *BDNF* methylation and miRNA regulation can disrupt neuronal plasticity and cognitive processes, further contributing to depressive symptoms (31, 32, 24). This indicates that depression is not solely a genetic condition but rather a disorder shaped by lifelong environmental interactions.

Our research also reveals that the biological basis of depression is too complex to be reduced to a single mechanism. Various pathways, ranging from the serotonin transport system (21) to the regulation of the HPA axis (12), neuronal plasticity (14), and neuroinflammation (13), highlight the necessity of a holistic approach to explain how depression affects both mood and cognitive functions. Moreover, interactions between genetic polymorphisms and epigenetic modifications in these pathways may determine not only disease susceptibility but also severity, course, and comorbidities of depression (7, 15, 29). Furthermore, genetic and epigenetic variations have been observed to influence individuals' responses to antidepressant treatments (21, 23). Studies suggest that targeting epigenetic mechanisms, could enhance treatment efficacy and promote sustained remission in MDD patients (30, 38). This suggests that treatment should not only focus on symptoms but also target the underlying biology.

Developing personalized treatment approaches could be particularly effective in cases of treatment-resistant depression. In conclusion, depression is a multifactorial disorder shaped by the interaction of genetic predisposition, epigenetic regulation, and environmental factors. A deeper understanding of these interactions will allow the identification of predictive biomarkers, the optimization of individualized therapies, and potentially the prevention of disease onset in high-risk populations (6, 10, 16, 29). A better understanding of this interaction is crucial for both preventing the disease and developing more effective and lasting treatment strategies.

Ethics

Acknowledgments

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ORIGINAL ARTICLE

ASSESSING THE PERFORMANCE OF WIDELY USED LARGE LANGUAGE MODELS ACROSS MEDICAL DISCIPLINES USING USMLE-STYLE EXAM QUESTIONS: AN IN-DEPTH EVALUATION

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ABSTRACT

Aims: Large language models are increasingly used in medical education and clinical decision-making. While previous studies have demonstrated that individual large language models can perform well on standardized medical exams, comparative evaluations across multiple large language models and medical disciplines remain limited. This study aimed to evaluate and compare the performance of seven large language models-generative pre-trained transformer-4o, DeepSeek-R1, DeepSeek-V3, Llama 3.3, Gemini 2.0 Flash, Claude 3.7 Sonnet, and OpenBioLLM on United States Medical Licensing Examination -style multiple- choice questions.

Methods: A total of 1000 questions were randomly selected from 25 medical disciplines from AMBOSS question-bank, excluding those with images, tables or charts. Each model was prompted with a standardized system and user instruction designed to produce a single letter answer without explanation. Evaluations were conducted across three independent runs per model using a temperature of 0.0; for models supporting seed control, predetermined seeds were used to ensure reproducibility. Version identifiers and access dates were documented to ensure reproducibility.

Results: Generative pre-trained transformer-4o achieved the highest accuracy (89.3%), followed by DeepSeek-R1 (87.0%) and Llama 3.3 (84.1%), while OpenBioLLM and DeepSeek-V3 scored the lowest (78.2% and 76.5%, respectively). Generative Pre-Trained Transformer-4o led in 14 of 25 disciplines, especially clinical ones, while DeepSeek-R1 excelled in public health-oriented subjects. Performance varied significantly across disciplines, with infectious diseases (91.4%), psychiatry (91.1%), and behavioral science (89.3%) showing the highest scores, while cardiology (67.5%) and genetics (76.1%) were the most challenging areas.

Conclusion: Generative pre-trained transformer-4o and DeepSeek-R1 outperformed other models across a wide range of medical disciplines. However, substantial variability across disciplines and models highlights current limitations in large language model reasoning, particularly in complex fields like cardiology. While these findings highlight the potential of large language models in medical education, further development and rigorous validation are required before they can be reliably integrated into clinical practice and medical education.

Keywords: Artificial intelligence, large language models, medical education

INTRODUCTION

Large language models (LLMs) are becoming essential tools across numerous fields, including medicine (1). Initially, LLMs were primarily developed by major technology companies using proprietary, closed-source frameworks, such as OpenAI's generative pre-trained transformer (GPT) series and Google AI's Gemini. However, the emergence of open-source LLMs is reshaping the field by expanding accessibility and flexibility, and creating new opportunities, particularly in the medical field.

The potential applications of such tools in medical education and clinical practice are being increasingly explored and their scope is expanding to address the needs of a broad audience ranging from medical students to experienced healthcare providers (2). As such, evaluating the performance of LLMs in medical knowledge assessment has become a key area of research interest, with

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numerous studies analyzing their ability to accurately answer questions from standardized medical exams to third-party question banks (3, 4).

Given the complex nature of questions used in medical exams, which requires both the ability to apply medical knowledge and clinical reasoning in real-world scenarios, medical students often refer to third-party resources including LLMs such as ChatGPT, DeepSeek and others (5). Notably, ChatGPT has been shown to achieve scores above the required threshold for Step 1, Step 2 clinical knowledge, and Step 3 United States Medical Licensing Examination (USMLE) exams (6). Recent research has also shown that DeepSeek-R1 demonstrates medical reasoning capabilities, suggesting its promising role in medical education and clinical decision-making (7). However, the accuracy of these tools may vary across disciplines, performing well in certain disciplines while generating false interpretations and reasonings in others.

Although previous research has demonstrated that individual LLMs can successfully pass specific medical licensing exams (8, 9), there is a lack of studies that compare the performance of the latest LLMs across different disciplines of medicine. In this study, we aim to assess the performance of multiple LLMs, including both proprietary and open-source models, in answering USMLE-style questions derived from AMBOSS, a third-party USMLE-style question-bank, covering both preclinical and clinical medical disciplines.

MATERIALS AND METHODS

This study did not require research ethics approval as it did not involve human subjects. To compare the performance of various LLMs, the study utilized 1000 USMLE-style multiple-choice questions (MCQs) sourced from AMBOSS (10), a non-public widely used medical education platform with a comprehensive question bank, to prevent learning effects and eliminate bias from publicly accessible question sets. To ensure diversity across different disciplines, 40 text based questions were randomly selected using a random number generator from each of the 25 medical disciplines (allergy and immunology, anatomy and embryology, behavioral science, biochemistry, biostatistics and epidemiology, cardiology, endocrinology, gastroenterology, genetics, hematology, histology and molecular biology, infectious diseases, legal medicine and ethics, microbiology, nephrology, neurology, obstetrics and gynecology, pathology, pediatrics, physiology, psychiatry, public health, pulmonology, rheumatology, and surgery) across different blocks. To ensure compatibility with LLM interfaces, questions that included images, charts, or tables were excluded. The final dataset included the question stem, five answer options (A-E), the correct answer (ground truth), and the corresponding category label. The question set likely reflects Step 1 content, though difficulty level was not formally stratified.

Seven LLMs were evaluated in this study (Supplementary Material S1). GPT-4o was accessed via the official OpenAI application programming interface (API) on March 13, 2025. Claude 3.7 Sonnet was accessed on March 13, 2025, and Gemini 2.0 Flash on March 15, 2025, both via their respective official APIs. Llama 3.3 70B was accessed through the Groq API on March 14, 2025. OpenBioLLM 70B, DeepSeek-V3, and DeepSeek-R1 were accessed via the Nebius API on March 19, 2025. These version identifiers and access dates were documented to ensure full transparency and reproducibility, as LLM capabilities may evolve over time with ongoing model updates. The models were used with their default parameters as provided by the official APIs, without further optimization or fine-tuning.

Each model received a standardized prompt comprising a system-level instruction and a user-level message. The system prompt instructed the model to act as a highly knowledgeable medical expert with extensive experience in clinical reasoning and to select the most evidence-based and clinically appropriate answer without explanation. The user prompt presented the question stem followed by the five answer choices labeled A-E and instructed the model to respond with only a single uppercase letter corresponding to its answer, without any punctuation or explanation. This prompt was applied uniformly across all runs and models.

Each model was evaluated across three independent runs to assess the consistency of performance. For models that support deterministic outputs via seed control (GPT-4o, Gemini 1.5 Flash, Llama 3.3 70B, DeepSeek V3, DeepSeek R1, and OpenBioLLM 70B), distinct predetermined random seeds were used for each run as recommended in recent work on reproducible LLM evaluation (11). A random seed serves as a fixed numerical starting point that regulates the model's internal randomization; by fixing the seed, the same input under the same conditions is expected to produce the same output, thereby enabling reproducibility. Varying the seed across runs allowed evaluation of performance under controlled, replicable conditions. The Claude 3.7 Sonnet model does not currently support seed control; hence, its responses were treated as stochastic across trials.

The temperature parameter was set to 0.0 for all models. In LLMs, temperature is a hyperparameter that influences the probability distribution used during text generation: higher temperatures increase variability by allowing the model to select less likely tokens, while lower temperatures narrow the distribution, producing more focused and deterministic outputs. Setting the temperature to 0.0 effectively eliminates randomness in token selection. This forces the model to consistently choose the most probable next token at each step, ensuring stable outputs across runs (12).

Output post-processing was minimal; however, for DeepSeek models, structured reasoning tags (e.g., <THINK>) were removed to isolate the final answer selection. No additional preprocessing was applied to the output of other models.

Statistical Analysis

All analyses were conducted in R (version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria). Accuracy was defined

as the proportion of correct responses for each of the seven language models. To assess whether overall accuracy differed among models, a global chi-square test of independence was performed on the 7×2 contingency table of model by response correctness. Upon obtaining a significant global χ^2 result (α=0.05), pairwise comparisons of proportions between every pair of models were carried out using two-sided chi-square tests. P-values below 0.05 were considered statistically significant.

RESULTS

A total of 1000 MCQs from 25 medical disciplines were administered to seven LLMs: GPT-4o, DeepSeek-R1, DeepSeek-V3, Llama 3.3, Gemini 2.0 Flash, Claude 3.7 Sonnet, and OpenBioLLM. Accuracy was defined as the proportion of correctly answered questions in each discipline. A detailed breakdown of accuracy for each LLM across different disciplines is provided (Table 1). Overall, GPT-4o achieved the highest average accuracy (89.3%), followed by DeepSeek-R1 (87.0%) and Llama 3.3 (84.1%). Gemini 2.0 Flash reached 82.7% and Claude 3.7 Sonnet 81.2%, while OpenBioLLM and DeepSeek-V3 recorded the lowest scores at 78.2% and 76.5%, respectively.

When analyzed across individual disciplines, GPT-4o outperformed all other models, achieving the highest score in 14 of the 25 disciplines, predominantly within clinical areas such as pulmonology and infectious diseases. DeepSeek-R1 closely followed, leading in 11 disciplines, with particularly strong results in population health domains like biostatistics and public health. While Claude 3.7 Sonnet, Llama 3.3 and Gemini 2.0 Flash showed the highest accuracy in a limited number of, neither OpenBioLLM nor DeepSeek-V3 ranked highest in any of the assessed disciplines (Figure 1). Overall, there was a statistically

Table 1: Overall accuracy of each model and its performance across medical disciplines.

Medical Specialties	LLM performance, accuracy ratio (%)						
	Claude 3.7 Sonnet	DeepSeek-R1	DeepSeek-V3	Gemini 2.0 flash	GPT-4o	Llama 3.3	OpenBio
Overall							
All questions	**81.2%**	**87.0%**	**76.5%**	**82.7%**	**89.3%**	**84.1%**	**78.2%**
Allergy and immunology	77.5%	87.5%	77.5%	80.0%	82.5%	82.5%	70.0%
Anatomy and embryology	90.0%	90.0%	87.5%	87.5%	90.0%	82.5%	80.0%
Behavioral science	92.5%	90.0%	85.0%	92.5%	90.0%	85.0%	90.0%
Biochemistry	72.5%	87.5%	70.0%	75.0%	85.0%	82.5%	80.0%
Biostatistics and epidemiology	85.0%	90.0%	80.0%	77.5%	77.5%	85.0%	80.0%
Cardiology	55.0%	75.0%	52.5%	65.0%	82.5%	67.5%	75.0%
Endocrinology	85.0%	82.5%	72.5%	82.5%	90.0%	87.5%	65.0%
Gastroenterology	80.0%	90.0%	77.5%	85.0%	97.5%	90.0%	82.5%
Genetics	75.0%	75.0%	65.0%	80.0%	92.5%	80.0%	65.0%
Hematology	82.5%	92.5%	77.5%	85.0%	90.0%	85.0%	90.0%
Histology and molecular biology	82.5%	90.0%	72.5%	80.0%	90.0%	87.5%	80.0%
Infectious diseases	95.0%	90.0%	92.5%	90.0%	97.5%	85.0%	90.0%
Legal medicine and ethics	90.0%	90.0%	77.5%	80.0%	82.5%	82.5%	82.5%
Microbiology	82.5%	87.5%	77.5%	87.5%	95.0%	80.0%	70.0%
Nephrology	72.5%	90.0%	72.5%	80.0%	87.5%	87.5%	70.0%
Neurology	77.5%	77.5%	77.5%	85.0%	92.5%	80.0%	80.0%
Obstetrics and gynecology	92.5%	82.5%	75.0%	92.5%	92.5%	87.5%	70.0%
Pathology	82.5%	87.5%	70.0%	85.0%	95.0%	85.0%	75.0%
Pediatrics	85.0%	90.0%	77.5%	77.5%	87.5%	90.0%	82.5%
Physiology	77.5%	80.0%	70.0%	72.5%	80.0%	77.5%	77.5%
Psychiatry	90.0%	97.5%	85.0%	87.5%	100.0%	90.0%	87.5%
Public health	77.5%	87.5%	75.0%	77.5%	85.0%	70.0%	75.0%
Pulmonology	72.5%	87.5%	85.0%	85.0%	92.5%	85.0%	87.5%
Rheumatology	72.5%	87.5%	77.5%	87.5%	87.5%	90.0%	67.5%
Surgery	85.0%	90.0%	82.5%	90.0%	90.0%	97.5%	82.5%

LLM: Large language model, GPT: Generative pre-trained transformer

significant difference in accuracy among the seven LLMs (χ^2 test, p<0.001). Pairwise comparisons revealed that GPT-4o achieved significantly higher accuracy than DeepSeek-V3, OpenBioLLM, Claude, and Gemini 2.0 (p<0.001 for all), establishing it as the top-performing model. DeepSeek-R1 also significantly outperformed both DeepSeek-V3 and OpenBioLLM (p<0.001), demonstrating consistent high performance. Llama 3.3 scored significantly higher than DeepSeek-V3 (p<0.05). No statistically significant differences were observed between GPT-4o and DeepSeek-R1, or among Claude, Gemini 2.0, and other non-leading models (Supplementary Material S2).

Discipline-Level Performance

Infectious diseases (n=6, 91.4%), psychiatry (n=4, 91.1%), and behavioral science (n=4, 89.3%) were the disciplines in which models achieved the highest average accuracies. Conversely, the lowest-performing disciplines were cardiology (n=6, 67.5%), physiology (n=5, 76.4%), biochemistry (n=5, 78.9%), and genetics (n=4, 76.1%) (Figures 2 and 3).

To assess whether LLMs performance varied between clinical and basic sciences, the 25 medical specialties were categorized into two groups: 12 basic science disciplines and 13 clinical science disciplines. Clinical disciplines such as infectious diseases and surgery generally achieved higher scores than basic science disciplines like biochemistry, genetics, and physiology; however, this difference was not statistically significant (p=0.055), and no LLM's performance differed significantly between the two groups.

Within-Model Across Discipline Performance

Statistically significant differences in performance across medical disciplines were observed in all 7 LLM. For Claude 3.7 Sonnet, performance in cardiology was significantly lower than in disciplines such as anatomy, psychiatry, and infectious diseases (p<0.05). DeepSeek-R1 performed better in psychiatry compared to several other disciplines. DeepSeek-V3 and Gemini 2.0 both showed reduced accuracy in cardiology relative to areas like infectious diseases and surgery (p<0.05). GPT-4o scored higher in psychiatry and infectious diseases than in biostatistics and epidemiology, and physiology. Llama 3.3 performed better in surgery and psychiatry than in cardiology and public health. OpenBioLLM showed higher accuracy in behavioral science and hematology than in genetics and endocrinology (p<0.05).

Within-Discipline Across Model Performance

GPT-4o consistently outperformed other models in cardiology, gastroenterology, genetics, microbiology, pathology, and psychiatry (p<0.05). In endocrinology, both GPT-4o (p=0.014) and Llama 3.3 (p=0.034) performed better than OpenBioLLM. OpenBioLLM also showed lower performance in nephrology and obstetrics and gynecology compared to multiple models. Additionally, Claude Sonnet 3.7 and Gemini 2.0 were significantly outperformed by GPT-4o in select disciplines.

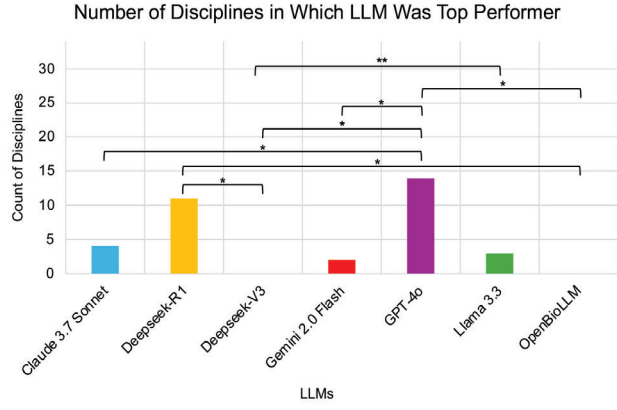

Figure 1: Number of medical disciplines in which each LLM was the top performer. This figure summarizes the distribution of first-place rankings across 25 medical disciplines. A top performer is defined as the model achieving the highest accuracy in each respective discipline. *indicates statistically significant difference at p<0.001; **Indicates statistically significant difference at p<0.05.
LLMs: Large language models, GPT: Generative pre-trained transformer

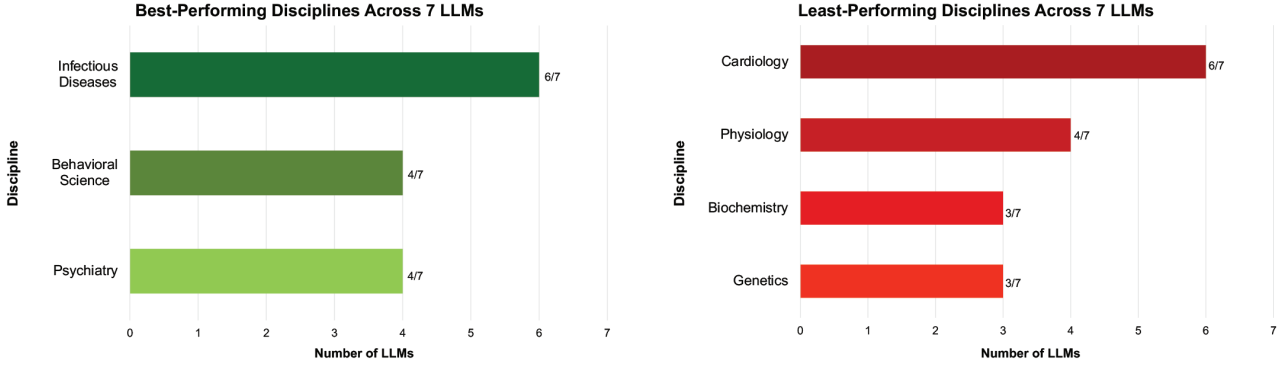

Figure 2: Best- and worst-performing medical disciplines across seven LLMs. Bars show the number of models that achieved the highest accuracy in each discipline (left) or the lowest accuracy (right), based on evaluations across 25 medical disciplines. Numbers at the end of each bar show how many models (out of 7) achieved that performance.
LLMs: Large language models

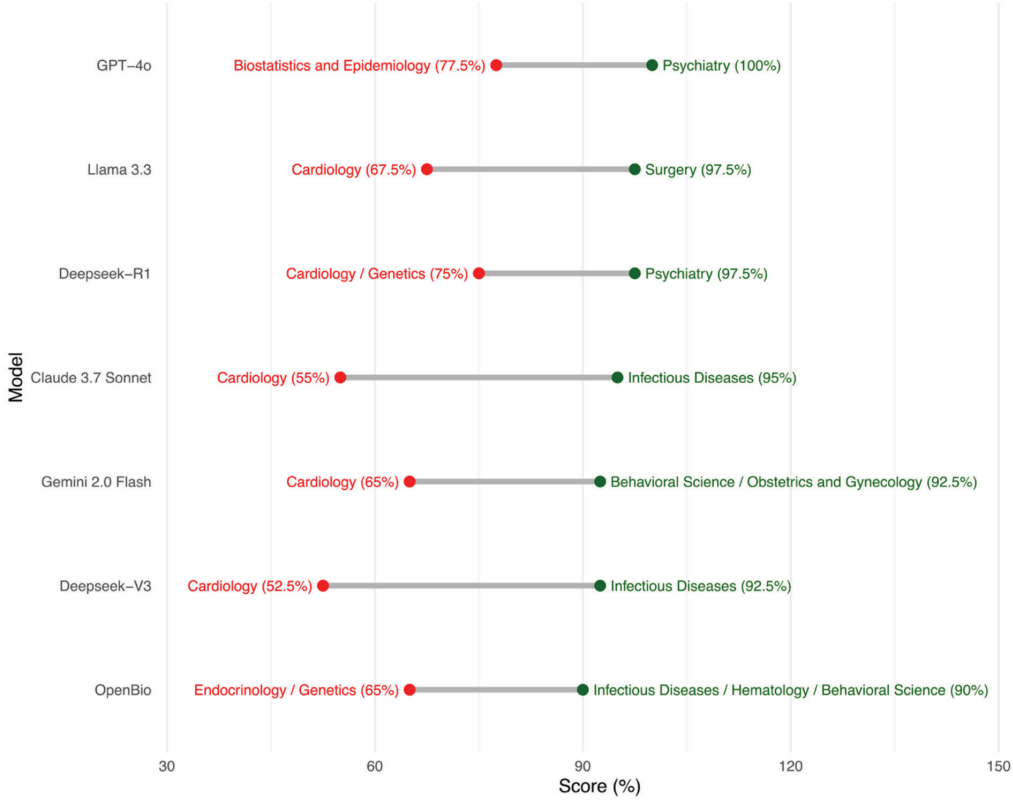

Figure 3: Best and worst performing medical disciplines for each LLM on USMLE-style questions. This dumbbell plot illustrates the highest- and lowest-performing medical disciplines for each LLM based on accuracy. Red dots indicate the lowest-performing disciplines and green dots indicate the highest-performing ones, with corresponding accuracy percentages shown in parentheses. This figure underscores the variability in domain-specific strengths and weaknesses among LLMs.
USMLE: United States Medical Licensing Examination, LLM: Large language model, GPT: Generative pre-trained transformer

When comparing across all specialties, the least variation in performance was observed in behavioral science (range 85.0% - 92.5%), whereas the greatest variation was noted in Cardiology (range 52.5% - 82.5%), highlighting disciplines where LLMs demonstrated stable versus highly divergent accuracy (Supplementary Material S3).

DISCUSSION

This study provides a comprehensive assessment of seven LLMs on 1000 USMLE-style questions from 25 medical disciplines. Among the evaluated models, GPT-4o and DeepSeek-R1 demonstrated comparable overall accuracy (89.3% and 87%, respectively), significantly outperforming DeepSeek-V3 (76.5%), OpenBioLLM (78.2%), Claude 3.7 Sonnet (81.2%), and Gemini 2.0 Flash (82.7%) ($p<0.001$). GPT's consistent success across more than half of the disciplines, particularly in clinical fields such as surgery and infectious diseases, suggests strong capabilities in both factual knowledge and applied clinical reasoning. Our findings confirm and extend prior work showing that GPT-4-based models consistently achieve high performance on medical knowledge tasks (13), underlining their potential utility in medical education and supporting earlier calls to strategically integrate high-performing LLMs into curricula (13). On the other hand, DeepSeek-R1 performed better in population health-oriented domains such as biostatistics and public health. While previous research has shown medical reasoning abilities of DeepSeek-R1, it exhibits limitations in more complex clinical scenarios (7). In contrast, OpenBioLLM and DeepSeek-V3 performed the worst, failing to lead in any single discipline. Although OpenBioLLM is specifically trained on biomedical content, its lower performance suggests that focusing only on medical material does not guarantee better overall performance in comprehensive medical exams like the USMLE.

A key finding from this study is the variation in LLM performance not only between models but also across different medical disciplines. On average, the highest-scoring areas were infectious diseases (91.4%), psychiatry (91.1%), and behavioral science (89.3%), while the lowest scores were observed in cardiology (67.5%), genetics (76.1%), and physiology (76.4%). These results suggest that certain areas of medicine are more compatible with current LLM capabilities, while others remain challenging across all models. The consistently poor performance across models in cardiology is particularly noteworthy, as this field often involves

complex cases and multiple health issues that require nuanced clinical reasoning, an area where LLMs commonly struggle (3). Our findings align with earlier studies showing that while LLMs like ChatGPT handle simple medical questions well, their performance drops with more complex clinical decision-making or specialized knowledge, sometimes producing incorrect or misleading answers (14). This may explain the lower accuracy seen in challenging areas like cardiology and genetics, where deeper reasoning is required.

When the 25 disciplines were grouped into basic sciences (e.g., biochemistry, pathology, physiology) and clinical sciences (e.g., pediatrics, surgery, infectious diseases), clinical subjects tended to score slightly higher. However, the overall difference was not statistically significant and no LLM in the study demonstrated a statistically significant difference in its own performance between basic and clinical sciences.

A strength of this study is the large and diverse question set, which systematically covers 25 medical disciplines and enables detailed comparisons across multiple models. Previous studies have compared only two or three LLMs on general question sets without focusing on discipline-specific performance. In addition, we evaluated two versions of the same LLM, allowing assessment of whether newer iterations demonstrated improved performance.

From an educational perspective, high-performing LLMs such as GPT-4o and DeepSeek-R1 could serve as useful assistants to medical training, particularly for reinforcing factual knowledge and supporting clinical reasoning in disciplines where their accuracy is consistently high. Future research should focus on expanding the analysis of USMLE-style questions by including imaging and multimedia content and covering a wide variety of clinical scenarios. This would provide a more comprehensive assessment of LLM capabilities and their ability to handle diverse, real-world clinical cases tested in the USMLE. Previous research indicates that it is important to identify which models perform better in specific contexts to enhance their practical applications, such as in diagnosis, treatment, and patient education (15). Additionally, future research is essential to improve and broaden these applications.

Study Limitations

This study contains several limitations. First, these questions are not actual USMLE exam questions, they are USMLE-style. All questions were sourced from AMBOSS, a widely used but proprietary platform. Thus, the discipline-level success rates reflect AMBOSS's specific question style and difficulty, which may limit applicability to actual exams. Future studies should use multiple question banks to improve generalizability. Second, it is important to note that no questions containing images, charts, or tables were included, in order to maintain consistency in comparison. While DeepSeek-R1 does not support image-based tasks, GPT-4o is capable of interpreting images. Lastly, as LLMs and their training data advance rapidly, the results of this work may not generalize to future iterations of these models.

CONCLUSION

In conclusion, while models like GPT-4o and DeepSeek-R1 demonstrated strong overall performance, all models showed notable variability depending on the medical discipline. While the potential of language models is considerable, it is important to interpret these findings carefully. Their limitations and risk of incorrect answers highlight the need for careful validation and further improvement before use in real healthcare or educational settings. Of note, while LLMs performed relatively well, it is important to recognize that becoming a physician involves far more than simply answering licensing exam questions correctly.

Ethics

Ethics Committee Approval: *This study did not require research ethics approval as it did not involve human subjects.*

Acknowledgments

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Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Surgical and Medical Practices: Z.S.Ö., B.B.K., E.A., Concept: Z.S.Ö., B.B.K., E.A., Design: Z.S.Ö., B.B.K., E.A., Data Collection or Processing: Z.S.Ö., B.B.K., Analysis and/or Interpretation: Z.S.Ö., E.A., Literature Search: Z.S.Ö., B.B.K., Writing: Z.S.Ö., B.B.K., E.A.*

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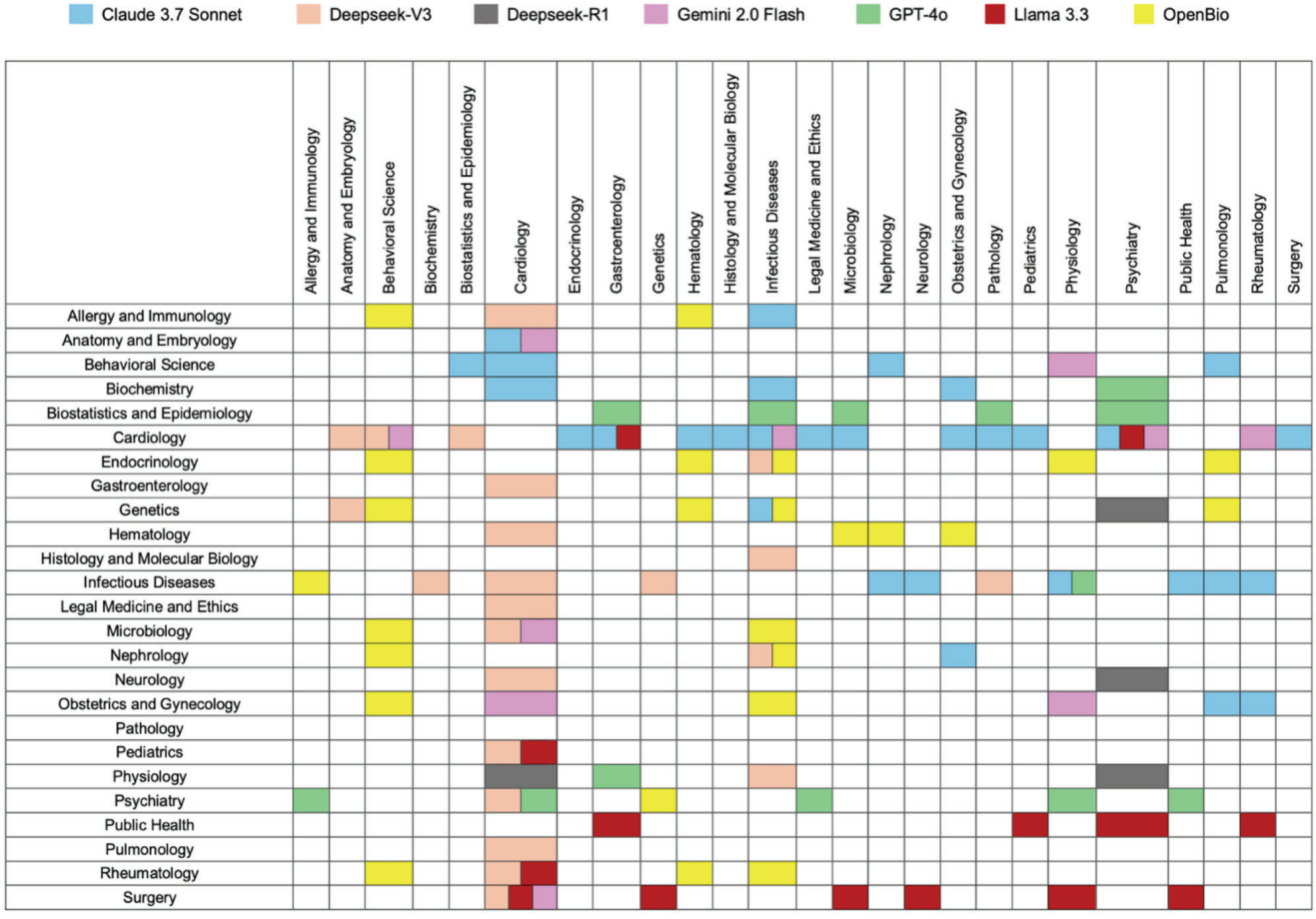
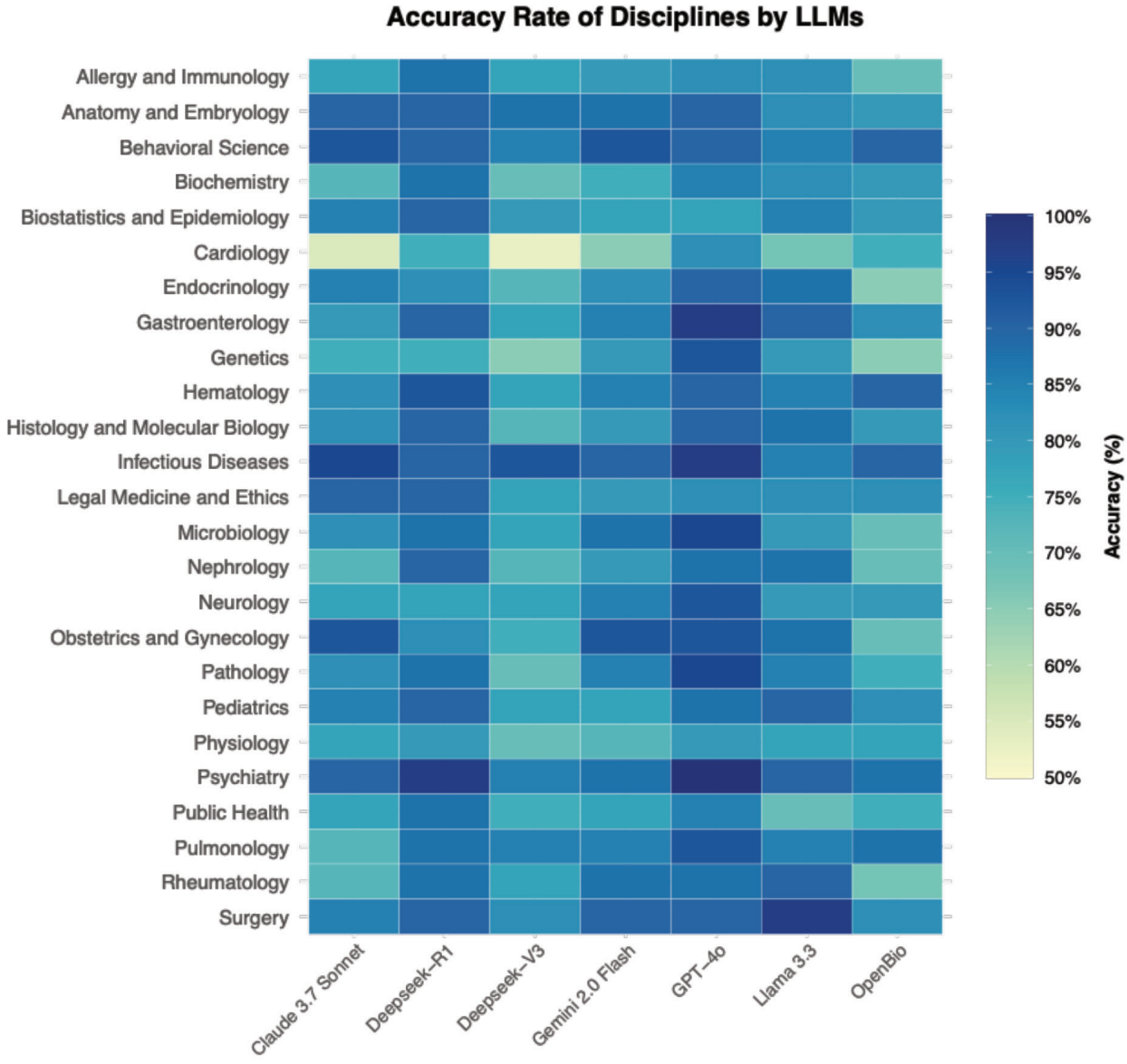
Supplementary Material S1: LLM configuration summary.

Model name	Version / identifier	API provider	Temperature	Seed support	Access date
GPT-4o	GPT-4o-2024-08-06	OpenAI API	0.0	✅ Yes	13 March 2025
Claude 3.7 sonnet	Claude-3-7-sonnet-20250219	Anthropic API	0.0	❌ No	13 March 2025
Gemini 2.0 flash	Gemini-2.0-flash (Feb 2025)	Google AI studio	0.0	✅ Yes	15 March 2025
LLaMA 3.3 70B	Meta-llama/Llama-3.3-70B-Instruct	Groq API	0.0	✅ Yes	14 March 2025
OpenBioLLM 70B	Aaditya/Llama3-OpenBioLLM-70B	Nebius API	0.0	✅ Yes	19 March 2025
DeepSeek V3	DeepSeek-ai/DeepSeek-V3	Nebius API	0.0	✅ Yes	19 March 2025
DeepSeek R1	DeepSeek-ai/DeepSeek-R1	Nebius API	0.0	✅ Yes	19 March 2025

This table provides an overview of the configuration details for each large language model evaluated in the study, including model version identifiers, API access sources, temperature settings, seed support status, and date of access. These parameters were standardized as much as possible to ensure comparability across models.
LLM: Large language model, API: Application programming interface, AI: Artificial intelligence, GPT: Generative pre-trained transformer



Supplementary Material S2: Pairwise comparisons between medical disciplines within each LLM. This cross-table shows statistically significant differences in performance between pairs of 25 medical disciplines across seven LLMs. Colored boxes indicate statistically significant differences in performance between disciplines for the corresponding LLM, with each LLM assigned a unique color (legend above the table). The absence of a colored box indicates no significant difference for any LLM. This cross-table highlights variation in discipline-specific performance across different LLMs.
LLM: Large language model, GPT: Generative pre-trained transformer



Supplementary Material S3: Heatmap showing the performance of each LLM across different medical disciplines. This heatmap illustrates the relative accuracy of LLM across 25 medical disciplines, based on responses to 1,000 USMLE-style multiple-choice questions. Each row represents a medical discipline, each column represents a LLM, and each box represents accuracy of that discipline in a particular LLM. Color intensity corresponds to performance, with darker shades indicating higher accuracy and lighter shades indicating lower accuracy (see color scale on the right).

USMLE: United States Medical Licensing Examination, LLM: Large language model, GPT: Generative pre-trained transformer

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CASE REPORT

PECTUS CARINATUM DEVELOPMENT AFTER THE NUSS PROCEDURE: A CASE REPORT

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ABSTRACT

Development of pectus carinatum is a very rare complication of the Nuss procedure. This complication may lead to early bar removal, which hinders sternal protrusion but induces the recurrence of pectus excavatum. We report a case of pectus carinatum development following a Nuss procedure and pectus excavatum recurrence after bar removal to discuss what could have been done better from today's perspective.

Keywords: Complications, funnel chest, minimally invasive surgery, pectus carinatum

INTRODUCTION

Pectus deformities include excavatum, carinatum, mixed-types and arcuatum. Those deformities are characterized by protrusion or depression and with or without rotation of the sternum due to the deformities of the costal cartilages or the sternum itself (1).

Pectus excavatum (PE), also called funnel chest, is accepted as the most common pectus deformity and characterized by sternal depression. Deformity may be congenital, up to 0.8% of newborns with PE deformity are noted but this ratio may be underreported (2). However, it should be considered that this deformity is not purely congenital. The majority of patients present with sudden depression of the sternum during the growth period or complain about the worsening of mild depression to severe depression (3).

Pectus carinatum (PC) is characterized by protrusion of the sternum and accepted as the second most common pectus deformity, whereas a study found that PC (0.86%) was more prevalent than PE (0.54%) in Turkish children (4).

Open surgery and reconstruction of the chest wall were mainstays for years, but the introduction of minimally invasive repair of PE, the Nuss procedure, has changed the era. The Nuss procedure uses pectus bar(s) inserted into the thorax to support the, thus correcting the deformity. Those bars are withdrawn after 2-3 years (5). Minimally invasive repair of PC, the Abramson procedure, has been developed upon this idea after all (6). Orthosis and vacuum bell treatments are new and effective treatment options for selected patients (7, 8). Surgery decisions are made jointly with patients' concerns and clinical judgments. While mostly body image concerns due to the appearance of their chest and psychosocial anxiety are motivating factors, in severe cases cardiac compression, mitral valve prolapse, and pulmonary function impairment may warrant the procedure as well (9).

Most of the complications related to the Nuss procedure, such as pneumothorax, pneumonia, and bar displacements, are well managed without causing serious comorbidities, but fatal cases due to cardiac perforation and lung injury were also reported in the literature (10-12). As bars are placed posterior to the sternum and anterior to the pericardium, excellent technique and maximum attention are required intraoperatively (13).

Development of PC, which is at the other side of the pectus spectrum compared to PE, after a Nuss procedure is very rarely reported in the literature. This case report presents an eight-year-old patient with PC development after a Nuss procedure and the recurrence of PE following bar removal.

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CASE REPORT

An eight-year-old female patient was brought to our clinic with a funnel chest. Our detailed physical examination and anamnesis revealed symmetrical and severe PE (Figure 1A). No accompanying diseases, family history, or previous surgeries were noted. The patient underwent a Nuss procedure with thoracoscopy in June 2011. A 220 mm-long bar was implanted in the patient using one stabilizer on the left end. No steel wires were used. The operation was performed successfully in 90 minutes without any perioperative complications (Figure 1B).

Excellent correction of the deformity was seen in the early postoperative period. No bulging area was noted within the postoperative three months. A significant sternal bump was noted in the postoperative sixth month. The patient was invited to the clinic in the postoperative seventh month for further evaluation of the chest. PC was noted in the seventh month, and bar removal surgery was planned (Figure 1C).

The bar removal was performed in the seventh month, which caused an indentation of the chest after 15 days. Ten months after bar removal (postoperative 17th month), significant PE was noted. The postoperative 36th month examination revealed worsened PE. The patient was seen and re-evaluated in the 55th and 120th months regarding PE (Figure 1D). The X-ray examination revealed the deformity of the chest during the same periods (Figure 2A-D).

DISCUSSION

Hereby, we have reported a case of a PE patient who had a very flexible sternum that was bent by the Nuss bars to a degree that is enough to cause PC. This flexibility would have likely induced the recurrence of PE after bar removal.

This clinical case is not similar to what Swanson and Colombani. (14) noted, where the development of PC was attributed to fibroelastic genetic disorders, as fibroelastic deficiencies were not noted in our patient. As Paya et al. (15) postulated in 2003, bar removal due to PC development hindered sternal protrusion, but early removal itself induced the recurrence of PE. Zhou et al. (16) reported one case of PC development after the Nuss procedure, and they suggested the patient use chest strap fixation, which is a kind of carinatum bracing, and did not remove the bar.

Donald Nuss found in his series that approximately 0.3% of patients developed PC after the Nuss procedure, and he suggested using carinatum bracing (5, 17).

A high-volume study found 0.8% overcorrection in their Nuss series, where most of those patients underwent premature bar removal just as our patient did (18).

We have reasoned that the patient's condition could have been managed better if it had been investigated from today's perspective.

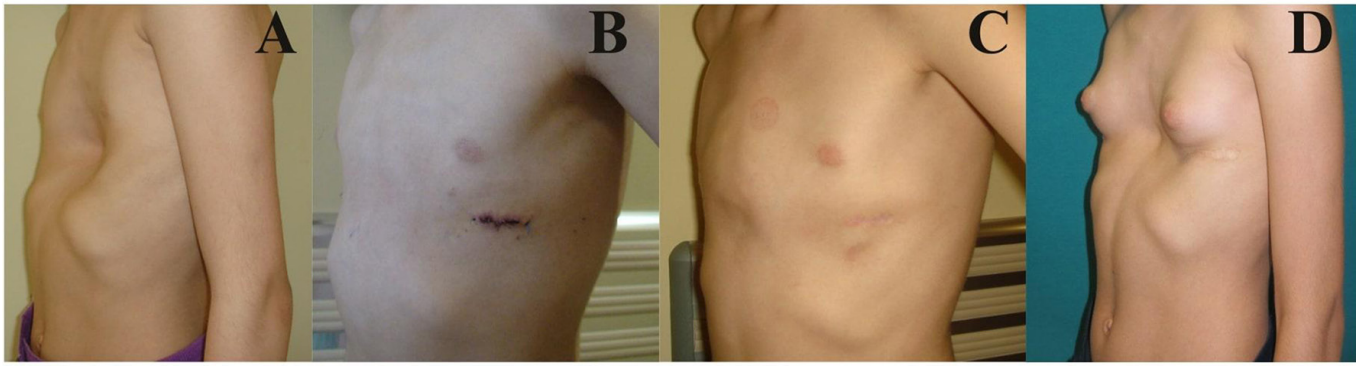

Figure 1: The patient's chest before the Nuss procedure (A). The patient's chest after the Nuss procedure (B). The patient's chest seven months after the Nuss procedure, before bar removal due to the development of pectus carinatum (C). The patient's chest four years after bar removal (55th month) due to the development of pectus carinatum (D).

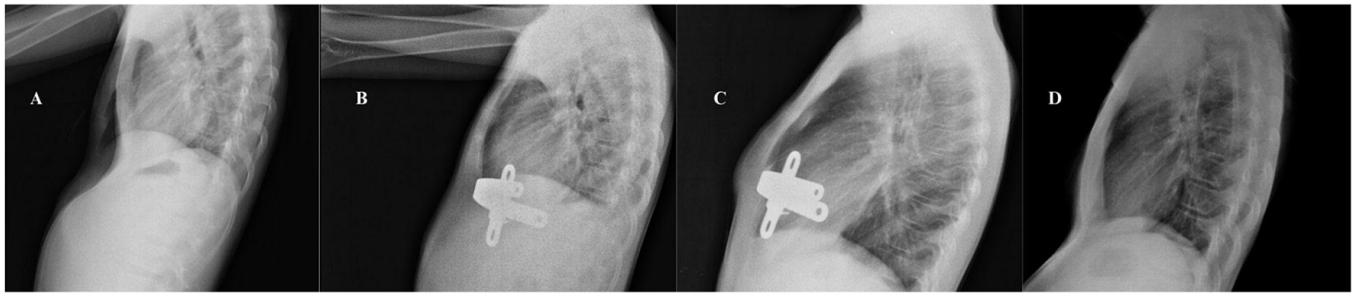

Figure 2: The patient's lateral chest X-ray before the Nuss procedure (A). The patient's lateral chest X-ray after the Nuss procedure (B). The patient's lateral chest X-ray seven months after the Nuss procedure, before bar removal due to the development of pectus carinatum (C). The patient's lateral chest X-ray four years after bar removal (55th month) due to the development of pectus carinatum (D).

In those times, Nuss bars were mostly retained for two years in our clinical practice, and this patient developed overcorrection at seven months (5). It was hypothesized that overcorrection would reverse, and the patient would be both excavatum and carinatum free after bar removal, but the patient unfortunately ended up having a recurrence of PE. Recently, pectus bars were retained up to three years. Considering that, a revision procedure with repositioning and less bending would have been a sensible option for this case.

Non-invasive techniques such as vacuum therapy could have been tried before the Nuss procedure, and success would have been likely when the patient's flexibility and age were taken into account (8, 19). Another point to consider is whether sternal protrusion could have been managed with external bracing orthoses like Donald Nuss suggested and Zhou et al. (16) tried (5). The patient could be given an external bracing orthosis while bars are still in situ if it was tolerable. The procedure would have also prevented the recurrence of PE, as early bar removal would not have been performed. If the patient could not tolerate bars and external bracing concomitantly, waiting up to two years and performing bar removal and then trying to control PC would have been another option.

Given both the rarity and reporting of this complication, there is no consensus on the management, and even guidelines do not mention this complication (1). Our clinical experience and output from this case were to offer vacuum bell therapy before the Nuss procedure for cooperative, willing, and flexible patients, where we measure the flexibility of the chest wall with a vacuum bell in the first examination. However, as the Nuss procedure is being performed frequently, it is important to be aware of this rare complication, and a careful revision procedure or orthotic support may be considered. The development of PC after a Nuss procedure is a very rare but possible complication that can be observed in flexible patients. Early bar removal due to this complication may lead to the recurrence of PE. Revision procedures, vacuums and external bracing orthoses may be used to manage this complication.

Ethics

Informed Consent: *An informed oral consent was obtained from the patient's legal guardians.*

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Surgical and Medical Practices: M.Y., Concept: Z.A., M.Y., Design: Z.A., M.Y., Data Collection or Processing: Z.A., M.Y., Analysis and/or Interpretation: Z.A., M.Y., Literature Search: Z.A., M.Y., Writing: Z.A., M.Y.*

Financial Disclosure: *The authors declared that this study received no financial support.*

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CASE REPORT

A RARE COMPLICATION IN A CASE OF PERSISTENT DIARRHEA: PEG CATHETER MIGRATION

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ABSTRACT

Percutaneous endoscopic gastrostomy is a common procedure performed for enteral feeding for patients who experience difficulty swallowing. Although generally safe, complications like infection, hemorrhage, gastrointestinal perforation, peritonitis, fistulisation, internal organ damage, and clogging of the catheter may occur. One of the rare complications is the misplacement of the percutaneous endoscopic gastrostomy catheter into neighboring organs or the migration of the catheter with time. In this case report, we focused on the diagnosis and treatment of persistent diarrhea due to migration of a percutaneous endoscopic gastrostomy catheter into the transverse colon.

A 70-year-old patient, with a history of cerebrovascular accident and who was under follow-up for inoperable lung cancer, was started on enteral feeding via a percutaneous endoscopic gastrostomy catheter due to dysphagia. A year later, the patient was admitted to the general surgery ward after applying to the emergency room experiencing watery diarrhea more than ten times a day that had been going on for a month. During evaluation, differential diagnoses of diarrhea including infectious, enteral feeding-related, and drug-associated causes were considered. An abdominal computed tomography revealed that the catheter had migrated to the transverse colon level. Subsequently, esophagogastroduodenoscopy and colonoscopy confirmed that the catheter was not in the stomach, but rather in the lumen of the transverse colon. The catheter was removed endoscopically and after the procedure, a new percutaneous endoscopic gastrostomy catheter has been inserted without complications.

This case emphasizes the importance of recognizing and appropriately managing a rare complication of percutaneous endoscopic gastrostomy. In patients presenting with gastrointestinal symptoms such as persistent diarrhea, a detailed history should be taken and this complication should be considered.

Keywords: Catheters, complication, endoscopy, gastrostomy, enteral nutrition, diarrhea

INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG) is a common procedure to provide enteral feeding by inserting a tube into the stomach of patients who experience feeding difficulties. Although considered to be generally safe, complications like infection, hemorrhage, and peritonitis can be observed (1). Migration of the catheter to adjacent organs is a rare complication, with an occurrence of 0.8% (2). In this case report, we review the diagnosis and treatment of a patient with a PEG tube who developed persistent diarrhea due to migration of the catheter into the transverse colon. In cases of colon migration of PEG catheters involving fistulas, more symptoms that signal it are present, such as fecal leakage at the PEG site. However, it is essential to be aware of and recognize the possibility of migration in cases of extensive diarrhea, despite otherwise unremarkable physical examination and laboratory results (3). We emphasize the importance of timely recognition and proper treatment of this complication to prevent mortal outcomes such as peritonitis or sepsis.

CASE REPORT

A 70-year-old patient with a history of cerebrovascular accident and a diagnosis of inoperable lung cancer was started on feeding via a PEG catheter due to difficulty swallowing liquids.

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Approximately one year later, the patient presented to the emergency room experiencing diarrhea with watery, yellow-green bowel movements without blood or mucus, more than ten times a day that had been going on for a month. The patient was admitted to the general surgery ward after it was deemed that emergency surgery was not necessary. Upon presentation, the patient did not have fever, nausea, vomiting, or abdominal pain and physical evaluation was unremarkable. Diarrhea occurred subsequent to PEG tube placement and feeding, without any preceding history of similar symptoms. During the evaluation in the general surgery ward, differential diagnoses of diarrhea such as infectious, enteral feeding-related, and drug-associated causes were considered. None were identified and there was no inflammation at the PEG site. Laboratory findings did not support infection. Stool samples were negative for leukocytes and erythrocytes. No antibodies against *Entamoeba histolytica, Giardia lamblia,* or *Clostridium difficile* A-B toxins were detected. There was no history of recent use of antibiotics. Enteral nutrition fed to the patient was evaluated to exclude enteral nutrition-associated diarrhea and the enteral feed was changed. Diarrhea persisted. Abdominal computed tomography (CT) revealed that the PEG catheter extended subcutaneously to the level of the transverse colon, 7 cm cranial to the umbilicus (Figure 1). In order to locate the catheter, gastroscopy and colonoscopy were planned. Gastroscopy showed that the catheter was not in the stomach and colonoscopy confirmed that the catheter was in the lumen of the transverse colon. Subsequently, the catheter was removed endoscopically (Figure 2). One month later, a new PEG catheter was inserted and it was confirmed to be functioning properly. No pathology after feeding was observed. An informed oral consent was obtained from the patient.

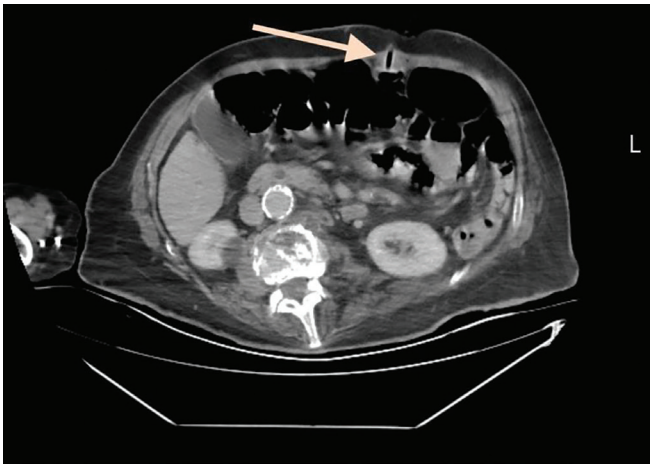

Figure 1: The PEG catheter as seen in the abdominal CT image indicated by the arrow.
PEG: Percutaneous endoscopic gastrostomy, CT: Computed tomography

DISCUSSION

Percutaneous endoscopic gastrostomy tube has been a widely used technique for enteral feeding since 1980 (4). The tube is placed into the stomach with gastroscopy and a percutaneous needle through the abdominal wall. After the tube has been placed, its location is secured with transillumination and direct pressure. The catheter is later secured to the skin with a balloon or a disk. This procedure's complication rate is low and it is considered safe (5). The most common complications include hemorrhage, infection, aspiration, pneumoperitoneum, tube dislodgement, and forming of granulation tissue (1). Migration of the PEG catheter to the neighbouring organs is a rare complication with studies reporting about 4% to 25% of patients suffer from placement-associated complications (6). Catheter migration to the gastric pylorus, duodenum, ileocecal valve, and transverse colon has been reported (7-9). Unintentional punctures of the stomach and transverse colon after the first insertion are the main contributing factors to the migration of PEG catheters. Other recognized risk factors include the overdistension of the stomach during esophagogastroduodenoscopy, high-riding transverse colon, and post-surgical adhesion (10).

Migration to the colon commonly presents with non-specific symptoms like diarrhea, abdominal pain, cramps, and non-bilious vomiting (7). Diarrhea is also a typical complication of enteral feeding and it is observed in 10-20% of the patients. Enteral feeding-associated diarrhea etiology includes infection, diet, protein malnutrition, and drug therapy (11). After these causes are excluded, other rare etiologies like migration should be considered.

Tube migration can be confirmed with abdominal CT, gastroscopy, and colonoscopy. Patient's management is dependent on the tube's localization and clinical presentation

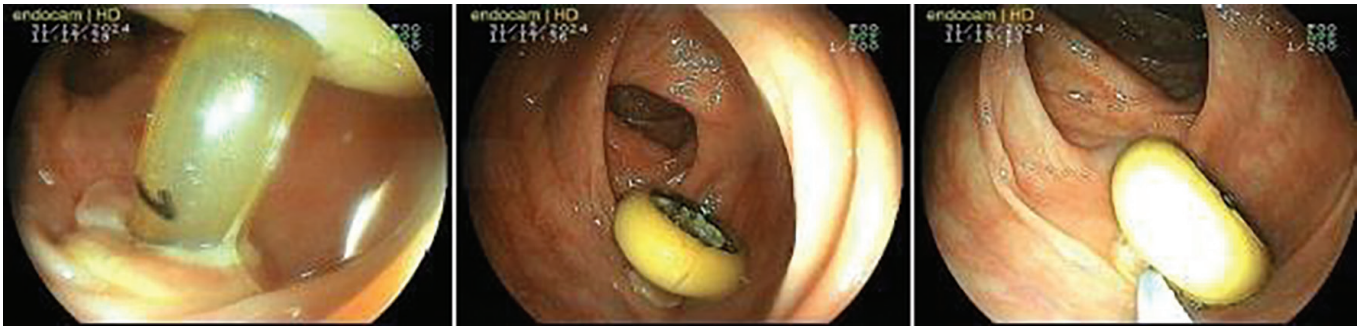

Figure 2: The PEG catheter as seen in colonoscopy images.
PEG: Percutaneous endoscopic gastrostomy

of the patient. With patients who are clinically stable the PEG catheter can be removed endoscopically and a new catheter can be inserted (8). However, it has been reported that external migration from the stomach can cause serious complications like acute pancreatitis, bowel obstruction, and perforation (9, 12, 13). Patients' clinical symptoms should be observed closely. If the complications advance, surgical intervention is needed.

Migration of a PEG catheter into the colon is a rare but potentially serious complication. In this case report, the diagnosis and treatment of a PEG catheter that migrated into the colon are evaluated in detail, with emphasis on its recognition and the appropriate management approach. It should be noted that these cases may present with non-specific symptoms such as diarrhea; therefore, clinicians should maintain a high index of suspicion for catheter migration in patients with PEG tubes presenting with unexplained gastrointestinal symptoms. This case also highlights that such complications may present even in the long term and supports the practice of endoscopic follow-up in affected patients.

Ethics

Informed Consent: *An informed oral consent was obtained from the patient.*

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Surgical and Medical Practices: M.D., D.A., Concept: İ.Ç., Ş.Y.D., M.D., D.A., Design: İ.Ç., Ş.Y.D., Data Collection or Processing: İ.Ç., Ş.Y.D., M.D., Analysis and/or Interpretation: İ.Ç., Ş.Y.D., M.D., D.A., Literature Search: İ.Ç., Ş.Y.D., Writing: İ.Ç., Ş.Y.D.*

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