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Mini Review

Personalized Vaccines: Unlocking the Next Era of Medical Innovation in Cancer Immunotherapy

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Abstract

Precision medicine represents a paradigm shift in healthcare, emphasizing individualized approaches to disease prevention, diagnosis, and treatment based on a patient's genetic, proteomic, and immunologic profile. In the field of oncology, this paradigm has gained traction, particularly with the integration of immunotherapeutic modalities. Among the most promising advancements are therapeutic cancer vaccines, which harness the body's immune system to fight tumors more effectively. However, clinical translation remains limited by biological, manufacturing, regulatory, and evidentiary barriers. This mini-review highlights recent developments in therapeutic vaccine engineering, discusses key barriers to clinical translation, and summarizes selected findings from contemporary human clinical studies of personalized cancer vaccines. Particular attention is also given to biomarker-guided patient selection and the investigation of therapeutic cancer vaccines in adjuvant or minimal-residual-disease settings to reduce postoperative recurrence. Current evidence is promising but remains largely early-stage and does not yet establish broad clinical benefit.

Introduction

Precision medicine, often called personalized or individualized medicine, customizes treatment to a patient's molecular and immune profile and has become central to modern oncology, particularly immuno-oncology. Personalized cancer immunotherapy is a rapidly evolving sphere of research and development that is moving toward highly individualized treatments, leveraging genetic analysis of patient tumors to develop vaccines that elicit specific immune responses against unique cancer antigens.[1]

The scope of precision medicine is broadening to include comprehensive strategies, incorporating advancements in early diagnostics. Emerging biomarkers such as genomic, proteomic, and imaging markers, coupled with artificial intelligence (AI)-driven biomarker discovery, are transforming personalized medicine by providing detailed information to guide treatment decisions.[2]

Genomic markers: Comprehensive genomic profiling involves analyzing a tumor's DNA and RNA to identify specific mutations, copy number variations, and other alterations. This information allows clinicians to match patients with specific targeted therapies, such as those targeting a particular gene mutation. It also studies how genetic variations affect drug response, helping to optimize drug efficacy and minimize adverse drug reactions. Moreover, analyzing circulating tumor DNA from blood samples can provide a non-invasive way to monitor treatment effectiveness, detect recurrence, and identify treatment resistance.

Proteomic markers: Protein analysis involves studying the large-scale set of proteins produced by an organism, which can reveal a tumor's functional state and its response to therapies. Proteomic data can help identify different molecular subtypes of a disease, leading to more precise diagnoses and treatments. It can also identify markers of resistance to certain drugs, which can inform treatment adjustments.

Imaging markers: Radiomics, coupled with AI-powered image analysis, extracts quantitative features from medical images (computed tomography, magnetic resonance imaging, and histopathology) that are not visible to the human eye. These markers can provide detailed information about tumor heterogeneity, shape, and boundaries, which can be used for diagnosis, staging, and predicting treatment response. AI systems can automate parts of the imaging analysis process, increasing efficiency and consistency for radiologists, and also help predict treatment needs and identify patients who may benefit from specific therapies.[3] These emerging biomarkers are transforming personalized medicine by providing detailed information to guide treatment decisions, helping to predict treatment response and disease heterogeneity. This mini-review aimed to highlight recent developments in therapeutic vaccine engineering, discuss key barriers to clinical translation, and

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summarize selected findings from contemporary human clinical studies of personalized cancer vaccines. Particular attention was also given to biomarker-guided patient selection and the potential role of therapeutic cancer vaccines in reducing postoperative recurrence or disease progression.

Cancer immunotherapy

Cancer is relentless because it learns to hide, bend, and reshape the immune system to survive. A useful way to frame immune evasion is the "three Cs": camouflage (reducing antigen visibility), coercion (reprogramming immune cells), and corruption (remodeling the microenvironment to suppress immunity). This scaffolds how tumors resist therapies and why single agents often fall short, as resistance emerges when these escape routes dominate.[4] Primary resistance reflects baseline non-inflamed phenotypes (few T cells, low programmed cell death protein-1/ligand (PD-1/PD-L1), antigen presentation deficits), while acquired resistance often involves adaptive upregulation of alternate checkpoints, loss of neoantigens, or IFN signaling defects after an initial response. Biomarkers tied to resistance include low T-cell infiltration, impaired antigen presentation, interferon pathway alterations, and metabolic signatures; these inform rational combinations to restore antitumor immunity. There are multiple strategies currently under investigation.[5]

Immune checkpoint inhibitors (ICIs): The advent of immune checkpoint inhibitors has revolutionized the field of cancer immunotherapy. ICIs that target Cytotoxic T-lymphocyte associated protein 4 (CTLA-4), PD-1, and PD-L1 have transformed care for multiple cancers by restoring antitumor T-cell activity and producing durable responses in subsets of patients.[6] ICIs are monoclonal antibodies that block inhibitory immune checkpoints, releasing constraints on T cells and enabling antitumor immunity.[7] Clinically approved examples include ipilimumab (anti–CTLA-4), pembrolizumab and nivolumab (anti–PD-1), and multiple anti–PD-L1 agents; these drugs produce profound and sometimes long-lasting tumor regressions but show variable overall response rates across tumor types and are limited by primary and acquired resistance and immune-related adverse events such as myocarditis.[8]

Adoptive cell therapies: Adoptive cell transfer comprises approaches that isolate, expand, and/or genetically modify autologous immune cells for reinfusion. TIL therapy isolates tumor-reactive lymphocytes from resected tumors, expands them *ex vivo*, and reinfuses them to achieve durable responses in selected patients with solid tumors. Two principal engineered T-cell strategies have been developed: chimeric antigen receptor (CAR) T cells, which recognize surface antigens in a human leukocyte antigen (HLA)-independent manner, and T-cell receptor (TCR)-engineered T cells, which recognize peptide–HLA complexes and therefore can target intracellular antigens.[9]

CAR T therapy: CAR T-cell therapy has achieved landmark clinical successes in hematologic malignancies, leading to multiple approvals by the U.S. Food and Drug Administration (FDA) and durable remissions in subsets of patients with B-cell malignancies and multiple myeloma; however, efficacy in solid tumors remains limited by tumor trafficking, the immunosuppressive tumor microenvironment, antigen heterogeneity, manufacturing complexity, cost, and treatment-related toxicities such as cytokine release syndrome and neurotoxicity.[10]

TCR-engineered T cells expand the antigenic repertoire to intracellular, HLA-presented peptides, offering opportunities to target more broadly expressed tumor antigens and essential oncogenic proteins. They can demonstrate high antigen sensitivity and physiologic signaling, which may improve persistence and tumor recognition; nevertheless, affinity enhancement and cross-reactivity can produce severe, unexpected off-target toxicities, including fatal cardiotoxicity seen in early affinity-enhanced anti–MAGE-A3 TCR trials due to titin cross-reactivity.[11]

Natural killer (NK) therapy: NK cells are innate lymphocytes with intrinsic antitumor activity and multiple effector mechanisms, including missing-self recognition and antibody-dependent cellular cytotoxicity. CAR NK therapies aim to combine CAR targeting with NK biology to produce off-the-shelf, allogeneic products with lower graft-versus-host risk and potentially improved safety relative to CAR T cells. CAR NK approaches promise allogeneic availability and reduced alloreactivity but face challenges including efficient gene delivery, *in vivo* persistence, scalable expansion, and target selection for solid tumors.[12]

Key limitations across immunotherapies include immune resistance mechanisms, antigen escape, limited penetration into solid tumors, immune-related toxicity, manufacturing complexity, and cost. In 2023, CAR-T eligibility and potential response were estimated at 3.9% and 3.4%, respectively, among U.S. patients with advanced or metastatic cancer.[13]

Vaccines

Vaccines are biological preparations that stimulate the immune system to develop active acquired immunity against infectious agents or malignant cells. Traditionally used for disease prevention, vaccines present defined antigens or antigenic material that the immune system recognizes as non-self, thereby priming adaptive humoral and cellular responses and establishing immunological memory. In oncology, the vaccine concept has been extended beyond prophylaxis to therapeutic applications that aim to induce or augment immune responses against established tumors.

Progress in vaccine engineering—especially in antigen design, delivery platforms, and adjuvant systems—has significantly enhanced the immunogenicity and specificity of these vaccines. Among the most transformative innovations is the advent of messenger RNA (mRNA) vaccine technology, which allows for rapid and scalable production of individualized vaccines encoding multiple neoantigens. mRNA vaccine platforms have demonstrated immunogenicity in clinical studies of infectious-disease vaccines; whether this translates into oncology-specific clinical benefit requires further evaluation.[14]

Conventional vaccine platforms

Common conventional vaccine platforms include live attenuated, inactivated, and toxoid vaccines, each with distinct immunological and logistical properties. Live attenuated vaccines use replication-competent but weakened organisms to elicit strong, durable immunity and often require only one or two doses for long-term protection (e.g., measles, mumps, and rubella). Inactivated vaccines contain killed pathogens and typically require multiple doses or boosters to maintain protection because they elicit weaker cellular immunity than live vaccines.[1] Toxoid vaccines present inactivated bacterial toxins to induce neutralizing antibodies (classically used for diphtheria and tetanus). Modern platforms also include subunit/protein, viral vector, DNA, and mRNA vaccines, which vary in antigen presentation, safety, manufacturability, and suitability for personalization.[15]

Therapeutic cancer vaccines: concept and vaccine selection

Therapeutic cancer vaccines are designed to treat existing malignancies by directing the immune system against tumor antigens

Table 1. Qualitative overview of selected therapeutic cancer vaccine settings

Cancer type	Selected evidence	Dominant challenges	Potential development directions
Melanoma	Early clinical studies have reported immunogenicity with personalized mRNA and other neoantigen vaccine platforms.[22,23]	Immune escape, antigen heterogeneity, durability, sequencing with ICIs, and endpoint standardization remain challenges.	Combinations with PD-1/PD-L1 blockade, next-generation delivery, and multiantigen targeting are under investigation.
Pancreatic cancer	Early adjuvant studies have reported persistent vaccine-induced T-cell responses in selected patients.[22,23]	Low mutation and neoantigen burdens, an immunosuppressive TME, and rapid relapse remain challenges.	Adjuvant and minimal-residual-disease settings and combinations with checkpoint or stroma-targeted approaches are under investigation.
Brain tumors (glioblastoma)	Early studies suggest immune activation with mRNA and cell-based vaccine concepts.[22,23]	Profound immunosuppression, intratumoral heterogeneity, the BBB, and steroid use remain challenges.	Local delivery and multimodal combinations with radiotherapy, chemotherapy, or ICIs remain investigational.

BBB, blood brain barrier; ICI, immune checkpoint inhibitors; IDO, indoleamine 2,3-dioxygenase; mRNA, messenger RNA; PD-1, programmed cell death protein 1; PD-L1, programmed cell death ligand 1; RT, radiotherapy; TME, tumor microenvironment. This table provides a qualitative overview and does not represent a head-to-head comparison of efficacy or safety.

rather than preventing infection. Vaccine strategies target either shared tumor-associated antigens expressed across patients or tumor-specific neoantigens arising from somatic mutations unique to an individual's tumor. Personalized pipelines typically involve tumor biopsy, next-generation sequencing, bioinformatic neoantigen prediction, antigen prioritization, and manufacture of a patient-specific vaccine product (peptide, RNA, DNA, or dendritic cell–loaded formulation). Neoantigen-targeted vaccines aim to exploit sequences not subject to central tolerance, improving the likelihood of eliciting high-avidity T-cell responses. Beyond treatment of established advanced disease, therapeutic cancer vaccines may be particularly relevant in adjuvant settings, where a lower tumor burden and minimal residual disease provide a rationale for investigating their potential to prevent recurrence.[16,17]

mRNA technology and the rise of personalized vaccines

The rapid acceleration of mRNA vaccine platforms, initially driven by the COVID-19 pandemic, is now significantly impacting cancer therapeutics, offering faster manufacturing and tailored antigen targeting. mRNA vaccine platforms offer rapid, modular, and non-integrating means to encode one or multiple antigens for *in vivo* expression by host cells. Advantages include short developmental timelines, scalable cell-free manufacturing via *in vitro* transcription, and flexibility to encode personalized neoantigen repertoires. Early clinical studies and reviews demonstrate that mRNA vaccines can induce polyclonal T-cell responses and are amenable to combination with checkpoint blockade and other immunotherapies, although regulatory approval for mRNA cancer vaccines remains pending.[16,17]

Mechanisms limiting efficacy and strategies to overcome them

Several biological and practical barriers limit therapeutic vaccine efficacy. Tumors employ immune evasion mechanisms such as antigen loss or heterogeneity, impaired antigen presentation, upregulation of inhibitory pathways (for example, PD-L1), recruitment of immunosuppressive cells, metabolic and enzymatic suppression, and hypoxia within the tumor microenvironment, all of which can blunt vaccine-induced responses.[18–20] High intratumoral heterogeneity may allow a vaccine to control the index lesion yet fail against metastatic or antigen-negative subclones. Practical constraints include complex, resource-intensive manufacturing for personalized and cell-based products, long turnaround times, and cost, which hamper broad clinical implementation.[21] Current development strategies focus on improved neoantigen prediction, standardized rapid manufacturing, optimized delivery and adjuvant systems, biomarker-guided patient selection, and rational combinations with checkpoint inhibitors or therapies that modulate the tumor microenvironment.[22,23]

Clinical landscape and regulatory status

Despite decades of research and innovation, relatively few therapeutic cancer vaccines have achieved regulatory approval. This reflects the inherent complexity of designing immunotherapies that can overcome tumor immune evasion, elicit durable responses, and demonstrate consistent efficacy across diverse patient populations. The development timeline—from antigen discovery through preclinical validation, clinical trials, and regulatory review—often spans 10–15 years, with many candidates failing due to limited immunogenicity or safety concerns.

As of 2025, several approved cancer immunotherapies have sometimes been grouped under the broad label of therapeutic cancer vaccines, although they represent distinct product classes.

- Sipuleucel-T: Approved for asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer, it is an autologous cellular immunotherapy that stimulates an immune response against prostatic acid phosphatase.[24]
- Bacillus Calmette-Guérin: Intravesical BCG is an immunotherapy used for carcinoma in situ and selected non-muscle-invasive bladder cancers.[25]
- Nadofaragene firadenovec: This adenoviral vector-based gene therapy is approved for high-risk BCG-unresponsive non-muscle-invasive bladder cancer with carcinoma in situ, with or without papillary tumors.[26]
- T-VEC (talimogene laherparepvec): Approved for selected unresectable melanoma lesions, T-VEC is an oncolytic viral therapy rather than a personalized cancer vaccine.[24]

These products illustrate distinct immunotherapeutic strategies, but they should not be treated as a single vaccine class. Their development underscores ongoing interest in delivery technologies and biomarker-guided patient selection. Selected successes and challenges of therapeutic cancer vaccine development are summarized qualitatively in Table 1.[22,23]

Emerging landscape of cancer vaccines

The landscape of cancer vaccine development has evolved significantly in recent years due to advances in target identification, formulation, manufacturing, and patient stratification. Within the last year, significant developments have been reported in vaccine engineering, personalized therapeutic strategies, and the broader integration of precision approaches across diverse medical fields. Notably, personalized and antigen-specific approaches are being evaluated clinically. TG4050 uses a modified vaccinia virus Ankara vector to deliver patient-specific neoantigens identified through AI and genomic profiling. It is being evaluated in a randomized phase I/II trial in resected HPV-negative head and neck squamous cell carcinoma (NCT04183166); available early findings remain preliminary.[27] Another example is VB10.16, a therapeutic DNA vaccine targeting human papillomavirus (HPV) 16 E6/E7 oncoproteins. It comprises three components: a fusion protein encoding HPV16 E6/E7, a dimerization domain, and a targeting unit that binds antigen-presenting cells. In a phase I/IIa trial, VB10.16 was well tolerated and elicited HPV16-specific T-cell responses in patients with high-grade cervical intraepithelial neoplasia.[28]

Advances in mRNA vaccine platforms

mRNA-based therapeutics have expanded beyond infectious diseases into oncology.[1] Early trials have explored applications in cardiovascular and genetic disorders; however, cancer poses unique challenges due to immune suppression and antigenic heterogeneity within the tumor microenvironment.[28]

Moderna's randomized phase IIb trial of mRNA-4157/V940 plus pembrolizumab in patients with resected high-risk melanoma reported recurrence-free survival with a hazard ratio of 0.561 (95% CI 0.309–1.017) versus pembrolizumab alone.[29] The vaccine encoded up to 34 patient-specific neoantigens. In a phase I study of 16 patients with resected pancreatic ductal adenocarcinoma, autogene cevumeran was administered sequentially with atezolizumab and mFOLFIRINOX; vaccine-induced T-cell responders had longer recurrence-free survival than nonresponders, an exploratory association that requires confirmation.[30]

mRNA vaccines are increasingly recognized for their versatility and rapid development potential. Targeting dendritic cells, key antigen-presenting cells, has emerged as a promising strategy for enhancing vaccine potency. Clinical data suggest that mRNA vaccines act synergistically with ICIs, modulating the immune response and improving outcomes. Self-amplifying RNA is a next-generation platform offering prolonged antigen expression, lower dosing, and reduced adverse effects. Although not yet FDA-approved, Japan has authorized a self-amplifying RNA-based COVID-19 vaccine, paving the way for oncology applications.[23]

Clinical trials are evaluating diverse therapeutic vaccine strategies across multiple cancers. Personalized cancer vaccines have progressed from small feasibility studies to phase II programs and randomized trials. A 2025 review identified 78 registered personalized cancer vaccine trials as of November 25, 2024, of which 56 were active. The trials encompassed diverse platforms and cancer types, but more than 90% were phase I studies, underscoring the early stage of the evidence.[31] Together, these approaches illustrate the diversification of vaccine platforms, but their clinical roles remain under investigation.

Regulatory framework

Personalized vaccines represent a novel product class, meaning existing regulatory standards are often insufficient. Developers face uncertainty, as approaches accepted by one agency may not be accepted by another, complicating a global development strategy. As of 2025, no personalized neoantigen or mRNA cancer vaccine had received FDA or EU marketing authorization. The regulatory landscape for personalized cancer vaccines remains complex and time-consuming, requiring robust evidence of safety, efficacy, and quality control, which is challenging to gather for highly individualized, small-batch products.[32]

For general vaccines such as the COVID-19 shot, the FDA has adopted an annual assessment for strain updates, similar to influenza vaccines, a model that might inform aspects of personalized medicine development. Moreover, ongoing efforts, including those by the World Health Organization, aim to establish universally applicable principles and standardized protocols for genomic data use to promote international collaboration and consistency in regulation.

The reliance on sensitive patient genomic data in personalized vaccine development raises significant ethical considerations. An individual's genome contains highly personal information with potential for misuse by employers, insurers, or governments. Robust data governance frameworks, encryption, and compliance with privacy regulations including the Health Insurance Portability and Accountability Act (HIPAA) in the U.S. are crucial to prevent unauthorized access and discrimination. Personalized vaccines are expected to have high manufacturing costs and logistical challenges, potentially limiting access in resource-limited settings. Regulatory frameworks must incorporate strategies to ensure equitable access and prevent disparities in healthcare delivery.[33]

Future directions and technologies

Precision medicine extends far beyond therapeutic vaccines, encompassing diagnostic and therapeutic advancements that are shaping a more personalized approach to healthcare. The goal is to tailor medical decisions, treatments, practices, or products to the individual patient based on their predicted response or risk of disease. Early detection and accurate diagnosis are foundational to effective precision medicine. Updated breast cancer screening guidance illustrates the continued refinement of risk-based early detection.[34] These diagnostic improvements allow for earlier intervention, which can significantly enhance the effectiveness of subsequent precision therapies, including therapeutic vaccines.

Recent advances in next-generation sequencing, neoantigen prediction algorithms, and nucleic acid-based platforms—particularly mRNA and DNA technologies—have revitalized interest in this approach, enabling the design of vaccines tailored to individual tumor mutational landscapes.[35] These innovations, coupled with improved delivery systems such as lipid nanoparticles and viral vectors, have yielded promising results in early-phase clinical trials, demonstrating the potential to elicit robust T-cell responses against tumor-specific antigens.[36]

Cancer vaccines are transitioning from artisanal production toward industrialized, automated, and decentralized manufacturing models. Advances in platform-ready technologies such as mRNA, viral vectors, and peptide backbones enable rapid personalization with patient-specific antigens, accelerating timelines and improving flexibility.[37] Dendritic cell vaccines have matured with standardized protocols for monocyte collection, differentiation, and antigen loading, reducing variability and streamlining release testing. Emerging "off-the-shelf" cellular vaccines, including mass-produced cDC1s, promise scalability and broader accessibility compared with individualized autologous products.

Moreover, digital and computational tools, including AI-ena-

bled pipelines and vector optimization platforms, are compressing the vaccine lifecycle from antigen discovery through robotic manufacturing and in-line analytics, enhancing precision and reducing batch variability. Bioprocess automation—including closed systems, modular skids, and integrated digital monitoring manufacturing execution system/laboratory information management system—supports global manufacturing networks and consistent technology transfer, drawing lessons from cell and gene therapy scale-up. End-to-end digitalization and data-driven quality-by-design approaches further improve reproducibility and cost efficiency.[38] Decentralized and near-patient manufacturing models reduce logistical friction associated with centralized hubs, potentially lowering costs, though they require harmonized quality assurance and regulatory oversight.

Limitations

In spite of all the recent advances, personalized immunotherapy is still limited by three main factors:

- *Data sources:* Patient data is fragmented, inconsistent, and often biased toward certain populations, reducing reliability.
- *Sample size:* Studies frequently involve small, non-diverse cohorts, which weakens statistical power and generalizability.
- *Follow-up duration:* Outcomes are usually tracked short-term, missing late effects and making long-term safety and effectiveness uncertain.
- These constraints hinder the accuracy, scalability, and long-term impact of personalized treatments. Moreover, other major challenges need to be addressed that include:
- *Cost-effectiveness:* High treatment and manufacturing costs may limit access. Effectiveness varies by cancer type and treatment, but predictive biomarkers can improve efficiency by targeting patients most likely to benefit.[39]
- *Reimbursement hurdles:* High upfront costs, limited large-scale trial data, and differing payment models across countries complicate coverage. Innovative approaches like performance-based or risk-sharing agreements are being tested, but navigating regulatory bodies adds further complexity.
- *Global disparities:* Access is highly unequal, with low- and middle-income countries lacking infrastructure, workforce, and representation in clinical trials. This worsens cancer outcomes, as patients are often diagnosed late and miss opportunities for advanced care.

While personalized immunotherapies hold promise for long-term savings and better outcomes, their high costs, reimbursement barriers, and unequal global access demand coordinated policy, funding, and infrastructure solutions.[40] This is a narrative mini-review without a reported systematic search or formal quality assessment; the selected evidence may therefore be incomplete and subject to selection bias.

Conclusions

Precision medicine and immunotherapy have reshaped cancer treatment. While checkpoint inhibitors have revolutionized outcomes for some patients, recent advances in cancer immunotherapy have catalyzed vaccine development as a novel treatment modality, with mRNA-based vaccines offering a flexible platform for personalized antigen delivery. Therapeutic cancer vaccines are designed to elicit targeted immune responses against tumor-specific antigens. These antigens are typically derived from the patient's own tumor, enabling personalized vaccines that are uniquely tailored to the molecular characteristics of each malignancy. Addressing tumor heterogeneity, optimizing delivery routes, and enhancing immune activation are critical for future success. mRNA-based vaccines may expand therapeutic options in selected indications, but their clinical benefit, manufacturing scalability, and role across cancer types require confirmation in larger randomized studies. Future studies should also determine whether biomarker-guided patient selection can identify individuals most likely to benefit and whether vaccination in adjuvant or minimal-residual-disease settings can reduce postoperative recurrence.

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Conflict of interest

JFM is the Founder and President of ImmunePCS LLC. The author declares no other conflicts of interest.

Author contributions

JFM is the sole author of the manuscript.

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