UMYU Scientifica, Vol. 4 NO. 4, December 2025, Pp 050 – 071
https://doi.org/10.56919/usci.2544.006
ISSN: 2955 – 1145 (print); 2955 – 1153 (online)
A periodical of the Faculty of Natural and Applied Sciences, UMYU, Katsina

REVIEW ARTICLE

A Systematic Review of Neoantigen Identification and Clinical Translation in Cancer Immunotherapy (2015–2025)

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ABSTRACT
Tumour neoantigens, which are products of tumour-specific mutations, are ideal targets for cancer immunotherapy because they are highly specific and have the potential to elicit a robust T-cell response. Nevertheless, clinical translation of neoantigen-based therapy is not uniform, and systematic analysis of the discovery, validation, and implementation plans is required. A systematic literature search was conducted across PubMed, Scopus, Web of Science, Google Scholar, and Embase in July, 2025, to identify articles on neoantigen discovery and clinical use. In accordance with the PRISMA, 20 studies were included. Among the 20 original papers, 65% (13/20) were based on computational prediction, and only 35% (7/20) contained experimental validation, such as mass spectrometry-based immunopeptidomics or cell-based T-cell assays. Some studies used clinical translation, most of which used personalised vaccines and T-cell therapies, and, in some cases, immune checkpoint inhibitors. A high level of technological heterogeneity and inconsistent accuracy in neoantigen prioritisation were identified as critical limitations to clinical reliability. Neoantigen-based immunotherapy (immunotherapy) presents a high potential, but it is limited by the inaccuracy of predictions and low levels of validation. To enhance the chances of a successful translation, we suggest incorporating immunopeptidomics regularly, implementing AI-based models, expanding the global HLA sample, accelerating the manufacturing process, and standardising validation pipelines.

ARTICLE HISTORY
Received August 21, 2025
Accepted December 11, 2025
Published December 16, 2025

KEYWORDS
Cancer Immunotherapy, Neoantigens, Bioinformatics, Immunopeptidomics, Immunology, Multi Omics.

INTRODUCTION
The impact of cancer immunotherapy on cancer treatment is tremendous, and it has transformed the field of oncology by leveraging the immune system to identify and destroy tumour cells. The immune checkpoint inhibitors, adoptive cell therapies, and cancer vaccines have shown significant clinical benefits, especially in tumours with high mutational burden that are novel, non-self antigens that arise due to tumour-specific genetic changes, including point mutations, alternative splicing, gene rearrangements, and viral insertions (Jiang *et al.*, 2019; Huang *et al.*, 2024; Xie *et al.*, 2025; Goloudina *et al.*, 2025).

The tumour neoantigens are cancer-specific peptides that are generated by mutations in the genome and are not expressed in normal tissues. They are highly immunogenic because the immune system can easily recognise them, as they appear only in tumour cells and are not affected by central or peripheral tolerance; they can reduce the risk of autoimmunity (Jiang *et al.*, 2019; Xie *et al.*, 2025; Goloudina *et al.*, 2025). Neoantigens can be derived from many sources, including non-synonymous mutations, gene fusions, and viral proteins, which can lead to tumour heterogeneity and affect prognosis and immunotherapy response (Zhang *et al.*, 2021; Huang *et al.*, 2024).

The neoantigens are the basis of personalised immunotherapy, including neoantigen-based vaccines and T-cell-based therapies. The methods will aim to induce strong, tumour-specific T cell responses, resulting in tumour cell destruction without harming normal tissues (Peng et al., 2019; Lang et al., 2022; Xie *et al.*, 2023). Clinical trials of personalised vaccines and adoptive cell therapies (TCR-T, CAR-T, TIL therapy) are underway and are demonstrating good safety and immunogenicity, as well as early efficacy (Jiang *et al.*, 2019; Aljabali *et al.*, 2025; Naffaa *et al.*, 2025).

However, despite the potential of neoantigen-based therapy, several obstacles remain. They are the precise discovery and confirmation of immunogenic neoantigens, tumour heterogeneity, immune evasion, the complexity of manufacturing and transportation, and the necessity of

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How to cite: Munir, Y. A., Magaji, M., Muhammad, A. S., Muhammad, A. D., & Hussaini, M. (2025). A Systematic Review of Neoantigen Identification and Clinical Translation in Cancer Immunotherapy (2015–2025). *UMYU Scientifica*, 4(4), 050 – 071. https://doi.org/10.56919/usci.2544.006

rapid, low-cost clinical translation (Zhang *et al*., 2021; Lang *et al*., 2022; Goloudina *et al*., 2025). These issues are vitally important to realising the full potential of individualised cancer immunotherapy.

The research area of this review is the dynamic environment of neoantigen discovery, prediction, and clinical use as therapeutic treatments in cancer immunotherapy. In particular, this review will help to sum up the available evidence on the current technologies for neoantigen discovery and prediction, the clinical challenges preventing broader implementation of neoantigen-based immunotherapies, and what strategies are emerging to address these obstacles and how do artificial intelligence and machine learning enhance neoantigen prediction accuracy, and what are the current limitations

The 2015-2025 period encompasses not only the essential development of neoantigen research as a concept but also its clinical implementation, where, by 2015, next-generation sequencing/bioinformatics technologies had matured enough, and by 2025, multiple neoantigen-based therapies were already in advanced phases of clinical trials.

This review provides comprehensive guidance for researchers, clinicians, and regulatory bodies navigating the rapidly evolving field of personalised cancer immunotherapy grounded in neoantigen science.

METHODOLOGY

2.1 Protocol and Reporting

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. A formal protocol was developed beforehand to guide the search strategy, eligibility criteria, and synthesis approach (Page *et al*., 2021; Isah *et al*., 2025; Salisu *et al*., 2021).

2.2 Eligibility Criteria

The inclusion of studies in the research was based on predefined criteria.

2.2.1 Inclusion criteria:

Original research articles relevant to neoantigen identification, prediction, validation or clinical translation in cancer, studies of human samples (tumour tissues, PBMCs, cell lines), studies detailing the sequencing of genomes, computational pipelines, immunopeptidomics, or the use of T-cell validation, clinical trials, observational studies, translational research and mechanistic studies. Full-text publications written in English were included in the research.

2.2.2 Exclusion criteria:

Abstracts of reviewed papers, editorial articles, commentaries, or letters without individual papers, preclinical research that does not involve any biological validation, only animal studies or in silico research, research that did not deal with any neoantigen technology or cancer immunotherapy were excluded from the research.

2.3 The sources of information and search strategy

A systematic literature search was conducted in PubMed, Scopus, Web of Science, Google Scholar, and Embase to identify studies published between 2015 and 2025. The search used keywords including "neoantigen," "tumour-specific antigen," "cancer immunotherapy," "personalised vaccine," "t-cell therapy," "CAR-T," "neoantigen prediction," and "immunopeptidomics," combining controlled vocabulary terms (MeSH in PubMed, EMTREE in Embase) with free-text searches. Combined with free-text searches. Searches were restricted to English-language studies and, where possible, to human studies.

2.4 Study Selection

Data retrieved from the search were initially sorted based on title "titles" and "abstracts" to remove potential duplicates. Next, the titles and abstracts of the different records were screened on the basis of this review's eligibility criteria to exclude records with irrelevant subjects or outcomes. All the review papers were also eliminated from this study. Lastly, only peer-reviewed publications were included in this study.

2.5 Data Extraction

The following variables of each of the included studies were gathered using a standardized data extraction form after adapted from Ziogas *et al.* (2021); Type of neoantigen identification technology, Genomic and computational methods (WES, WGS, RNA-seq, prediction tools, AI models), Proteomic/immunopeptidomics workflow (mass spectrometry platforms, HLA ligandome profiling), Validation methods (T-cell assays, ELISPOT, tetramer staining, functional assays), Cancer type and study population.

2.6 Quality Assessment

Risk of bias for non-randomised studies was assessed using the ROBINS-I tool to evaluate confounding, participant selection, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and reporting bias (Sterne et al., 2019; Minozzi *et al*., 2019). Domain ratings were assigned as Low, Moderatea and Serious risk of bias (Igelström *et al*., 2021). All assessments were cross-checked for consistency, and final ratings were tabulated and visualised to provide an integrated appraisal of methodological rigour across studies.

2.7 Data Synthesis

A narrative synthesis approach was adopted due to substantial methodological and clinical heterogeneity among studies. Results were categorised into major thematic domains: Genomic sequencing–based identification, Computational prediction and machine

learning approaches, proteomic and immunopeptidomic identification, experimental validation strategies, clinical translation of neoantigen-targeted vaccines and T-cell therapies

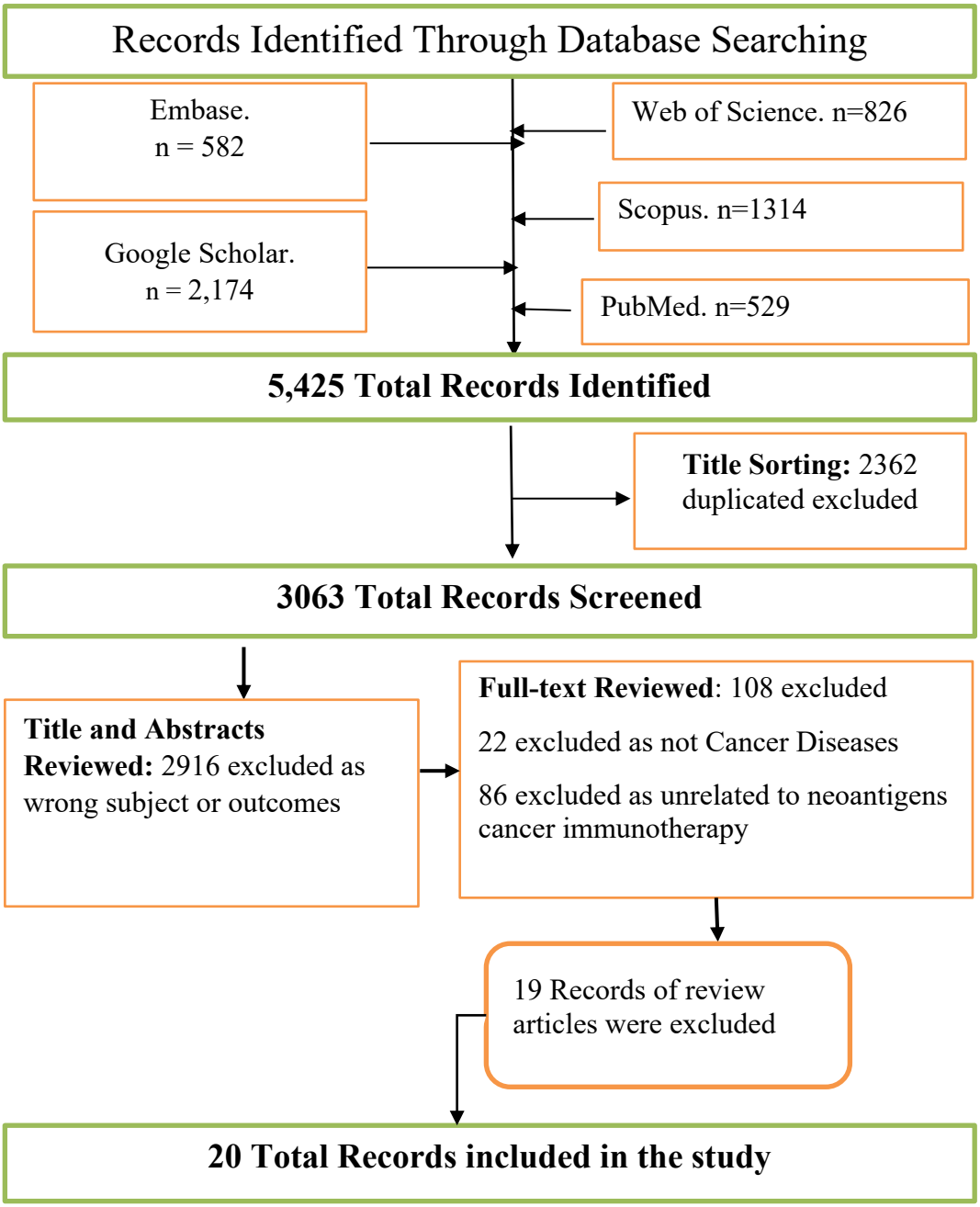

Figure 1: PRISMA Flow diagram

RESULTS

3.1 Study Selection

A total of 5,425 records were identified from all sources. After removing 2,362 duplicates, 3,063 records remained for screening. Title and abstract screening excluded 2,506 records that were not related to cancer neoantigens. The 151 full-text articles assessed led to the exclusion of 93 studies for reasons such as non-cancer focus or lack of neoantigen relevance; 19 review studies were further excluded. Ultimately, 20 studies were included in the review, reporting original research articles on neoantigen technologies, validation methods, and clinical translation and applications in cancer immunotherapy as summarised in Figure 1.

3.1.1 Quality Assessment of the included studies

The risk of bias (Figure 2) for all 20 included studies was evaluated using the ROBINS-I tool. The heatmap visualizes judgments across the seven pre-specified domains: (1) bias due to confounding, (2) bias in selection of participants, (3) bias in classification of interventions, (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias in measurement of outcomes, and (7) bias in selection of the reported result. Each row represents an individual study, and each column a bias domain.

Figure 2. Assessment of included non-randomised studies

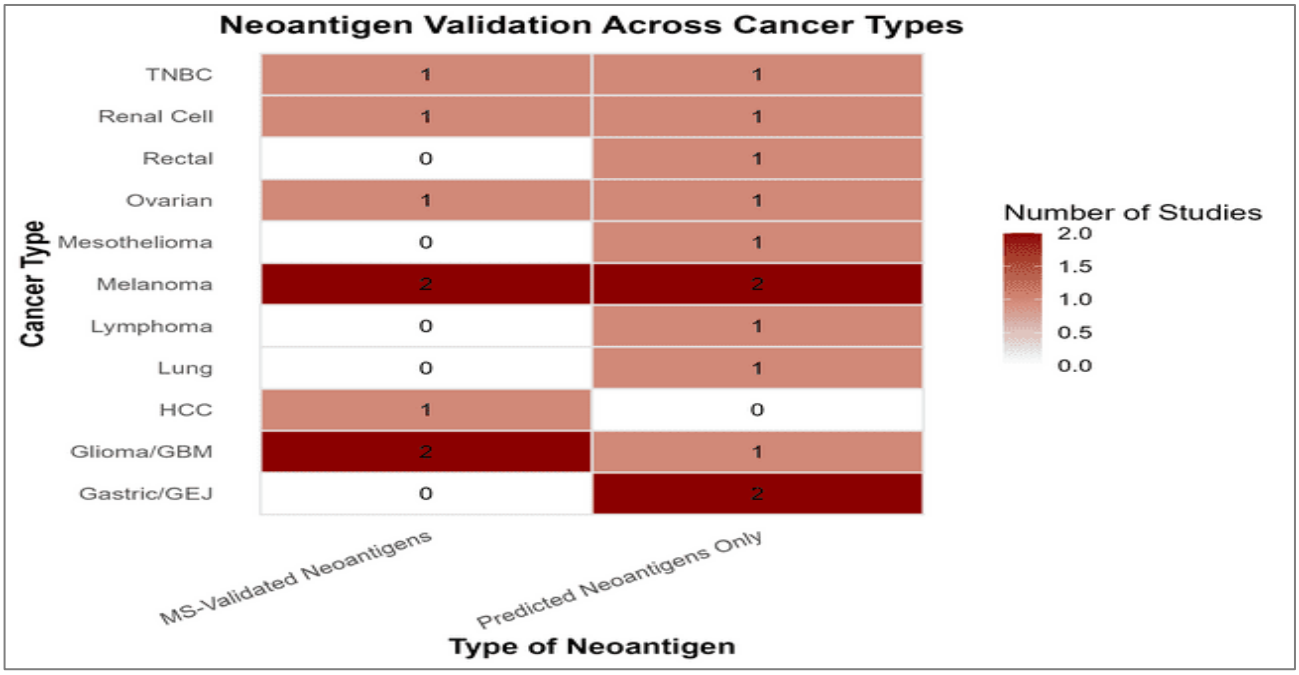

Figure 3. Landscape of Neoantigen Validation Across Major Cancer Types.

3.2 Characteristics of Included Studies Evaluating Neoantigens identification and translation in cancer immunotherapy.

The clinical and translational studies evaluating neoantigen-based approaches across diverse cancer types, summarised in Table 1, showed that most studies focus on mutational neoantigens (SNVs/INDELs) identified via WES/RNA-seq, while non-mutated tumour-associated antigens and tumour lysates are included in early-phase trials. Sample sizes range from small immunogenicity cohorts to large diagnostic or predictive studies, with validation approaches spanning T-cell assays, clinical outcomes (PFS, OS, RFS), and in silico or computational analyses. Early-phase studies primarily assess safety and immunogenicity, whereas later-phase trials focus on efficacy endpoints, and some large cohorts employ circulating biomarkers for risk prediction. Overall, the data illustrate the evolution toward personalised immunotherapy, methodological heterogeneity, integration of computational tools, and generally moderate to high study quality, highlighting both advances and the need for standardised validation to enhance cross-study comparability.

Table 1. Summary of Clinical and Translational Studies on Neoantigens in Cancer Immunotherapy

Author (Year)	Country	Cancer Type	Sample Size	Neoantigen Source	Methods	Validation Method	Phase/Outcome	Quality Score
Weber *et al.*, 2024	USA/AUS	Melanoma	157	SNV/INDEL	WES/RNA	Clinical outcome, T-cell response	Phase 2b, RFS/OS	9
Wang *et al.*, 2022	China	Solid tumors (advanced)	20	SNV/INDEL	WES/RNA	T-cell response, clinical	Phase 1, safety/ORR	7
Dillman *et al.*, 2018	USA	Melanoma	42	Tumor lysate (multiple)	Cell culture	Clinical outcome, DTH	Phase 2, OS	7
Sarivalasis *et al.*, 2019	Switzerland	Ovarian carcinoma	30	SNV/INDEL	WES/RNA	T-cell response	Phase 1/2, immunogenicity	8
Hernandez-Aya *et al.*, 2019	USA	TNBC	100	SNV/INDEL	WES/RNA	T-cell response, clinical	Phase 2, PFS/OS	7
Bunse *et al.*, 2022	Germany	Glioma	48	SNV (IDH1R132H)	WES/RNA	T-cell response, clinical	Phase 1, safety/immunogenicity	8
Fennell *et al.*, 2025	UK	Mesothelioma	336	SNV/INDEL	WES/RNA	In silico, clinical	Phase 3, PFS/OS	8
Bolen *et al.*, 2016	France/USA	Lymphoma	249	SNV/INDEL	WES/RNA	In silico, gene expression	Phase 3, PFS	7
Buchroithner *et al.*, 2018	Austria	Glioblastoma	76	Tumor lysate	Cell culture	Clinical outcome	Phase 2, PFS/OS	6
Storkus *et al.*, 2021	USA	Melanoma	16	Non-mutated TBVA	Peptide synthesis	T-cell response, clinical	Phase 2, ORR/PFS	7
Dai *et al.*, 2020	China	HCC	21	CD133 (non-mutated)	Cell culture	Clinical outcome, biomarkers	Phase 2, PFS/OS	7

To be continued next page

Table 1 continued

Author (Year)	Country	Cancer Type	Sample Size	Neoantigen Source	Methods	Validation Method	Phase/Outcome	Quality Score
Wei *et al.*, 2023	China	Pleural effusion	2352	N/A	ML/AI, lab data	Diagnostic accuracy	Retrospective, AUC	6
Janjigian *et al.*, 2022	USA/Global	Gastric/GEJ	900	N/A	N/A	Clinical outcome	Phase 3, EFS	7
Wang *et al.*, 2023	Global	TNBC	243	N/A (spatial predictors)	Imaging mass cytometry	Clinical outcome	Phase 2, pCR	8
McDermott *et al.*, 2018	USA/Global	RCC	305	SNV/INDEL	WES/RNA	In silico, clinical	Phase 2, PFS/OS	8
Vidal *et al.*, 2021	Spain	Rectal cancer	180	ctDNA (SNV/INDEL)	NGS	Clinical outcome	Phase 2, DFS/OS	7
Yuan *et al.*, 2025	USA	Colonic adenoma	32	MUC1 (non-mutated)	scRNA-seq	T-cell response	Phase 1/2, immunogenicity	7
Cai *et al.*, 2019	China	Gastric	14,929	N/A (risk prediction)	Serology, ML	Diagnostic accuracy	Cross-sectional, AUC	6
Sullivan *et al.*, 2020	UK	Lung	12,208	Autoantibody (non-mutated)	Serology	Diagnostic accuracy	Phase 4, stage shift	7
Borger *et al.*, 2025		Melanoma	157	SNV/INDEL	WES/RNA	Clinical outcome, T-cell response	Phase 2b, RFS/OS	9

SNV – Single Nucleotide Variant, **INDEL** – Insertion–Deletion Mutation, **mHsp70** – Membrane Heat Shock Protein 70, **ctDNA** – Circulating Tumor DNA, **IDH1** – Isocitrate Dehydrogenase 1, **CD133** – Cluster of Differentiation 133, **WES** – Whole-Exome Sequencing, **RNA-seq** – RNA Sequencing **scRNA-seq** – Single-Cell RNA Sequencing, **Bioinformatics / Computational Tools pVACseq** – Personalized Variant Antigen Predictor Sequencing Pipeline, **DC vaccine** – Dendritic Cell Vaccine, **ICI** – Immune Checkpoint Inhibitor, **CAR-T** – Chimeric Antigen Receptor T-cell Therapy, **NK cell therapy** – Natural Killer Cell Therapy **IHC** – Immunohistochemistry, **OS** – Overall Survival, **PFS** – Progression-Free Survival, **DFS** – Disease-Free Survival **RFS** – Recurrence-Free Survival, **DMFS** – Distant Metastasis-Free Survival, **EFS** – Event-Free Survival, **pCR** – Pathologic Complete Response, **TNBC** – Triple-Negative Breast Cancer, **NSCLC** – Non–Small Cell Lung Cancer, **HCC** – Hepatocellular Carcinoma, **RCC** – Renal Cell Carcinoma, **GEJ** – Gastroesophageal Junction, **USA** – United States of America, **UK** – United Kingdom

Table 2. Key Technologies in Neoantigen Identification

Technology/Tool	Main Features	References
pVACtools	End-to-end workflow, visualisation, vaccine design	Hundal *et al.*, 2020
NeoPredPipe	High-throughput, multi-region analysis	Schenck *et al.*, 2018
Neopepsee	Machine learning, improved specificity.	Kim *et al.*, 2018
EDGE	Deep learning, improved predictive value	Bulik-Sullivan *et al.*, 2018
Proteogenomics	Mass spectrometry validation, peptide detection	Wen *et al.*, 2020; Ren *et al.*, 2024; Luo *et al.*, 2025

Key: pVACtools – Personalised Variant Antigen Calling tools, NeoPredPipe – Neoantigen Prediction Pipeline, Neopepsee – Neoantigen Peptide Selection and Evaluation Engine, EDGE – Epitope Discovery using Genetic and Epigenetic features.

Table 3. Synthesis of Scientific Rationale Supporting Advances in Neoantigen Identification and Immunotherapy

Claim	Reasoning	References
NGS and bioinformatics enable rapid, patient-specific neoantigen identification	Multiple high-quality studies and clinical trials support this workflow.	Chen *et al.*, 2019; Richters *et al.*, 2019; Gopanenko *et al.*, 2020; Lang *et al.*, 2022
Mass spectrometry-based immunopeptidomics provides direct validation of neoantigen presentation.	Direct detection of MHC-bound peptides in patient samples	Chen *et al.*, 2019; Zhang *et al.*, 2019
Neoantigen-based vaccines and T cell therapies can induce durable clinical responses.	Clinical trials and case studies report durable responses in some patients.	Chen *et al.*, 2019; Lang *et al.*, 2022; Li *et al.*, 2023
AI and multi-omics integration improve neoantigen prediction accuracy	Emerging evidence from recent computational and experimental studies	Bulik-Sullivan *et al.*, 2018; Tang *et al.*, 2020; Zeng *et al.*, 2025
Only a small fraction of predicted neoantigens are truly immunogenic	Experimental validation rates remain low; need for improved prioritisation	Miller *et al.*, 2024; Tokita *et al.*, 2024
Tumour heterogeneity and immune evasion limit the efficacy of neoantigen-based therapies.	Observed in clinical and preclinical studies; ongoing challenge	Roudko *et al.*, 2020; Chen *et al.*, 2021

Key: NGS – Next-Generation Sequencing, MHC – Major Histocompatibility Complex, AI – Artificial Intelligence, T cell therapies – Therapies involving T lymphocytes, including TCR-T (T Cell Receptor-Engineered T Cells) and CAR-T (Chimeric Antigen Receptor T Cells

3.2.1 Evidence map cancer types have MS-validated neoantigens vs only predicted

The comparative analysis shown in Figure 3 revealed the heterogeneity in validation approaches, with malignancies such as melanoma and glioma demonstrating a greater propensity for experimental confirmation. In contrast, studies in lymphoma, lung, and gastroesophageal cancers relied predominantly on computational prediction. This disparity underscores the variable translational maturity of neoantigen research across oncological indications and highlights a critical area for methodological advancement in the field.

3.3 Neoantigen identification and predictions

The field of neoantigen identification has rapidly evolved with high-throughput sequencing and powerful technological and computational methods (Table 2), allowing the finding of patient-specific immunotherapy targets (Richters *et al.*, 2019; Hundal *et al.*, 2020; Roudko *et al.*, 2020; Lang *et al.*, 2022). Mass spectrometry-based immunopeptidomics, as described in Table 3, has emerged as the gold standard for experimental validation, despite being more technically difficult and less scalable than computational techniques (Tokita *et al.*, 2024; Huber *et al.*, 2024). The integration of multi-omics data with AI-driven prediction models enhances the accuracy and clinical relevance of neoantigen selection (Huber *et al.*, 2024; Zeng *et al.*, 2025). However, tumour heterogeneity poses a difficulty in translating these discoveries into effective therapeutics. Nevertheless, tumour heterogeneity, immune evasion, and the need to fully validate immunogenicity are some of the issues that lead to the challenge of applying these insights to successful therapy (Chen *et al.*, 2019; Li *et al.*, 2023; Naffa *et al.*, 2025).

The precise and effective recognition of neoantigens is a bedrock for the successful development of personalised cancer immunotherapies, which are exclusive targets essential for the regulation of T-cell-mediated anti-tumour immune functions (Mork *et al.*, 2024). Neoantigen discovery is a complex process that involves multifaceted mechanisms combining superior genomic, computational, and proteomic approaches and is ultimately validated by an experimental procedure that verifies immunogenicity (Borden *et al.*, 2022). Three decades of technological advancements have seen these technologies improve substantially over the last ten years, allowing researchers to systematically discover the varied topography of

tumour-specific antigens that can be used to trigger therapeutic intervention (Chen *et al.*, 2021).

3.3.1 Genomic Approaches

The sequencing technologies that underlie neoantigen identification include genomic sequencing, which provides the raw data on which tumour-specific alterations are initially identified. The main genomic methods used for neoantigen identification include next-generation sequencing (NGS) and high-throughput single-cell sequencing, as well as proteomic techniques such as mass spectrometry and other bioinformatics tools (Chen *et al.*, 2021).

3.3.1.1 Whole-Exome Sequencing

Whole-Exome Sequencing (WES) is commonly used to detect somatic DNA mutations, such as single-nucleotide variants (SNVs) and small insertions/deletions (indels), which are major sources of neoantigens (Capietto *et al.*, 2022). Such mutations alter peptide sequences that, when bound to major histocompatibility complex (MHC) molecules, can trigger T-cell recognition (Xia *et al.*, 2023). It is important to identify these mutated peptides to design cancer vaccines and predict cancer reactions to immunotherapies (Xia *et al.*, 2023). WES is a relatively inexpensive method for surveying the protein-coding genome, including most known neoantigens, thereby providing a complete list of possible neoepitopes in a given tumour (Borden *et al.*, 2022).

3.3.1.2 Whole Genome Sequencing

In addition to SNVs and indels, genomic studies have recently been broadened to encompass structural variations (SVs), which are also common in cancer and play an important role in the the neoantigen repertoire (Shi *et al.*, 2023). These larger genomic rearrangements, including gene fusions, which may result in the creation of new proteins and, thus, neoantigens, require Whole-Genome Sequencing (WGS) for detection (Capietto *et al.*, 2022). An example of a computational approach that includes SV annotation, protein fragmentation, and MHC-binding prediction to predict SV-derived neoantigens is NeoSV, which demonstrates that SV can make quantitative and qualitative contributions to the entire neoantigen landscape (Shi *et al.*, 2023).

3.3.1.2 RNA-Sequencing (RNA-seq)

Moreover, RNA-seq will become even more important for understanding the dynamic processes of the tumour cell transcriptome, providing information on neoantigens and post-transcriptional changes. Splicing variants neoantigens, such as occur due to misregulated splicing of RNA and are an important but not yet well-exploited pool of universal antigens (Li *et al.*, 2024; Capietto *et al.*, 2022).

New computational tools such as NeoSplice have been designed to predict these neoantigens using k-mers from RNA-seq data, differential expression transcript alignment, and transcript MHC-binding prediction, with high sensitivity and precision (Chai *et al.*, 2022). Similarly, the Isoform peptides of the RNA to Immunotherapy target Screening (IRIS) computational platform uses large-scale normal transcriptomic data and combines several screening methods to discover alternative splicing (AS)-derived tumour antigens, including microexon-encoded antigens (Pan *et al.*, 2023).

RNA-seq data is also essential for determining neoantigens present in other non-canonical sources. For example, A-to-I RNA editing may contribute to transcriptomic and proteomic diversity in cancer, producing peptides that are inherently displayed by human leukocyte antigen (HLA) molecules and can activate CD8+ T cells (Zhou *et al.*, 2020).

A comprehensive and systematic pipeline for identifying these neoantigens is called PREP and is an integrated RNA-editing-based pipeline designed to identify all such neoantigens across different cancer types (Zhou *et al.*, 2020). Moreover, DNA methyltransferase inhibitors (DNMTi) and Histone deacetylase inhibitors (HDACi) could then be used as epigenetic therapies to derepress endogenous retroviral element (ERV)-encoded promoters and express new polyadenylated transcripts (TINPATs), resulting in HLA-presented neopeptides (Goyal *et al.*, 2023).

The presentation of these ERV-derived neoantigens is confirmed by Deep RNA sequencing and the combination of immunopeptidomics, which have shown that RNA is an important, but poorly examined, source of cancer antigens (Tretter *et al.*, 2023; Goyal *et al.*, 2023). Combining DNA and RNA sequencing with MS-based immunopeptidomics is therefore critical for complete proteogenomic-based neoantigen discovery, which can identify a large repertoire of non-canonical, non-HLA-binding peptides (Tretter *et al.*, 2023).

3.3.2 Prediction (MHC-binding tools, ML/AI models)

3.3.2.1 Major Histocompatibility Complex (MHC) Binding Tools.

3.3.2.1.1 Neoantigen Prioritisation is the use of computational tools.

After identifying genetic variants using genomic sequencing, computational prediction methods are imperative to filter large volumes of information and focus on potential neoantigens likely to be immunogenic. Bioinformatics tools are essential for analysing high-throughput sequencing and mass spectrometry data, as well as biological databases, to identify neoantigens. Functionally, the typical standard workflow of neoantigen prediction will consist of a series of steps: calling genetic variants between tumour and blood samples, ranking the affinity of mutated peptides to MHC class I and II molecules, T cell receptor (TCR) interaction prediction, and lastly, immunogenicity of these tumour epitopes (Borden *et al.*, 2022).

3.3.2.1.2 MHC Binding Traditional Prediction Tools.

Peptide-MHC binding affinity is the primary predictor in traditional computational methods, including MHCflurry

and NetMHCpan (Tang *et al.*, 2020). These algorithms are developed to predict the strength of interaction between a particular peptide and a specific MHC allele, a prerequisite for T-cell presentation. Nevertheless, the use of binding affinity predictions alone has not been proven to be predictive of actual immunogenicity because not every MHC-binding peptide is capable of triggering a strong immune response (Tang *et al.*, 2020; Chen *et al.*, 2021).

3.3.3 Models of Machine Learning and Artificial Intelligence.

3.3.3.1 Neoantigen Prediction affected by AI and ML.

The implementation of Artificial Intelligence (AI) and Machine Learning (ML) has changed the concept of neoantigen prediction, providing strong tools to identify the multidimensional nature of omics data and extract important neoantigen characteristics (Yu *et al.*, 2023; Mani *et al.*, 2025). Newly developed deep learning tools and pipelines based on ML algorithms have been shown to provide significant advantages for boosting existing computational pipelines in neoantigen prediction (Cai *et al.*, 2023). For example, the AI system PIONEERtm has already been successfully applied to the identification of tumour-derived neoantigens for incorporation into therapeutic cancer vaccines, demonstrating the feasibility of AI in this context (Mork *et al.*, 2024).

3.3.3.2 ML-based Neoantigens Pipelines that are integrated and hybrid.

Hybrid or combined ML algorithms are now being used to build more integrated neoantigen-predicting pipelines that no longer rely on traditional machine learning models (Yu *et al.*, 2023). One of them is NeoDisc, an end-to-end clinical proteogenomic pipeline that unites state-of-the-art publicly available and in-house immunopeptidomics, genomics, and transcriptomics software with in silico identification, prediction, and prioritisation of tumour-specific and immunogenic antigens (Huber *et al.*, 2024). NeoDisc is better than other pipelines at prioritising immunogenic neoantigens over their candidates, thanks to a variety of features that enable rule-based and machine-learning methods to uncover personalised antigens (Huber *et al.*, 2024). On the same note, TruNeo is a computational pipeline that predicts and discriminates highly immunogenic neoantigens by including several biological processes other than the prediction of affinity between peptides and MHC (Tang *et al.*, 2020). The high number of recall of immunogenic neoantigens in TruNeo relative to both MHCflurry and NetMHCpan is an essential benefit of the comprehensive method (Tang *et al.*, 2020).

3.3.3.3 Specialised Neoantigens Type Prediction.

Computational prediction has also been extended to specific neoantigen forms. An example of such a method is the approach of predicting splice-variant neoantigens, which could be a source of patient-specific tumour antigens (Chai *et al.*, 2022). It relies on k-mberg using RNA-seq data, matching differentially expressed transcripts to a graph genome, and predicting transcript MHC binding (Chai *et al.*, 2022). Another open-source computational workflow is the Splicing Neo Antigen Finder (SNAF), which is a splicing-derived MHC-bound peptide predictor that uses highly accurate deep immune genomic prediction (DeepImmuno) (Li *et al.*, 2024). To predict HLA-epitope interactions, DeepNetBim is a network-based deep learning architecture that leverages both binding and immunogenicity data, demonstrating increased predictive performance with centrality measures and greater accuracy than other state-of-the-art architectures (Yang *et al.*, 2021). The user-friendly bioinformatic pipeline nextNEOpi is another program that predicts neoepitope binding and measures immunogenicity- and patient-specific aspects related to immunotherapy response (Rieder *et al.*, 2021).

3.3.3.4 Predication Structural and Anchor-Based Predictions.

Another variable that may be underappreciated in prediction pipelines is the position of a mutation within a peptide relative to the anchor positions in the MHC of patients with a particular MHC. There are T cell receptor recognition-crucial peptide residues and anchor-causing MHC ones. By computationally predicting MHC anchors for frequent HLA alleles, scientists can identify misclassified neoantigen candidates and enhance the predictive power of clinical research (Xia *et al.*, 2023).

3.3.4 Proteomic/Immunopeptidomics (Mass Spectrometry, HLA Ligandome)

3.3.4.1 Overview of Mass Spectrometry–Based Immunopeptidomics

While genomic and computational approaches predict potential neoantigens, mass spectrometry (MS)-based immunopeptidomics provides the crucial direct evidence of actual peptide presentation on the cell surface by human leukocyte antigen (HLA) molecules (Becker & Riemer, 2022). This state-of-the-art methodology is essential for capturing the breadth and depth of the immunopeptidome across various HLA allotypes and cell types, making it indispensable for effective and safe cancer immunotherapy design (Zhang & Bassani Sternberg, 2023).

3.3.4.2 The summary of Mass Spectrometry-Based Immunopeptidomics

Although genomic and computational methods can predict the potential presence of neoantigens, the direct detection of peptides bound to human leukocyte antigen (HLA) molecules on the cell surface is provided by mass spectrometry (MS)-based immunopeptidomics (Becker and Riemer, 2022). It is a state-of-the-art technique needed to capture the scope and detail of the immunopeptidome across multiple HLA allotypes and cell types, thus being indispensable to the effective and safe design of cancer immunotherapy (Zhang & BassaniSternberg, 2023).

3.3.4.3 Workflow and MS Acquisitions Strategies (DDA, DIA, Targeted)

The standard approach to MS-based immunopeptidomics will entail immunoaffinity purification of HLA complexes from tumour samples, followed by MS profiling of the purified peptides (Zhang and BassaniSternberg, 2023). There are various methods of performing this profiling, such as data-dependent acquisition (DDA), data-independent acquisition (DIA), or targeted methods (Zhang and Bassani Sternberg, 2023). DDA is typically used in discovery-based immunopeptidomics experiments because it produces high-quality reference peptide fingerprints (Pak *et al.*, 2021).

Nevertheless, DDA is not ideal in terms of sensitivity and reproducibility due to stochastic selection of abundant ions, which reduces its applicability to wholesome mapping of complex samples (Pak *et al.*, 2021). On the contrary, DIA selectively breaks down all ions within specific isolation m/z ranges, producing a more detailed sample map (Pak *et al.*, 2021). One of the major problems facing DIA in translational research is the need for DDA-based spectrum libraries, which is not always feasible for analysing noncanonical or personalised neoantigens, particularly when using small amounts of biological samples, such as small tissue biopsies (Pak *et al.*, 2021). To address this, multi-HLA spectral libraries and MS/MS prediction workflows demonstrated a two- to three-fold increase in identification with large-scale (even low-sample) sample-free libraries, without negative impacts on specificity (Pak *et al.*, 2021).

3.3.4.4 The integration of proteogenomics (Genomics + Transcriptomics + MS)

The immunopeptidomics approach is further enhanced when combined with genomic and transcriptomic data, forming a proteogenomic framework. It is an effective approach to identify neoantigens encoded by canonical open reading frames and non-canonical or novel peptides from presumably non-coding genomic regions (Zhang and BassaniSternberg, 2023; Huber *et al.*, 2024). For example, a multi-omics data set combining DNA and RNA sequencing with MS-based immunopeptidomics has been used to identify numerous tumour-specific/tumour-associated antigens and to identify a wide range of non-canonical HLA-binding peptides in cancer patients (Tretter *et al.*, 2023).

3.3.4.5 Proteogenomic Pipelines and antigen presentation defects.

Mass spectrometric immunopeptidomics data are directly incorporated into proteogenomic pipelines, such as NeoDisc, which allow the identification of tumour-specific and immunogenic antigens of various origins and their prioritisation (Huber *et al.*, 2024). This is a holistic method that can detect flaws in the cellular antigen presentation apparatus, which can affect the heterogeneous tumour antigenic profile (Huber *et al.*, 2024). Additionally, MS-based immunopeptidomics has played a major role in identifying neoantigens induced by treatment. An example is that an integrated genomic and proteomic approach showed that interferon-gamma (IFN-g) treatment can modify antigen presentation, resulting in the emergence of distinct MHC-I- and MHC-II-presented peptides, as well as alterations in proteasome subunits (Olsson *et al.*, 2021).

3.3.4.6 Detection of Non-Canonical and Treatment-Induced Neoantigens

Immunopeptidomics also plays a critical role in confirming the presence of neoantigens derived from less conventional sources. Neoantigens from less conventional sources are also a major concern, and immunopeptidomics is essential for verifying their existence. As an illustration, the expression of A-to-I RNA editing variant peptides has been demonstrated by mass spectrometry data, which validates their possible role as neoantigens (Zhou *et al.*, 2020). Equally, immunopeptidomics has also revealed HLA presentation of spectra-validated neopeptides derived from endogenous retroviral element (ERV)-derived transcripts activated by epigenetic therapies, uncovering new sources of immunogenic targets (Goyal *et al.*, 2023). Mass spectrometry-based immunopeptidomics has been applied to whole exome sequencing of neoantigenic cancer peptides in a model of murine mammary carcinoma, demonstrating its utility even in low-mutational-burden tumours (Mohsen *et al.*, 2022). The latest developments in MS technology and computational tools are constantly enabling the identification of tumour antigens with increased sensitivity and accuracy, leading to more effective immunotherapies (Zhang & BassaniSternberg, 2023).

3.3.5 Experimental validation (T-cell assays, ELISPOT, tetramer staining)

3.3.5.1 General summary of experimental validation of Neoantigens.

Once the potential neoantigens have been identified using genomic and computational pipelines and their presentation confirmed by immunopeptidomics, it is essential to determine their immunogenicity and capacity to trigger a specific anti-tumour immune response by experimentally validating the identified neoantigens. This step goes beyond prediction and demonstration to prove their T-cell functionality, which is essential to the tool of cancer immunotherapy (Becker and Riemer, 2022). The idea is to ensure that the targeted neoantigens can elicit T-cell immunity against cancer (Pao *et al.*, 2022).

3.3.5.2 T-Cell Neoantigen Immunogenicity T-Cell Functional Assays.

Among the main strategies of experimental validation, one can identify a set of T-cell studies that evaluate T-cell activation and functionality in neoantigen presentation. Such assays aid in assessing the immunogenicity of predicted binding molecules, since many are not immunogenic (Yang *et al.*, 2021). For example, immunogenicity and recognition of alternative splicing-derived neoepitopes, assessed by in vitro priming with single-cell sequencing, have shown high activity of

transduced T cell receptors (TCRs) against individual peptides (Pan *et al.*, 2023).

3.3.5.3 Elisa T-Cell response Neoantigen-Specific ELISpot assays.

ELISpot assays are a sensitive and common technique to estimate the number of antigen-specific T cell responses, where the amount of cytokine (interferon-gamma (IFN-g) released upon neoantigen stimulation is a reliable measure of cellular immune response (Mork *et al.*, 2024). ELISpot assays have often been used to verify that patients receiving neoantigen vaccines have neoantigen-specific T cell responses. For example, a DNA plasmid vaccine (GNOS-PV02) customised to individual neoantigens in advanced hepatocellular carcinoma patients demonstrated T cell responses to neoantigens, confirmed in a large proportion of post-assessable patients by ELISpot (Yarchoan *et al.*, 2024). Equally, in a dose-escalation trial of the personalised peptide-based neoantigen vaccine EVX-01, the intensity of the immune response, as measured by an IFN-γ ELISpot assay, correlated with the administered vaccine dose, indicating strong immunogenicity (Mork *et al.*, 2024). Moreover, ELISpot tests were employed to validate the idea that shared frameshift neoantigens produced during early carcinogenesis redirected their potential to induce T-cell responses and could be used to develop vaccines (Bolivar *et al.*, 2024). The induction of elevated CD107a, CD137, and IFN-g, and the secretion of IFN-g in CD8+ T cells, as measured by flow cytometry and ELISpot assays in hepatobiliary tumour organoids, has also been used to define immunogenic peptides (Wang *et al.*, 2022).

3.3.5.4 Staining of Neoantigen-Specific T Cells by Tetramers.

Another important method is staining for Tetramers, which directly determines and counts the number of T cells specific to the neoantigen. MHC multimers (tetramers or pentamers) are artificial compounds of MHC molecules loaded with a certain peptide and can bind and identify T cells with the cognate TCR (Bolivar *et al.*, 2024). This technique enables straightforward visualisation and counting of T cells targeting neoantigens, which is a clear indication of an induced immune response. The immunogenicity of identified mutated neoantigens predicted by tetramer-based methods was validated in a study of Lynch syndrome colorectal neoplasia (Bolivar *et al.*, 2024).

3.3.5.5 Additional Experimental Approaches for Neoantigen Validation

In addition to those direct assays, other experimental methods are added to the validation. Another significant factor in neoantigen presentation, experimentally tested by competitive binding assays, is peptide-MHC stability (Xia *et al.*, 2023). Single-cell analysis, such as T cell receptor (TCR) bulk sequencing and single-cell RNA sequencing, has become increasingly useful for studying the dynamics of tumour-infiltrating T cells and T-cell receptor clonotypes induced by vaccination (DAlise *et al.*, 2024; Yarchoan *et al.*, 2024). For example, the expansion and diversification of vaccine-induced TCR clonotypes in post-treatment biopsies from patients with clinical responses were observed during a phase Ib trial of the viral vector-based personalised vaccine NOUS-PEV (DAlise *et al.*, 2024). Likewise, in high-stage HCC patients receiving a personalised DNA vaccine, TCR b-chain bulk sequencing data showed vaccination-enhanced T cell clone expansion and tumour infiltration, whereas single-cell analysis showed post-vaccination T cell clonal expansion of the cytotoxic T cell phenotype (Yarchoan *et al.*, 2024).

3.3.5.6 Neoantigen-Based Therapeutics Experimental validation integration.

A combination of these experimental validation methods is important to overcome the gap between computational predictions and clinically effective immunotherapies. They enable the identification of high-confidence, immunogenic neoantigens that may be integrated into individualised cancer therapy, eventually improving the effectiveness and safety of cancer therapy (Borden *et al.*, 2022; Becker & Riemer, 2022).

3.4 Clinical Translation

The path of neoantigens from their discovery in laboratory facilities to actual use in clinical care, is a major shift in the paradigm of cancer immunotherapy. Therapies that use neoantigens are progressively being applied in the clinical setting and are proving to be an efficient and promising field of cancer therapy. These targeted therapies will leverage the patient's immune system to specifically target and kill cancer cells, promising long-term responses and minimal off-target toxicity (Xie *et al.*, 2023).

3.4.1 Passive vaccines refer to personalised Neoantigen Vaccines

Individualised neoantigen vaccines are a novel approach to cancer immunotherapy.(Table 4) which aims to induce de novo T cell responses to the individual neoantigens present in a specific patient's tumour (Blass *et al.*, 2021). Such vaccines are designed to enhance and expand the endogenous repertoire of tumour-specific T cells, based on the fact that neoantigens are highly immunogenic and are not subject to central or peripheral tolerance (Xie *et al.*, 2023).

3.4.1.1 Peptide Vaccine

A notable form of vaccine is peptide-based, which is usually made of synthetic peptides that represent selected neoepitopes and can be adjuvanted to enhance immune responses (Biswas *et al.*, 2023). Adjuvants enhance vaccine efficacy (Biswas *et al.*, 2023). For example, the liposomal adjuvant CAF09b was used to develop the peptide-based neoantigen vaccine EVX-01, which was tested in patients with metastatic melanoma. Clinical study evidence (NCT03715985, not final) showed that EVX-01 was safe and could induce EVX-01-specific T cell responses, including CD4+ and CD8+ T cells (Mork *et al.*, 2024). The induced immune responses were confirmed by

competitive binding assays, and encouraging initial clinical anti-tumour efficacy was observed (Mork *et al.*, 2022). A separate study developed a multi-target vaccine comprising short or long neoantigenic peptides conjugated to virus-like particles (VLPs) as a bedside formulation, which showed enhanced production of neoantigen-specific CD4+ and CD8+ T cells that produced interferon-gamma and tumour-necrosis factor in a murine mammary carcinoma model (Mohsen *et al.*, 2022).

Table 4. Clinical Applications of Cancer Immunotherapies

Clinical Application	Key Features & Outcomes	Citations
Peptide Vaccines	Most common; safe; induce T-cell responses; most effective in melanoma, lung, and brain cancers	Kim *et al.*, 2018; Ding *et al.*, 2021; Niemi *et al.*, 2022
mRNA Vaccines	Customizable and safe; rapidly growing use; promising results in early-phase trials	Cafri *et al.*, 2020; Niemi *et al.*, 2022; Rappaport *et al.*, 2024
Dendritic Cell Vaccines	Induce both CD4+ and CD8+ T-cell responses; safe; show promise in treating advanced cancers	Li *et al.*, 2017; Ding *et al.*, 2021; Kamigaki *et al.*, 2024
Adoptive T-Cell Therapy (TILs/TCR)	Can induce tumor regression; highly personalized therapy	Jiang *et al.*, 2019
Combination with Checkpoint Inhibitors	Enhances efficacy of other therapies; best results in advanced or refractory cancers	Gao *et al.*, 2020; Niemi *et al.*, 2022; Rappaport *et al.*, 2024

Key: mRNA – Messenger Ribonucleic Acid, CD4+ T cells – Helper T Lymphocytes (coordinate immune responses), CD8+ T cells – Cytotoxic T Lymphocytes (directly kill infected or cancerous cells), TILs – Tumor-Infiltrating Lymphocytes, TCR – T Cell Receptor, Checkpoint Inhibitors – Immunotherapy drugs that block immune checkpoints (e.g., PD-1, CTLA-4), enhancing T cell activity

3.4.1.2 RNA Vaccine

RNA vaccines, especially messenger RNA (mRNA) vaccines, can provide a scalable and flexible platform for immunotherapy against cancer, as they can be produced quickly and encode multiple neoantigens (Mani *et al.*, 2025). Such vaccines require the best possible design to induce a strong and specific immune response, where bioinformatics and AI can greatly contribute to the design, prediction, and optimisation of these vaccines (Mani *et al.*, 2025). An mRNA cancer vaccine targeting tandem neoantigens as a lipopolyplex (LPP) has shown great promise. This mRNA vaccine, designed by LPP, induced strong neoantigen-specific CD8+ T cells to control tumour growth in murine tumour models, resulting in long-term memory T cells that prevent tumour cell rechallenge (Fan *et al.*, 2024). Notably, two cancer patients were immunised with this LPP-based personalised cancer vaccine, and meaningful neoantigen-specific T cell and clinical responses occurred, which underscores the need for further clinical trials (Fan *et al.*, 2024). AI-based methods are also being used to optimise mRNA-lipid nanoparticle (LNP) formulations, improve delivery and stability, and, eventually, improve pharmacokinetics and pharmacodynamics (Mani *et al.*, 2025).

3.4.1.3 DNA Vaccine

Other modalities of presenting the neoantigen information to the immune system include DNA vaccines. A therapeutic cancer vaccine (PVC) based on a DNA plasmid (GNOS-PV02) encoding up to 40 neoantigens is a personalised vaccine that has been studied. This vaccine was also tested as a combination vaccine with plasmid-encoded interleukin-12 and pembrolizumab in a phase 1/2 trial in patients with advanced hepatocellular carcinoma (HCC), and proved to be safe, immunogenic, and clinically active (Yarchoan *et al.*, 2024). The presence of neoantigen-specific T cell responses was also established, and clinical responses were linked to the number of neoantigens the vaccine encodes, demonstrating the significance of comprehensive neoantigen targeting (Yarchoan *et al.*, 2024).

3.4.1.4 Dendritic cell

Vaccines based on dendritic cells (DC) utilise the natural role of dendritic cells as professional antigen-presenting cells (APCs) (Tang *et al.*, 2021). The immune-activating function of the DCs lies in the uptake, processing, and presentation of antigens to the T cells (Tang *et al.*, 2021). Individualised neoantigen-pulsed DC vaccines have become safe, immunogenic, and practically viable treatment modalities, especially in melanoma and glioblastoma patients, offering new hope for cancer treatment (Tang *et al.*, 2021). It is based on the fact that neoantigens can only elicit anti-tumour activity when they are taken up by APCs and displayed to T cells (Tang *et al.*, 2021). Hundreds of approved DC vaccine trials are registered on ClinicalTrials.gov, with many currently running, thereby indicating the stability, reliability, and safety of this methodology (Tang *et al.*, 2021).

3.4.2 Neoantigen-Targeted T- cell Therapies.

Adoptive therapy with neoantigen-reactive T cells is a very promising direction in cancer immunotherapy, building on the fact that tumour-specific antigens can induce a strong immune response. This treatment mode typically entails the isolation, growth, and repurposing of a patient's native T cells, which are naturally tumour-infiltrating lymphocytes (TILs), or genetically modified T cells that express new receptors, including T cell receptors (TCRs) or chimeric antigen receptors (CARs) (Morotti *et al.*, 2021). These treatments exploit the fact that T cells have an innate capacity to identify and kill cancer cells that express specific neoantigens on their surfaces (Pao *et al.*, 2022). Early clinical trials have provided strong evidence of long-term response and, in a few instances, even cure, in individuals undergoing adoptive T-cell therapy, especially for solid tumours (Morotti *et al.*, 2021). The effective

translation of these therapies, however, depends on precise identification of tumour-specific antigens and the cognate T-cell receptors, which remains a major challenge, particularly in solid tumours (Pang *et al.*, 2023).

3.4.3 Combination Approaches

Neoantigen vaccines and T-cell therapies can be combined with other standard cancer interventions, including immune checkpoint inhibitors (ICIs), radiotherapy, or chemotherapy, to become much more effective (Lahiri *et al.*, 2023). This approach to combinatorics relies on the fact that although anti-tumour T cell responses can be induced or enhanced by neoantigen-targeted therapy, the tumour microenvironment often induces immunosuppression, rendering them inefficient (Chen *et al.*, 2021). Immune checkpoint therapies (ICTs), an inhibitory system with PD-1/PD-L1, have transformed the treatment of cancer by reactivating depleted T cells and eliciting antitumor effects (Sharma *et al.*, 2021; Zhang *et al.*, 2021). Nevertheless, ICIs are only helpful for subgroups of patients and are associated with primary and secondary resistance (Sharma *et al.*, 2021; Kirtane *et al.*, 2021). Neoantigen-based therapies and ICIs are expected to overcome those mechanisms of resistance, enable a more potent influx of tumour-specific T cells, and, at the same time, take the brakes off their activity (Liu *et al.*, 2022).

3.4.4 Clinical Trial Outcomes

Initial clinical trials of both personalised neoantigen vaccines and adoptive cell therapies have been very promising, demonstrating strong neoantigen-specific T-cell responses, tumour regressions, and overall tolerable safety profiles (Blass & Ott, 2021). These preliminary results highlight the potential of neoantigen-based immunotherapies in the field of oncology (Xie *et al.*, 2023). An example is the potential use of personalised therapeutic cancer vaccines targeting neoantigens, which have been shown to be feasible, safe, and immunogenic in patients with melanoma and glioblastoma (Blass & Ott, 2021). The objectives of these vaccines are to trigger de novo T cell responses to patient-specific tumour neoantigens and to expand the endogenous repertoire of tumour-specific T cells (Blass & Ott, 2021).

3.4.4.1 Efficacy

Regarding efficacy, initial signs of anti-tumour effects with personalised neoantigen-based vaccines have been observed in patients with melanoma and other cancers (Blass & Ott, 2021). In a phase I/II trial of a personalized DNA plasmid vaccine (GNOS-PV02) plus pembrolizumab in the treatment of advanced hepatocellular carcinoma (HCC), an objective response rate was 30.6, 8.3 of which patients had a complete response (Yarchoan *et al.*, 2024). Importantly, the clinical responses in this study correlated with the neoantigen-encoding counts during vaccination, and neoantigen-specific T cell responses were also observed in a high proportion of patients who could be assessed with ELISpot tests (Yarchoan *et al.*, 2024). Likewise, dose-escalation clinical trials of the EVX-01 neoantigen vaccine in a peptide formulation with adjuvant demonstrated responses (6 partial responses, 2 complete responses) in 8 of 12 patients with metastatic melanoma, with all 4 patients in the highest dose group responding with significant tumour regression (Mork *et al.*, 2024). The research also confirmed that there was a correlation between the intensity of the immune response, assessed by IFN-g ELISpot, and the number of individual vaccine doses, as well as a quality score and superior complete responses (Mork *et al.*, 2024). It was also demonstrated that autogene cevumeran, a phase I trial of an adjuvant personalised mRNA neoantigen vaccine in pancreatic ductal adenocarcinoma (PDAC) patients, induced T-cell activity that correlated with a delay in disease recurrence (Rojas *et al.*, 2023). Personalised vaccines, such as NOUS-PEV, which are based on a viral vector, have demonstrated the ability to elicit strong neoantigen-specific immunity in both CD4+ and CD8+ T cells in metastatic melanoma patients (DAlise *et al.*, 2024).

3.4.4.2 Safety

Concerning safety, the preliminary studies have, on the whole, achieved manageable safety profiles. For example, the EVX-01 peptide vaccine had a favourable tolerance profile, with no moderate adverse events reported in the first dose-level group (Mork *et al.*, 2022). The NOUS-PEV regimen was also considered safe, with no serious adverse events associated with the treatment and only mild vaccine-related reactions (DAlise *et al.*, 2024). The customised DNA vaccine in advanced HCC patients reported injection-site reactions as the most frequent treatment-associated adverse event; however, no dose-limiting toxicities or treatment-associated grade 3 events were recorded (Yarchoan *et al.*, 2024). Such safety data plays an essential role in advancing the evolution of neoantigen-targeted therapy and its broader use.

DISCUSSION

4.1 Summary of Main Findings

The key findings of the review indicate significant progress in the discovery of neoantigens and their clinical application. The combination of multi-omics data from Whole Exome/Genome Sequencing (WES/WGS) and RNA-seq with mass spectrometry-based immunopeptidomics has significantly improved the precision of tumour-specific antigen discovery. With the advent of AI and machine learning architectures, computational prediction pipelines have undergone another revolution, with the prioritisation of immunogenic neoantigens enhanced. There are promising safety profiles and potential to elicit tumour-specific T-cell responses with different neoantigen-based platforms, such as peptide, mRNA, and DNA vaccines, as well as adoptive T-cell therapies. Positive objective response rates and associations between the quantity of vaccine-encoded neoantigens and clinical benefit in early-stage trials in several cancer types, including melanoma and

hepatocellular carcinoma support the promise of these individual immunotherapies.

4.2 Challenges & Limitations

Neoantigen-based immunotherapy is a revolutionary treatment method for cancer, but various obstacles hinder clinical delivery of the technology.

4.2.1 Tumour Heterogeneity

One of the main constraints on neoantigen targeting is tumour heterogeneity. (Aljabali *et al.*, 2025) Tumour heterogeneity and clonal evolution have a significant influence on vaccine-based treatment and require multi-epitope targeting and adaptive vaccine development. Such heterogeneity exists at numerous scales, including genomic, epigenetic, and immunological scales, and makes it challenging to identify tumour-cell neoantigens that can be universally targeted across patients with tumours. Clonality-sensitive neoantigen maps have been shown to enhance response prediction in melanoma and heterogeneous NSCLC. Also, (Obermayer *et al.*, 2024) the study of paired primary and metastatic tumours indicates genetic differences that vary by histology, and variants may be negatively selected. Knowledge of clonal structure appears vital for predicting neoantigens to develop an effective vaccine.

4.2.2 The limitation of this prediction accuracy

The correct neoantigen identification is one of the bottlenecks. (Aljabali *et al.*, 2025) The existing neoantigen prediction algorithms have high false-positive and false-negative rates and need to be further combined with multi-omics data and machine learning to achieve better results (Zhang *et al.*, 2025). Neoantigen prediction requires accurate prediction of immunogenomics and immunopeptidomics, but combining the two strategies improves accuracy while suffering from tumour heterogeneity, HLA diversity, and immune evasion. The field has also progressed with (Vo *et al.*, 2025) AI-based methods that have improved the detection of MHC-bound peptides such as low-abundance, noncanonical, and posttranslationally modified epitopes, as well as the peptide-spectrum matching and prediction of the T-cell epitopes. Nevertheless, there are still critical gaps in modelling noncanonical peptides and in explaining the defects in antigen processing.

4.2.3 HLA Diversity

Human leukocyte antigen diversity poses a daunting challenge for individualising neoantigen therapies. HLA molecules are polymorphic, which implies that prediction algorithms trained on small sample sizes of alleles might fail to perform well for poorly represented groups (Zhang *et al.*, 2025). The issue of HLA diversity remains problematic, and further development of HLA diversity depends on dynamic monitoring of the tumour microenvironment and the combination of multi-omics to enhance computational models. Also, the structural and functional diversity of HLA alleles means that more accurate binding-prediction models are required to recognise the peptides presented.

4.2.4 Scalability Barriers: the manufacturing.

Complexity and scalability Manufacturing complexity and scalability are important economic and technical challenges. (Aljabali *et al.*, 2025) Production remains complicated, time-consuming, and expensive, requiring greater standardisation and automation. The present-day design of neoantigen vaccines has been based on personalisation, synthesis of peptides, quality assurance, and validation- in each case increasing the cost and time of the production process. These issues go beyond the aspect of cost. The sphere faces serious problems in acceleration manufacturing, and existing methods have not delivered breakthrough results due to difficulties in design validation, response examination, and acceleration of manufacturing. Standardised procedures, automated production tools, and cost-cutting measures are in high demand to bring neoantigen therapies to clinically and economically viable scales.

4.2.5 Time to Treatment Constraints.

A lengthy period of time between the diagnosis of a tumor and the administration of vaccines is a severe clinical constraint. Neoantigen therapy is a personalised therapy and thus requires tumour tissue sequencing, bioinformatic prediction, peptide synthesis, manufacturing control, and immunological validation, all of which entail months rather than weeks (Wang *et al.*, 2023). Very high, costly, and lengthy preparation procedures, along with ambiguity in prediction algorithms, prevent the use of highly personalised approaches in solid tumour treatments. The problem of this temporal bottleneck, especially in aggressive malignancies such as pancreatic cancer or glioblastoma, is that the disease may rapidly progress during the manufacturing process, making treatment ineffectual or even outdated altogether.

4.2.6 Immune Escape Mechanisms

The tumour microenvironment employs various immune-evasion strategies, significantly reducing the efficacy of neoantigen vaccines. Intratumor heterogeneity, immune escape, and intrinsic immunogenicity, which are frequently limited by the nature of single neoepitopes, still limit clinical efficacy. Such escape routes have multiple routes simultaneously (Aljabali *et al.*, 2025). An immunosuppressive tumour microenvironment is overcome with combination therapies such as immune checkpoint inhibitors and adoptive cell therapies, which enhance treatment outcomes. This highlights that neoantigen vaccines do not work alone and need to be combined with measures to address immunosuppression (Zhang *et al.*, 2025). Another severe issue is immune evasion, and future research directions should focus on dynamic tumour microenvironment monitoring and the development of future models. Immunomodulatory methods should be incorporated in order to improve clinical efficacy.

4.3. Comparison of the Review with Past Reviews.

This review will significantly contribute to the existing body of knowledge because it incorporates the most recent data from clinical trials and technological innovations that emerged in 2023-2024 (Xie *et al.*, 2023). Although the extensive literature on personalised peptide-based and mRNA vaccines provided the basis for the present review, the analysis also covers the growing field of combination vaccines, off-the-shelf shared neoantigens, and CRISPR-engineered neoantigen-targeted therapies, which represent paradigm shifts in the field (Fan *et al.*, 2023).

The most important difference is the increasing awareness of the fact that common or overlapping neoantigens may be manipulated to target patient cohorts, specifically in mismatch repair-deficient cancers and certain tumour types (Gurung *et al.*, 2023; Peri *et al.*, 2021). This criticises the traditional paradigm of entirely individualised medicine and offers the benefit of being scalable, which was not possible before (Roudko *et al.*, 2021). Also, previous reviews have been conservative about the role of non-canonical sources of neoantigens, such as RNA editing events, ERV-derived transcripts, and structural variants, which are now shown to have a strong impact on therapy response (Tretter *et al.*, 2023).

Single-cell TCR sequencing combined with multi-omics profiling is another important improvement in methodology that is not fully covered in the literature before, allowing immune responses to vaccines to be studied on a mechanistic level never before (DAlise *et al.*, 2024), (Yarchoan *et al.*, 2024). Intelligence-based systems such as PIONEERtm and more advanced deep learning algorithms have evolved from research concepts into clinical trials in vaccine manufacturing pipelines, thereby reducing time-to-treatment (Mork *et al.*, 2024).

4.4 Review Strengths and limitations.

The main advantage of this review is its comprehensive and up-to-date overview of a fast-changing field, spanning a broad range from peptide vaccines to CRISPR-adjusted T cells. It is evidence-based, focusing more on information from recent clinical trials to determine real-world efficacy and safety, and includes a multi-omics perspective that is missing from narrower reviews. Nevertheless, the review also pledges significant shortcomings. The included study sample exhibits a high degree of heterogeneity in terms of patient populations, treatment regimens, and outcome measures, making it impossible to conduct any meta-analysis or even to make direct cross-trial comparisons. Moreover, the external validity of the results is limited by the non-representation of the global HLA in the underlying study, with the majority of the clinical data and prediction algorithms biased against alleles found in European and North American populations, which presents equity issues.

FUTURE DIRECTIONS

5.1 Multi-omics Integration

The following stage of neoantigen discovery will need a smooth combination of the DNA, RNA, ribosomal, protein and spatial data to create detailed proteogenomic maps of tumours (Tretter *et al.*, 2023; Zhang *et al.*, 2023). Modern research shows that RNA-based variant detection identifies a significantly larger proportion of immunologically relevant candidates than DNA-based methods, suggesting a lack of completeness in existing genomic-only pipelines (Tretter *et al.*, 2023). New technologies such as spatial transcriptomics can be used to characterise neoantigen presentation, immune cell infiltration, and TME composition in intact tissue architecture, thereby mapping molecular phenotypes to functional immunological activity (Cai *et al.*, 2023). These spatial datasets, combined with single-cell sequencing, should allow the first-ever resolution of tumour-immune interactions, thereby resolving the obscurity around therapeutic efficacy and resistance (Christodoulou & Zaravinos, 2023).

5.2 AI/Deep Learning Advances

Instead of limiting itself to the existing method of ranking epitopes, AI applications will be used to rationalise the construction of optimal multi-epitope vaccines, rewire TCRs to achieve better tumour recognition, and predict immunosuppressive pathway activation (Cai et al., 2023; Mani *et al.*, 2025). International clinical trial datasets and immunogenomic databases can be pooled to train machine learning models that identify generalizable principles of neoantigen immunogenicity, independent of an individual patient's heterogeneity (Li *et al.*, 2024). DeepTCR and other similar systems will also be capable of predicting the likelihood of TCR-epitope recognition based on the primary sequence and structural context, significantly decreasing the scale of the screen needed to develop adoptive cell therapies (Sidhom *et al.*, 2021). Discovery of synthetic neoantigens with increased immunogenicity and tolerance can be accelerated with generative AI methods (Bravi, 2024).

5.3 Shared/Off-The-Shelf Neoantigens

The advent of recurrent neoantigen identification in certain cancer forms and in HLA types also presents never-before-seen opportunities to scale and allogeneic cell-based therapies, as well as simplified vaccine platforms (Gurung *et al.*, 2023; Peri *et al.*, 2021). Mismatch repair-deficient tumours, such as those that generate predictable frameshift neoantigen repertoires shared in 30-50% of cases with the disease, allow the development of a standard therapeutic product (Roudko *et al.*, 2021). Combining large-scale immunopeptidomic databases (with HLA representation across populations worldwide) with TCR repertoire sequencing will increase the speed at which truly shared, highly immunogenic neoepitopes with cross-population relevance can be identified (Olivier *et al.*, 2023). The solution is expected to make neoantigen immunotherapy more democratic, especially in limited

healthcare systems that cannot afford individualised vaccine production (Sei *et al.*, 2023).

5.4 mRNA-Based Platforms

The mRNA vaccines will evolve with improved lipid nanoparticle chemistries, dose reduction, self-amplifying RNA technology, and co-delivery of immunomodulatory cargos such as checkpoint inhibitor RNA or danger-associated molecular patterns (Mani *et al.*, 2025; Wang *et al.*, 2023). The demonstrated ability to manufacture a rapid clinical product (<1-2 weeks) opens new opportunities for truly personalised, real-time adaptive vaccination strategies (Rojas *et al.*, 2023). The mRNA sequence design, optimised with AI, featuring species-adapted codon usage and predicted secondary structures to induce immunogenicity, will most likely become part of next-generation platforms, which are currently in the preclinical phase (Mani *et al.*, 2025).

5.5 Rapid Manufacturing Technologies.

Hospital-based personalised vaccine or CART cell manufacturing, leveraging point-of-care (PoC) platforms and closed-loop benchtop setups, will bypass centralised manufacturing bottlenecks that now take 2-3 months from tumour sampling to therapeutic delivery (Fan *et al.*, 2023). More affordable and much faster alternatives to viral vectors engineering based on transposon gene delivery systems (Sleeping Beauty, piggyBac) can be used to create adoptive cell therapy with similar efficiency (Sandoval-Villegas *et al.*, 2021; Wagner *et al.*, 2022). High-throughput tetramer staining and single-cell TCR sequencing based on automated immunopeptidomic screening will reduce the epitope validation timescale (weeks) to days, allowing optimisation of clinical trials in real time (Christodoulou & Zaravinos, 2023).

5.6 CRISPR-Neoantigen T Cell Engineered.

CRISPR-Cas9 engineering of adoptive T cells will be engineered to become a regular procedure in order to perform: (1) disrupt endogenous TCR mispairing; (2) target the implantation of engineered neoantigen-specific TCRs into specific safe-harbor loci; (3) knock out immunosuppressive pathways (PD-1, LAG-3, TIM-3); (4) implant IL-15 or IL-18 transgenes to increase persistence (Chen *et al.*, 2024) Base-editing methods can be used to allow the seamless replacement of the sub-optimal TCR sequences without the formation of off-target double-strand breaks, which additionally increases the manufacturing fidelity and clinical safety (Boti *et al.*, 2023). Off-the-shelf HLA-engineered allogeneic T cell products will likely become a clinically viable alternative to custom production, given cost and access constraints (Flahou *et al.*, 2021).

5.7 Growing HLA Global Representation.

Recent neoantigen prediction pipelines perform worse systematically beyond HLA allele frequencies >5% in training datasets, which addresses the "Missing HLA problem" that disproportionately affects non-European populations (Olivier *et al.*, 2023). The underlying equity problem, when unchecked, is that it may lead to the creation of a two-tier system in which neoantigen therapies are variously available to patients from ancestry groups that are highly represented in the research sample, with lasting ethical consequences for precision oncology (Pagliuca *et al.*, 2022).

CONCLUSION

This review synthesises a decade of progress (2015-2025) in neoantigen research, demonstrating that these tumour-specific antigens provide a viable foundation for personalised cancer vaccines and T-cell therapies. Early-phase clinical trials consistently show the ability to induce neoantigen-specific T-cell immunity, with promising objective response rates (30.6% in advanced HCC) when combined with checkpoint blockade. However, the evidence remains limited by methodological heterogeneity across studies, reliance on computational prediction rather than direct proteomic validation, and a predominance of early-phase trials with small sample sizes. The external validity of current findings is constrained by a lack of global HLA representation in both prediction algorithms and clinical trial cohorts.

RESEARCH PRIORITIES

To advance the field, a multi-pronged approach is essential:

I. Mechanistic Knowledge of Resistance: The systematic profiling of the treatment-resistant tumours using multi-omics and spatial analysis will determine actionable resistance pathways that can be combined to be therapeutically applied.

II. HLA Equity and Global Representation: The scientific and ethical responsibility is the active development of research on neoantigen to cover the global genetic diversity.

III. Long-term Durability Studies: Follow-up (>3-5 years) studies of neoantigen-treated groups will conclusively determine whether there is any sustainability in therapeutic responses and history of cumulative toxicity.

IV. Shared Neoantigen Strategies: Once common neoepitopes have been identified and validated in clinical studies across multiple types of cancer, the shared neoantigen strategies will be utilised to develop scalable allogeneic platforms that could be implemented in resource-limited environments.

V. Predictive Biomarkers: A combination of tumour immunological based on neoantigen load (Clonal), T cell infiltration (CD8) and PD-L1 on T cells, and neoantigen characteristics to predict responders in advance.

REFERENCES

Aljabali, A. A. A., Hamzat, Y., Alqudah, A., & Alzoubi, L. (2025). Neoantigen vaccines: advancing personalized cancer immunotherapy.

Exploration of Immunology, 5, 1003190. [Crossref]

Becker, J. P., & Riemer, A. B. (2022). The Importance of Being Presented: Target Validation by Immunopeptidomics for Epitope-Specific Immunotherapies. Frontiers Media. [Crossref]

Biswas, N., Chakrabarti, S., Padul, V., Jones, L., & Ashili, S. (2023). Designing neoantigen cancer vaccines, trials, and outcomes. Frontiers Media. [Crossref]

Blass, E., & Ott, P. (2021). Advances in the development of personalized neoantigen-based therapeutic cancer vaccines. Nature Reviews Clinical Oncology. [Crossref]

Bolen, C., McCord, R., Frampton, G., Bourgon, R., Punnoose, E., Szafer-Glusman, E., … Venstrom, J. (2016). Mutation load and a functional T effector signature may distinguish immunologically distinct and clinically relevant lymphoma subsets. *Blood, 128*(22), 913–913. [Crossref]

Bolivar, A. M., Duzagac, F., Deng, N., Reyes-Uribe, L., Chang, K., Wu, W., Bowen, C....., & Vilar, E. (2024). Genomic Landscape of Lynch Syndrome Colorectal Neoplasia Identifies Shared Mutated Neoantigens for Immunoprevention. Gastroenterology. [Crossref]

Borden, E. S., Buetow, K. H., Wilson, M. A., & Hastings, K. T. (2022). Cancer Neoantigens: Challenges and Future Directions for Prediction, Prioritization, and Validation. Frontiers Media. [Crossref]

Borgers, J. S., Lenkala, D., Kohler, V., Jackson, E. K., Linssen, M. D., Hymson, S., ... & van Buuren, M. M. (2025). Personalized, autologous neoantigen-specific T cell therapy in metastatic melanoma: A phase 1 trial. *Nature Medicine, 31*(3), 881–893. [Crossref]

Boti, M. A., Athanasopoulou, K., Adamopoulos, P. G., Sideris, D. C., & Scorilas, A. (2023). Recent Advances in Genome-Engineering Strategies. Multidisciplinary Digital Publishing Institute. [Crossref]

Bravi, B. (2024). Development and use of machine learning algorithms in vaccine target selection. Nature Portfolio. [Crossref]

Buchroithner, J., Erhart, F., Pichler, J., Widhalm, G., Preusser, M., Stockhammer, G., … Marosi, C. (2018). Audencel immunotherapy based on dendritic cells has no effect on overall and progression-free survival in newly diagnosed glioblastoma: A phase II randomized trial. *Cancers, 10*(10), 372. [Crossref]

Bulik-Sullivan, B., Busby, J., Palmer, C., Davis, M., Murphy, T., Clark, A., Busby, M....., & Yelensky, R. (2018). Deep learning using tumor HLA peptide mass spectrometry datasets improves neoantigen identification. *Nature Biotechnology*, 37, 55-63. [Crossref]

Bunse, L., Rupp, A., Poschke, I., Bunse, T., Lindner, K., Wick, A., … Platten, M. (2022). AMPLIFY-NEOVAC: A randomized, 3-arm multicenter phase I trial to assess safety, tolerability and immunogenicity of IDH1-vac combined with an immune checkpoint inhibitor targeting programmed death-ligand 1 in isocitrate dehydrogenase 1 mutant gliomas. *Neurological Research and Practice, 4*(1), 17. [Crossref]

Buonaguro, L., & Tagliamonte, M. (2023). Peptide-based vaccine for cancer therapies. Frontiers Media. [Crossref]

Cafri, G., Gartner, J., Zaks, T., Hopson, K., Levin, N., Paria, B., Parkhurst, M....., & Rosenberg, S. (2020). mRNA vaccine-induced neoantigen-specific T cell immunity in patients with gastrointestinal cancer. *The Journal of clinical investigation.* [Crossref]

Cai, Q., Zhu, C., Yuan, Y., Feng, Q., Feng, Y., Hao, Y....., & Li, J. (2019). Gastrointestinal Early Cancer Prevention & Treatment Alliance of China (GECA). Development and validation of a prediction rule for estimating gastric cancer risk in the Chinese high-risk population: a nationwide multicentre study. *Gut*, *68*(9), 1576–1587. [Crossref]

Cai, Y., Chen, R., Gao, S., Li, W., Liu, Y., Su, G.....,& Zhang, X. (2023). Artificial intelligence applied in neoantigen identification facilitates personalized cancer

Capietto, A.-H., Hoshyar, R., & Delamarre, L. (2022). Sources of Cancer Neoantigens beyond Single-Nucleotide Variants. Multidisciplinary Digital Publishing Institute. [Crossref]

Chai, S., Smith, C. C., Kochar, T. K., Hunsucker, S. A., Beck, W., Olsen, K., Vensko, S....., & Vincent, B. G. (2022). NeoSplice: a bioinformatics method for prediction of splice variant neoantigens. Oxford University Press. [Crossref]

Chen, I., Chen, M. Y., Goedegebuure, S. P., & Gillanders, W. E. (2021). Challenges targeting cancer neoantigens in 2021: a systematic literature review. Informa. [Crossref]

Chen, R., Fulton, K., Twine, S., & Li, J. (2019). Identification of mhc peptides using mass spectrometry for neoantigen discovery and cancer vaccine development. Mass spectrometry reviews. [Crossref]

Chen, X., Zhong, S., Zhan, Y., & Zhang, X. (2024). CRISPRCas9 applications in T cells and adoptive T cell therapies. BioMed Central. [Crossref]

Christodoulou, M., & Zaravinos, A. (2023). Single-Cell Analysis in Immuno-Oncology. Multidisciplinary Digital Publishing Institute. [Crossref]

Dai, H., Tong, C., Shi, D., Chen, M., Guo, Y., Chen, D., … Shen, P. (2020). Efficacy and biomarker analysis of CD133-directed CAR T cells in advanced hepatocellular carcinoma: A single-arm, open-label, phase II trial. *Oncoimmunology, 9*(1), 1846926. [Crossref]

DAlise, A., Leoni, G., Cotugno, G., Siani, L., Vitale, R., Ruzza, V., Garzia, I....., & Bechter, O. (2024). Phase I Trial of Viral Vector-Based Personalized Vaccination Elicits Robust Neoantigen-Specific Antitumor T-Cell Responses. Clinical Cancer Research. [Crossref]

Dillman, R., Cornforth, A., Nistor, G., McClay, E., Amatruda, T., & Depriest, C. (2018). Randomized phase II trial of autologous dendritic cell vaccines versus autologous tumor cell vaccines in metastatic melanoma: 5-year follow up and additional analyses. *Journal for Immunotherapy of Cancer, 6*(1), 33. [Crossref]

Ding, Z., Li, Q., Zhang, R., Xie, L., Shu, Y., Gao, S., Wang, P....., & Yang, L. (2021). Personalized neoantigen pulsed dendritic cell vaccine for advanced lung cancer. Signal Transduction and Targeted Therapy, 6, *Article* 26. [Crossref]

Fan, T., Xu, C., Wu, J., Cai, Y., Cao, W., Shen, H., Zhang, M.....…, & Dong, C. (2024). Lipopolyplex-formulated mRNA cancer vaccine elicits strong neoantigen-specific T cell responses and antitumor activity. Science Advances. [Crossref]

Fan, T., Zhang, M., Yang, J., Zhu, Z., Cao, W., & Dong, C. (2023). Therapeutic cancer vaccines: advancements, challenges and prospects. Springer Nature. [Crossref]

Fennell, D., Hill, K., Zhang, M., Poile, C., Ewings, S., Baitei, E., … Griffiths, G. (2025). Constitutive inflammation and epithelial-mesenchymal transition dictate sensitivity to nivolumab in CONFIRM: A placebo-controlled, randomised phase III trial. *Nature Communications, 16*, 1457. [Crossref]

Flahou, C., Morishima, T., Takizawa, H., & Sugimoto, N. (2021). Fit-For-All iPSC-Derived Cell Therapies and Their Evaluation in Humanized Mice With NK Cell Immunity. Frontiers Media. [Crossref]

Gao, S., Zhu, Z., Wang, J., Fang, J., Zhao, Y., Liu, Z., Wei, G....., & Xu, Q. (2020). Abstract 5577: Effective personalized neoantigen-based cancer vaccine combined with immune checkpoint inhibitor in the treatment of a patients with advanced squamous cell lung cancer failed with multi-line treatments. *Immunology*. [Crossref]

Goloudina, A., Chevalier, F., Authié, P., Charneau, P., & Majlessi, L. (2025). Shared neoantigens for cancer immunotherapy. Molecular Therapy Oncology, 33. [Crossref]

Gopanenko, A. V., Kosobokova, E. N., & Kosorukov, V. S. (2020). Main Strategies for the Identification of Neoantigens. *Cancers,* 12(10), 2879. [Crossref]

Goyal, A., Bauer, J., Hey, J., Papageorgiou, D., Stepanova, E., Daskalakis, M., Scheid, J....., & Plass, C. (2023). DNMT and HDAC inhibition induces immunogenic neoantigens from human endogenous retroviral element-derived transcripts. Nature Portfolio. [Crossref]

Gupta, S. K., Nerli, S., Kandy, S. K., Mersky, G. L., & Sgourakis, N. G. (2023). HLA3DB: comprehensive annotation of peptide/HLA complexes enables blind structure prediction of T cell epitopes. Nature Portfolio. [Crossref]

Gurung, H. R., Heidersbach, A., Darwish, M., Chan, P. P. F., Li, J., Beresini, M. H., Zill, O. A....., & Rose, C. M. (2023). Systematic discovery of neoepitopeHLA pairs for neoantigens shared among patients and tumor types. Nature Portfolio. [Crossref]

Hernandez-Aya, L., Gao, F., Goedegebuure, P. X., Ademuyiwa, F., Park, H., Peterson, L., … Gillanders, W. (2019). A randomized phase II study of nab-paclitaxel + durvalumab + neoantigen vaccine versus nab-paclitaxel + durvalumab in metastatic triple-negative breast cancer (mTNBC). *Journal of Clinical Oncology, 37*(15_suppl), TPS1114. [Crossref]

Huang, P., Wen, F., Tuerhong, N., Yang, Y., & Li, Q. (2024). Neoantigens in cancer immunotherapy: focusing on alternative splicing. Frontiers in Immunology, 15. [Crossref]

Huber, F., Arnaud, M., Stevenson, B. J., Michaux, J., Benedetti, F., Thevenet, J., Bobisse, S.…..., & Bassani-Sternberg, M. (2024). A comprehensive proteogenomic pipeline for neoantigen discovery to advance personalized cancer immunotherapy. Nature Biotechnology. [Crossref]

Hundal, J., Kiwala, S., McMichael, J., Miller, C., Xia, H., Wollam, A., Liu, C....., & Griffith, M. (2020). pVACtools: A Computational Toolkit to Identify and Visualize Cancer Neoantigens. Cancer Immunology Research, 8, 409 - 420. [Crossref]

Igelström, E., Campbell, M., Craig, P., & Katikireddi, S. (2021). Cochrane's risk of bias tool for non-randomized studies (ROBINS-I) is frequently misapplied: A methodological systematic review. Journal of Clinical Epidemiology, 140, 22 - 32. [Crossref]

Isah, M., Olugbemi, P., Tomo, A., Farida, A., Muhammad, A. J., Bilyaminu, G., … Sul'ain, M. D. (2025). From Lab to Market - A Critical Review of Pharmacological Properties , Bioavailability , Formulation , and Commercialization Challenges of Cymbopogon citratus (Lemongrass). *Umyu Scientifica*, **4**(**3**), 367–380. [Crossref]

Janjigian, Y., Van Cutsem, E., Muro, K., Wainberg, Z., Al-Batran, S., Hyung, W., … Tabernero, J. (2022). MATTERHORN: Phase III study of durvalumab plus FLOT chemotherapy in resectable gastric/gastroesophageal junction cancer. *Future Oncology*. Advance online publication. [Crossref]

Jiang, T., Shi, T., Zhang, H., Hu, J., Song, Y., Wei, J., Ren, S., & Zhou, C. (2019). Tumor neoantigens: from basic research to clinical applications. Journal of Hematology & Oncology, 12. [Crossref]

Kamigaki, T., Takimoto, R., Okada, S., Ibe, H., Oguma, E., & Goto, S. (2024). Personalized Dendritic-cell-based Vaccines Targeting Cancer Neoantigens. *AntiCancer Research*, 44, 3713 - 3724. [Crossref]

Kim, S., Kim, H., Kim, E., Lee, M., Shin, E., & Paik, S. (2018). Neopepsee: accurate genome-level prediction of neoantigens by harnessing sequence and amino acid immunogenicity information. *Annals of Oncology*, 29, 1030–1036. [Crossref]

Kirtane, K., Elmariah, H., Chung, C. H., & AbateDaga, D. (2021). Adoptive cellular therapy in solid tumor

malignancies: review of the literature and challenges ahead. BMJ. [Crossref]

Kumar, A., Dixit, S., Srinivasan, K., Dinakaran, M., & Vincent, P. M. D. R. (2024). Personalized cancer vaccine design using AI-powered technologies. Frontiers Media. [Crossref]

Lahiri, A., Maji, A., Potdar, P. D., Singh, N., Parikh, P. M., Bisht, B., Mukherjee, A., & Paul, M. K. (2023). Lung cancer immunotherapy: progress, pitfalls, and promises. BioMed Central. [Crossref]

Lang, F., Schrörs, B., Löwer, M., Türeci, Ö., & Şahin, U. (2022). Identification of neoantigens for individualized therapeutic cancer vaccines. Nature Reviews Drug Discovery, 21, 261 - 282. [Crossref]

Lhuillier, C., Rudqvist, N.-P., Yamazaki, T., Zhang, T., Charpentier, M., Galluzzi, L., Dephoure, N., Clement, C. C., Santambrogio, L., Zhou, X. K., Formenti, S. C., & Demaria, S. (2021). Radiotherapy-exposed CD8+ and CD4+ neoantigens enhance tumor control. American Society for Clinical Investigation. [Crossref]

Li, G., Mahajan, S., Ma, S., Jeffery, E. D., Zhang, X., Bhattacharjee, A., Venkatasubramanian, M., Weirauch, M. T., Miraldi, E. R., Grimes, H. L., Sheynkman, G., Tilburgs, T., & Salomonis, N. (2024). Splicing neoantigen discovery with SNAF reveals shared targets for cancer immunotherapy. American Association for the Advancement of Science. [Crossref]

Li, J., Xiao, Z., Wang, D., Jia, L., Nie, S., Zeng, X., & Hu, W. (2023). The screening, identification, design and clinical application of tumor-specific neoantigens for TCR-T cells. *Molecular Cancer*, 22. [Crossref]

Li, L., Goedegebuure, S., & Gillanders, W. (2017). Preclinical and clinical development of neoantigen vaccines. Annals of oncology: *official journal of the European Society for Medical Oncology*, 28 suppl_12, xii11-xii17. [Crossref]

Liu, L., Chen, J., Zhang, H., Ye, J., Moore, C., Lu, C., Fang, Y., Fu, Y., & Li, B. (2022). Concurrent delivery of immune checkpoint blockade modulates T cell dynamics to enhance neoantigen vaccine-generated anti-tumor immunity. Nature Cancer. [Crossref]

Luo, S., Peng, H., Shi, Y., Cai, J., Zhang, S., Shao, N., & Li, J. (2025). Integration of proteomics profiling data to facilitate discovery of cancer neoantigens: A survey. *Briefings in Bioinformatics, 26*(2), bbaf087. [Crossref]

Mani, S., Li, X., Chen, K., Maghsoudloo, M., Kaboli, P. J., Hashemi, M., Khoushab, S., & Li, X. (2025). Computational biology and artificial intelligence in mRNA vaccine design for cancer immunotherapy. Frontiers Media. [Crossref]

McDermott, D., Huseni, M., Atkins, M., Motzer, R., Rini, B., Escudier, B., … Powles, T. (2018). Clinical activity and molecular correlates of response to atezolizumab alone or in combination with bevacizumab versus sunitinib in renal cell carcinoma. *Nature Medicine, 24*(6), 749–757. [Crossref]

Miller, A., Koşaloğlu-Yalçın, Z., Westernberg, L., Montero, L., Bahmanof, M., Frentzen, A., Lanka, M., Premlal, A., Seumois, G., Greenbaum, J., Brightman, S., Zavala, K., Thota, R., Naradikian, M., Makani, S., Lippman, S., Sette, A., Cohen, E., Peters, B., & Schoenberger, S. (2024). A functional identification platform reveals frequent, spontaneous neoantigen-specific T cell responses in patients with cancer. *Science Translational Medicine*, 16. [Crossref]

Minozzi, S., Cinquini, M., Gianola, S., Castellini, G., Gerardi, C., & Banzi, R. (2019). Risk of bias in nonrandomized studies of interventions showed low inter-rater reliability and challenges in its application.. Journal of clinical epidemiology, 112, 28-35 . [Crossref]

Mohsen, M. O., Speiser, D. E., Michaux, J., Pak, H., Stevenson, B. J., Vogel, M., Inchakalody, V., Brot, S. D., Dermime, S., Coukos, G., BassaniSternberg, M., & Bachmann, M. F. (2022). Bedside formulation of a personalized multi-neoantigen vaccine against mammary carcinoma. BMJ. [Crossref]

Mørk, S. K., Kadivar, M., Bol, K. F., Draghi, A., Westergaard, M. C. W., Skadborg, S. K., … Svane, I. M. (2022). Personalized therapy with peptide-based neoantigen vaccine (EVX-01) including a novel adjuvant, CAF®09b, in patients with metastatic melanoma. OncoImmunology, 11(1). [Crossref]

Mørk, S. K., Skadborg, S. K., Albieri, B., Draghi, A., Bol, K. F., Kadivar, M., Westergaard, M. C. W., Granhj, J. S., Borch, A., Petersen, N. V., Thuesen, N., Rasmussen, I. S., Andreasen, L. V., Dohn, R. B., Yde, C. W., Noergaard, N., Lorentzen, T., Soerensen, A. B., KleineKohlbrecher, D., … Svane, I. M. (2024). Dose escalation study of a personalized peptide-based neoantigen vaccine (EVX-01) in patients with metastatic melanoma. BMJ. [Crossref]

Morotti, M., Albukhari, A., Alsaadi, A., Artibani, M., Brenton, J. D., Curbishley, S. M., Dong, T., Dustin, M. L., Hu, Z., McGranahan, N., Miller, M. L., Santana-Gonzalez, L., Seymour, L. W., Shi, T., Loo, P. V., Yau, C., White, H., Wietek, N., Church, D. N., … Ahmed, A. A. (2021). Promises and challenges of adoptive T-cell therapies for solid tumours. Springer Nature. [Crossref]

Naffaa, M., Al-Ewaidat, O., Gogia, S., & Begiashvili, V. (2025). Neoantigen-based immunotherapy: advancing precision medicine in cancer and glioblastoma treatment through discovery and innovation. Exploration of Targeted Anti-tumor Therapy, 6. [Crossref]

Niemi, J., Sokolov, A., & Schiöth, H. (2022). Neoantigen Vaccines; Clinical Trials, Classes, Indications, Adjuvants and Combinatorial Treatments. *Cancers,* 14. [Crossref]

Obermayer, A., Shaw, T., Chang, D., Davis, J., Teer, J. K., Yu, X., ... & Tarhini, A. A. (2024). Analysis of clonal heterogeneity within paired primary and metastatic tumor samples of patients with solid tumors and implications for neoantigen-based personalized cancer vaccines [abstract]. Cancer Research, 84(6_Suppl), Abstract nr 3886. [Crossref]

Olivier, T., Haslam, A., Tuia, J., & Prasad, V. (2023). Eligibility for Human Leukocyte AntigenBased Therapeutics by Race and Ethnicity. American Medical Association. [Crossref]

Olsson, N., Heberling, M. L., Zhang, L., Jhunjhunwala, S., Phung, Q., Lin, S., Anania, V. G., Lill, J. R., & Elias, J. E. (2021). An Integrated Genomic, Proteomic, and Immunopeptidomic Approach to Discover Treatment-Induced Neoantigens. Frontiers Media. [Crossref]

Ou, X., Ma, Q., Yin, W., Ma, X., & He, Z. (2021). CRISPR/Cas9 Gene-Editing in Cancer Immunotherapy: Promoting the Present Revolution in Cancer Therapy and Exploring More. Frontiers Media. [Crossref]

Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., ... & Moher, D. (2021*)*. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ, 372*, n71. [Crossref]

Pagliuca, S., Gurnari, C., Rubio, M. T., Visconte, V., & Lenz, T. L. (2022). Individual HLA heterogeneity and its implications for cellular immune evasion in cancer and beyond. Frontiers Media. [Crossref]

Pak, H., Michaux, J., Huber, F., Chong, C., Stevenson, B. J., Mller, M., Coukos, G., & BassaniSternberg, M. (2021). Sensitive Immunopeptidomics by Leveraging Available Large-Scale Multi-HLA Spectral Libraries, Data-Independent Acquisition, and MS/MS Prediction. Elsevier BV. [Crossref]

Pan, Y., Phillips, J. W., Zhang, B., Noguchi, M., Kutschera, E., McLaughlin, J., Nesterenko, P. A., Mao, Z., Bangayan, N. J., Wang, R., Tran, W., Yang, H. T., Wang, Y., Xu, Y., Obusan, M. B., Cheng, D., Lee, A., Kadash-Edmondson, K. E., Champhekar, A. S., … Xing, Y. (2023). IRIS: Discovery of cancer immunotherapy targets arising from pre-mRNA alternative splicing. National Academy of Sciences. [Crossref]

Pang, Z., Lu, M.-m., Zhang, Y., Gao, Y., Bai, J.-j., Gu, J.-y., Xie, L., & Wu, W.-z. (2023). Neoantigen-targeted TCR-engineered T cell immunotherapy: current advances and challenges. [Crossref]

Pao, S.-C., Chu, M.-T., & Chung, W. (2022). Therapeutic Vaccines Targeting Neoantigens to Induce T-Cell Immunity against Cancers. Multidisciplinary Digital Publishing Institute. [Crossref]

Peng, M., Mo, Y., Wang, Y., Wu, P., Zhang, Y., Xiong, F., Guo, C., Wu, X., Li, Y., Li, X., Li, G., Xiong, W., & Zeng, Z. (2019). Neoantigen vaccine: an emerging tumor immunotherapy. Molecular Cancer, 18. [Crossref]

Peng, X., Lei, Y., Feng, P., Jia, L., Ma, J., Zhao, D., & Zeng, J. (2023). Characterizing the interaction conformation between T-cell receptors and epitopes with deep learning. *Nature machine intelligence*, 5(4), 395-407. [Crossref]

Peri, A., Greenstein, E., Alon, M., Pai, J. A., Dingjan, T., Reich-Zeliger, S., Barnea, E., Barbolin, C., Levy, R., Arnedo-Pac, C., Kalaora, S., Dassa, B., Feldmesser, E., Shang, P., Greenberg, P., Levin, Y., Benedek, G., Levesque, M. P., Adams, D. J., … Samuels, Y. (2021). Combined presentation and immunogenicity analysis reveals a recurrent RAS.Q61K neoantigen in melanoma. American Society for Clinical Investigation. [Crossref]

Rappaport, A., Kyi, C., Lane, M., Hart, M., Johnson, M., Henick, B., Liao, C., Mahipal, A., Shergill, A., Spira, A., Goldman, J., Scallan, C., Schenk, D., Palmer, C., Davis, M., Kounlavouth, S., Kemp, L., Yang, A., Li, Y., Likes, M., Shen, A., Boucher, G., Egorova, M., Veres, R., Espinosa, J., Jaroslavsky, J., Tardif, L., Acrebuche, L., Puccia, C., Sousa, L., Zhou, R., Bae, K., Hecht, J., Carbone, D., Johnson, B., Allen, A., Ferguson, A., & Jooss, K. (2024). A shared neoantigen vaccine combined with immune checkpoint blockade for advanced metastatic solid tumors: phase 1 trial interim results. *Nature medicine*. [Crossref]

Ren, Y., Yue, Y., Li, X., Weng, S., Xu, H., Liu, L., Cheng, Q., Luo, P., Zhang, T., Liu, Z., & Han, X. (2024). Proteogenomics offers a novel avenue in neoantigen identification for cancer immunotherapy. *International immunopharmacology*, 142 Pt A, 113147. [Crossref]

Richters, M., Xia, H., Campbell, K., Gillanders, W., Griffith, O., & Griffith, M. (2019). Best practices for bioinformatic characterization of neoantigens for clinical utility. *Genome Medicine*, 11. [Crossref]

Rieder, D., Fotakis, G., Auerhofer, M., Geyeregger, R., Paster, W., Trajanoski, Z., & Finotello, F. (2021). nextNEOpi: a comprehensive pipeline for computational neoantigen prediction. Oxford University Press. [Crossref]

Rojas, L. A., Sethna, Z. M., Soares, K., Olcese, C., Pang, N., Patterson, E., Lihm, J., Ceglia, N., Guasp, P., Chu, A., Yu, R., Chandra, A., Waters, T., Ruan, J., Amisaki, M., Zebboudj, A., Odgerel, Z., Payne, G., Derhovanessian, E., … Balachandran, V. (2023). Personalized RNA neoantigen vaccines stimulate T cells in pancreatic cancer. Nature. [Crossref]

Roudko, V., Bozkus, C. C., Greenbaum, B. D., Lucas, A. L., Samstein, R. M., & Bhardwaj, N. (2021). Lynch Syndrome and MSI-H Cancers: From Mechanisms to Off-The-Shelf Cancer Vaccines. Frontiers Media. [Crossref]

Roudko, V., Bozkus, C. C., Orfanelli, T., McClain, C. B., Carr, C., O'Donnell, T., Chakraborty, L., Samstein, R., Huang, K. L., Blank, S. V., Greenbaum, B., & Bhardwaj, N. (2020). Shared Immunogenic Poly-Epitope Frameshift

Mutations in Microsatellite Unstable Tumors. *Cell*, 183(6), 1634–1649.e17. [Crossref]

Salisu, B., Anua, M. S., Wan Ishak, W. R., & Mazlan, N. (2021). A Review on Hepatocellular Carcinoma Attributable to Chronic Aflatoxins ' Exposure in Malaysia for the Last Two Decades. *Malaysian Journal of Medicine and Health Sciences*, **17**(**3**), 223–232. [Link]

Sandoval-Villegas, N., Nurieva, W., Amberger, M., & Ivics, Z. (2021). Contemporary Transposon Tools: A Review and Guide through Mechanisms and Applications of Sleeping Beauty, piggyBac and Tol2 for Genome Engineering. Multidisciplinary Digital Publishing Institute. [Crossref]

Sarivalasis, A., Boudousquié, C., Balint, K., Stevenson, B., Gannon, P., Iancu, E., … Kandalaft, L. (2019). A Phase I/II trial comparing autologous dendritic cell vaccine pulsed either with personalized peptides (PEP-DC) or with tumor lysate (OC-DC) in patients with advanced high-grade ovarian serous carcinoma. *Journal of Translational Medicine, 17*(1), 256. [Crossref]

Schenck, R., Lakatos, E., Gatenbee, C., Graham, T., & Anderson, A. (2018). NeoPredPipe: high-throughput neoantigen prediction and recognition potential pipeline. *BMC Bioinformatics,* 20. [Crossref]

Sei, S., Ahadova, A., Keskin, D. B., Bohaumilitzky, L., Gebert, J., Doeberitz, M. V. K., Lipkin, S. M., & Kloor, M. (2023). Lynch syndrome cancer vaccines: A roadmap for the development of precision immunoprevention strategies. Frontiers Media. [Crossref]

Sharma, P., Siddiqui, B. A., Anandhan, S., Yadav, S. S., Subudhi, S. K., Gao, J., Goswami, S., & Allison, J. P. (2021). The Next Decade of Immune Checkpoint Therapy. American Association for Cancer Research. [Crossref]

Shi, Y., Jing, B., & Xi, R. (2023). Comprehensive analysis of neoantigens derived from structural variation across whole genomes from 2528 tumors. BioMed Central. [Crossref]

Sidhom, J.-W., Larman, H. B., Pardoll, D. M., & Baras, A. S. (2021). DeepTCR is a deep learning framework for revealing sequence concepts within T-cell repertoires. Nature Portfolio. [Crossref]

Sterne, J., Hernán, M., McAleenan, A., Reeves, B., & Higgins, J. (2019). Assessing risk of bias in a non-randomized study. Cochrane Handbook for Systematic Reviews of Interventions. [Crossref]

Storkus, W., Maurer, D., Lin, Y., Ding, F., Bose, A., Lowe, D., … Kirkwood, J. (2021). Dendritic cell vaccines targeting tumor blood vessel antigens in combination with dasatinib induce therapeutic immune responses in patients with checkpoint-refractory advanced melanoma. *Journal for Immunotherapy of Cancer, 9*(9), e003675. [Crossref]

Sullivan, F., Mair, F., Anderson, W., Armory, P., Briggs, A., Chew, C., … Schembri, S. (2020). Earlier diagnosis of lung cancer in a randomised trial of an autoantibody blood test followed by imaging. *The European Respiratory Journal, 57*(2), 2000670. [Crossref]

Tang, L., Zhang, R., Zhang, X., & Yang, L. (2021). Personalized Neoantigen-Pulsed DC Vaccines: Advances in Clinical Applications. Frontiers in Oncology. [Crossref]

Tang, Y., Wang, Y., Wang, J., Li, M., Peng, L., Wei, G., Zhang, Y., Li, J., & Gao, Z. (2020). TruNeo: an integrated pipeline improves personalized true tumor neoantigen identification. BMC Bioinformatics. [Crossref]

Tokita, S., Fusagawa, M., Matsumoto, S., Mariya, T., Umemoto, M., Hirohashi, Y., Hata, F., Saito, T., Kanaseki, T., & Torigoe, T. (2024). Identification of immunogenic HLA class I and II neoantigens using surrogate immunopeptidomes. *Science Advances*, 10. [Crossref]

Tretter, C., Krätzig, N. A., Pecoraro, M., Lange, S., Seifert, P., Frankenberg, C. V., Untch, J. Z....., & Krackhardt, A. M. (2023). Proteogenomic analysis reveals RNA as a source for tumor-agnostic neoantigen identification. [Crossref]

Vidal, J., Casadevall, D., Bellosillo, B., Pericay, C., García-Carbonero, R., Losa, F., … Montagut, C. (2021). Clinical impact of presurgery circulating tumor DNA after total neoadjuvant treatment in locally advanced rectal cancer: A biomarker study from the GEMCAD 1402 trial. *Clinical Cancer Research, 27*(10), 2890–2898. [Crossref]

Vo, T. H., McNeela, E., O'Donovan, O., Rani, S., & Mehta, J. P. (2025). Artificial Intelligence and the Evolving Landscape of Immunopeptidomics. Proteomics. Clinical applications, 19(6), e70018. [Crossref]

Wagner, D. L., Koehl, U., Chmielewski, M., Scheid, C., & Stripecke, R. (2022). Review: Sustainable Clinical Development of CAR-T Cells Switching From Viral Transduction Towards CRISPR-Cas Gene Editing. Frontiers Media. [Crossref]

Wang, W., Yuan, T., Ma, L., Zhu, Y., Bao, J., Zhao, X., Zhao, Y....., & Chen, L. (2022). Hepatobiliary Tumor Organoids Reveal HLA Class I Neoantigen Landscape and Antitumoral Activity of Neoantigen Peptide Enhanced with Immune Checkpoint Inhibitors. Wiley. [Crossref]

Wang, Y., Kumari, M., Chen, G., Hong, M.-H., Yuan, J. P.-Y., Tsai, J.-L., & Wu, H. (2023). mRNA-based vaccines and therapeutics: an in-depth survey of current and upcoming clinical applications. BioMed Central. [Crossref]

Weber, J., Carlino, M., Khattak, A., Meniawy, T., Ansstas, G., Taylor, M., … Zaks, T. (2024). Individualised neoantigen therapy mRNA-4157 (V940) plus pembrolizumab versus pembrolizumab monotherapy in resected melanoma (KEYNOTE-942): A randomised, phase 2b study. *The Lancet, 403*, 632–644. [Crossref]

Wei, T., Zhang, J., Cheng, Z., Jiang, L., Li, J., & Zhou, L. (2023). Development and validation of a machine learning model for differential diagnosis of malignant pleural effusion using routine

laboratory data. *Therapeutic Advances in Respiratory Disease, 17*. [Crossref]

Wen, B., Li, K., Zhang, Y., & Zhang, B. (2020). Cancer neoantigen prioritization through sensitive and reliable proteogenomics analysis. *Nature Communications*, 11. [Crossref]

Xia, H., McMichael, J. F., BeckerHapak, M., Onyeador, O. C., Buchli, R., McClain, E., Pence, P....., & Griffith, M. (2023). Computational prediction of MHC anchor locations guides neoantigen identification and prioritization. American Association for the Advancement of Science. [Crossref]

Xie, N., Shen, G., Gao, W., Huang, Z., Huang, C., & Fu, L. (2023). Neoantigens: promising targets for cancer therapy. Springer Nature. [Crossref]

Yang, X., Zhao, L., Fang, W., & Li, J. (2021). DeepNetBim: deep learning model for predicting HLA-epitope interactions based on network analysis by harnessing binding and immunogenicity information. BioMed Central. [Crossref]

Yarchoan, M., Gane, E. J., Marron, T., Perales-Linares, R., Yan, J., Cooch, N., Shu, D....., & Sardesai, N. (2024). Personalized neoantigen vaccine and pembrolizumab in advanced hepatocellular carcinoma: a phase 1/2 trial. Nature Network Boston. [Crossref]

Yu, Q., Jiang, M., & Wu, L. (2022). Spatial transcriptomics technology in cancer research. Frontiers Media. [Crossref]

Yuan, D., McKeague, M., Raghu, V., Schoen, R., Finn, O., & Benos, P. (2025). Immune cell transcriptional profiles from pre-vaccination peripheral blood predict immune response to preventative MUC1 cancer vaccine. *European Journal of Cancer, 228*, 115685. [Crossref]

Zeng, J., Lin, Z., Zhang, X., Zheng, T., Xu, H., & Liu, T. (2025). Leveraging artificial intelligence for neoantigen prediction. *Cancer research*. [Crossref]

Zhang (2022). Neoantigens in precision cancer immunotherapy: from identification to clinical applications. Chinese Medical Journal. [Crossref]

Zhang, B., & BassaniSternberg, M. (2023). Current perspectives on mass spectrometry-based immunopeptidomics: the computational angle to tumor antigen discovery. BMJ. [Crossref]

Zhang, Y., Chen, T. T., Li, X., Lan, A. L., Ji, P. F., Zhu, Y. J., & Ma, X. Y. (2025). Advances and challenges in neoantigen prediction for cancer immunotherapy. Frontiers in immunology, 16, 1617654. [Crossref]

Zhang, Z., Lu, M., Qin, Y., Gao, W., Li, T., Su, W., & Zhong, J. (2021). Neoantigen: A New Breakthrough in Tumor Immunotherapy. Frontiers Media. [Crossref]

Zhou, C., Wei, Z., Zhang, L., Yang, Z., & Liu, Q. (2020). Systematically Characterizing A-to-I RNA Editing Neoantigens in Cancer. Frontiers Media. [Crossref]

Ziogas, I. A., Evangeliou, A. P., Giannis, D., Hayat, M. H., Mylonas, K. S., Tohme, S. and Tsoulfas, G. (2021). The role of immunotherapy in hepatocellular carcinoma: a systematic review and pooled analysis of 2,402 patients. *The oncologist*, 26(6): 1036-1049[Crossref]