Zakariya *et al.*
*European Journal of Medical Research* (2024) 29:25
https://doi.org/10.1186/s40001-023-01625-2

European Journal of Medical Research

REVIEW

Open Access

# Refining mutanome-based individualised immunotherapy of melanoma using artificial intelligence

Farida Zakariya[1,2], Fatma K. Salem[3], Abdulwhhab Abu Alamrain[4], Vivek Sanker[5], Zainab G. Abdelazeem[6], Mohamed Hosameldin[7], Joecelyn Kirani Tan[8], Rachel Howard[9], Helen Huang[10†] and Wireko Andrew Awuah[11*†]

## Abstract

Using the particular nature of melanoma mutanomes to develop medicines that activate the immune system against specific mutations is a game changer in immunotherapy individualisation. It offers a viable solution to the recent rise in resistance to accessible immunotherapy alternatives, with some patients demonstrating innate resistance to these drugs despite past sensitisation to these agents. However, various obstacles stand in the way of this method, most notably the practicality of sequencing each patient's mutanome, selecting immunotherapy targets, and manufacturing specific medications on a large scale. With the robustness and advancement in research techniques, artificial intelligence (AI) is a potential tool that can help refine the mutanome-based immunotherapy for melanoma. Mutanome-based techniques are being employed in the development of immune-stimulating vaccines, improving current options such as adoptive cell treatment, and simplifying immunotherapy responses. Although the use of AI in these approaches is limited by data paucity, cost implications, flaws in AI inference capabilities, and the incapacity of AI to apply data to a broad population, its potential for improving immunotherapy is limitless. Thus, in-depth research on how AI might help the individualisation of immunotherapy utilising knowledge of mutanomes is critical, and this should be at the forefront of melanoma management.

**Keywords** Mutanome, Melanoma, Immunotherapy, Artificial intelligence

†Helen Huang and Wireko Andrew Awuah share last-authorship.

*Correspondence:
Wireko Andrew Awuah
andyvans36@yahoo.com
[1] Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria, Nigeria
[2] Division of Experimental Medicine, Faculty of Medicine and Health Sciences, McGill University, Montreal, Canada
[3] Faculty of Veterinary Medicine, South Valley University, Qena 83523, Egypt
[4] Faculty of Medicine, Al-Quds University, Abu Dis, Palestine
[5] Research Assistant, Dept. Of Neurosurgery, Trivandrum Medical College, Trivandrum, India
[6] Division of Molecular Biology, Department of Zoology, Faculty of Science, Alexandria University, Alexandria, Egypt
[7] Faculty of Pharmacy, Zagazig University, Sharqia, Egypt
[8] Faculty of Medicine, University of St Andrews, St Andrews, Scotland, UK
[9] School of Clinical Medicine, University of Cambridge, Cambridge, England
[10] Faculty of Medicine and Health Science, Royal College of Surgeons in Ireland, Dublin, Ireland
[11] Medical Institute, Sumy State University, Zamonstanksya 7, Sumy 40007, Ukraine

## Introduction

Melanoma is a rare type of skin tumour, accounting for 1.1% of cancer deaths per year [1]. The annual incidence of melanoma has rapidly increased worldwide [2]. However, there has been a reduction in the mortality rate due to advancements in immunotherapy [3]. There are significant regional melanoma variations around the world that are attributed to racial skin phenotypes and sun exposure [4], which is the most implicated cause of melanoma globally [5]. Moreover, melanoma occurs mainly in young and middle-aged people, with an increasing incidence after age 25 and decreasing after 50, particularly in females [6].

The pathophysiology of melanoma involves mutations in genes regulating proteins, tight junctions, the cell cycle, deoxyribonucleic acid (DNA) damage, and remodelling of chromatin related to the melanocytes [5]. *BRAF* and *NRAS* are the most implicated genes, contributing 54.4% and 30.7% due to mutations at the V600 codon and Q61 codon, respectively [5]. Various treatment approaches have been developed in the management of melanoma, and these approaches have been continually refined, with new modalities added to better streamline the available options and increase survival rates. Available treatment options include surgical excision, chemotherapy, targeted therapy using *BRAF*, *NRAS*, and *C-Kit* inhibitors, radiation, and immunotherapy [1].

With the advent of immunotherapy, the median survival rate of advanced melanoma has improved from 9 months to 6 years [7]. Due to the variability in mutations in melanoma, knowledge of the status of individual mutations can help in patient stratification and aid targeted immunotherapy. In recent times, understanding individual mutations known as mutanomes has gained traction as a potential means for managing advanced cancers refractory to known therapies [8]. Advancement in artificial intelligence (AI) has sparked the debate that rapid sequencing of the mutanome and streamlining therapy options that trigger the immune system to target individual mutations will significantly improve therapy outcomes [9]. Particularly in melanoma, where adoptive cell therapy is proving to be a promising option for mutation-targeted immunotherapy, interest in artificial intelligence for refining this approach is increasing. One of the main reasons why AI is becoming more prominent in refining available immunotherapy options for melanoma is the increasing rate of reported resistance and refraction experienced by patients [10]. It is becoming apparent that finding approaches that utilise the differences in individual mutations and targeting these mutations on a personalised basis will help reduce the rate at which treatment failure occurs. However, due to the heterogeneity of melanoma, developing vaccines or personalising therapy for each patient is a tedious and expensive endeavour. Thus, this review seeks to highlight the applicability of AI in refining melanoma immunotherapy through exploring the differences in individual mutations.

## Methodology

This narrative review systematically investigates the potential applications of artificial intelligence in advancing research on mutanome-based individualisation of immunotherapy for melanoma management. Employing a rigorous methodology, the review encompasses a diverse range of study designs, including observational, case–control, cohort, and randomised controlled trials, with consideration for both paediatric and adult populations. The inclusion criteria, meticulously formulated, strictly adhere to English-language publications, spanning the period from 2001 to 2023 to align with contemporary practices.

To ensure a thorough exploration of the subject matter, the literature search utilised reputable databases such as ScienceDirect and PubMed. A thoughtfully selected set of search terms, including "mutanome", "melanoma", "immunotherapy", and "artificial intelligence", tailored the search to the specific focus of interest. Additionally, a manual search enriched the review by identifying references related to recently published, disease-specific reviews. Notably, stand-alone abstracts and unpublished studies were deliberately excluded.

Through this comprehensive and meticulous approach, the review aims to provide a scholarly assessment of the integration of AI technology in refining current research on mutanome-based individualisation of immunotherapy for melanoma management. The employed methodology is summarised in Table 1 for clarity and reference.

## Melanoma

### Aetiology of malignant melanoma

Melanoma is caused by multifactorial interactions between the body and the environment [11]. Melanoma is mainly derived from the accumulation of several mutations in melanocyte genes. *NRAS*, *BRAF*, and *PTEN* are some of the most significant genes in the development of melanoma [12–15, 17, 17]. There are also various genes for which mutations can be inherited, resulting in hereditary melanoma, such as *CDKN2A*, *CDK4*, *TP53*, *BRCA1*, *BRCA2*, and *PTEN* [18].

Environmental factors such as exposure to ultraviolet rays, which is considered the leading risk factor for melanoma [19] can disrupt melanocytes either directly by causing oxidative stress [20, 21] or indirectly by causing several mutations that induce carcinogenesis [22, 23]. Moreover, the risk of developing melanoma rises substantially with overexposure to sun and ultraviolet (UV)

**Table 1** Summary of the methodology employed in the study

| Methodology steps | Description |
|---|---|
| Literature search | ScienceDirect, PubMed |
| Inclusion criteria | Full-text articles published in English |
| | Various study designs, such as observational, case–control, cohort, cross-sectional, and randomised controlled trials |
| | Studies involving paediatric and adult populations |
| | Studies published between 2001 and 2023 |
| Exclusion criteria | Stand-alone abstracts and unpublished studies. Non English Studies |
| Search terms | "Mutanome", "melanoma", "immunotherapy" and "artificial intelligence" |
| Additional search | A manual search was conducted to find references for recently published, procedure-specific reviews |

rays in addition to recurring sunburns, particularly in younger age groups [24, 25]. It is also influenced by the skin phototype, as among the six skin phototypes, those with fair skin, blue eyes, and blond or red hair (Phototypes I and II) are the most vulnerable to developing skin melanoma due to their high sensitivity to UVB rays [26].

Another environmental factor is the geographical location, as melanoma incidence shows various rates in different regions, with the highest incidence rates in Australia and New Zealand [27]. More interestingly, it was found that acral melanoma on the hands' palms and the feet soles is more prevalent in people working with herbicides such as dichlorprop, atrazine, propanil, and paraquat, and it has a higher incidence in those using these herbicides at home than in those who do not [28]. Also, the susceptibility to skin melanoma is significantly influenced by the status of immunity, as immunosuppressive diseases such as Acquired Immunodeficiency Syndrome (AIDS) increase the risk of developing skin melanoma due to the inability of compromised immunity to effectively protect the body against the formation and development of solid tumours [29, 30].

### Clinical manifestation of melanoma

Melanoma can manifest in different forms depending on the primary location of melanocyte transformation. They broadly occur from mutations in the skin melanocytes known as cutaneous melanoma; the iris, choroid, and ciliary body melanocytes collectively referred to as uveal melanomas; and the mucosal melanocytes leading to mucosal melanoma [31]. Of the three, cutaneous melanoma is the most predominant, accounting for 91.2% of all melanoma cases. The National Comprehensive Cancer Network (NCCN) set a new standard in 2017 to classify cutaneous melanoma into 4 types: chronic sun damage (CSD), non-chronic sun damage (non-CSD), acral, and mucosal melanomas. CSD-melanomas are asymmetric, flat, yellowish-brown, brown, or black macules with irregular borders. Non-CSD melanomas are divided mainly into superficial spreading melanoma (SSM), which begins as an asymptomatic tan to black macules that then grow radically, and nodular melanoma (NM), which commonly appears as blue or black, but sometimes pink to red nodules that lack Asymmetry, Border, Colour, Diameter and Evolving (ABCDE) features and can turn into elevated nodules, ulcers, or bleeding. Acral melanoma (AM) is characterised by irregular pigmentation, parallel ridges, and multicomponent lesions on hairless areas such as the palms, fingernails, soles, and toenails. Mucosal melanoma can be found in the lips, eyelids, oral cavity, intestinal mucosa, vulva, and many other sites. It appears as structureless, grey areas in early dermoscopic diagnosis and as lesions with a multicomponent pattern in advanced dermoscopic diagnosis [32].

### Limitations and challenges in the management of malignant melanoma

The surgical removal option is primarily used for localised melanoma [33]. It can be used in some metastatic melanoma cases as well, but it is not considered to be curative, and other treatment options are still needed, such as chemotherapy. Although chemotherapy was the only curative option for metastatic melanoma until recently, its usage has decreased since the appearance of immunotherapies and targeted therapies [34]. To treat melanoma, numerous targeted therapies have been developed, among which the *BRAF* inhibitors vemurafenib and dabrafenib are the most promising [35, 36]. Despite their high efficacy, secondary resistance within a short time has been observed in most of the patients with *BRAF*-mutated melanomas [35–37]. Because of the high expense and severe side effects of the current treatments, research is still ongoing to overcome the limitations and complications, improve safety, and find other drug options [34].

### The use of targeted therapy in malignant melanoma

A variety of cancer inhibitors are used in targeted therapy, including mitogen-activated protein kinase (MEK) inhibitors (trametinib), *BRAF* inhibitors (vemurafenib and dabrafenib), cyclin-dependent kinase (CDK) inhibitors (ribociclib, abemaciclib, and palbociclib), and c-Kit inhibitors (imatinib) [38]. Trametinib is a monotherapy-approved MEK1/MEK2 inhibitor used to treat *BRAF* V600-mutant metastatic melanoma [39]. Although vemurafenib is a *BRAF* mutant inhibitor with high selectivity and efficacy against metastatic melanoma with *BRAF* V600 and non-V600E mutations [38], treatment resistance develops in most patients [40]. Dabrafenib is a subsequent-generation *BRAF* mutant inhibitor. The Food and Drug Administration (FDA) approved it for the treatment of unresectable or metastatic *BRAF* V600E-mutated melanomas [41, 42]. Ribociclib, abemaciclib, and palbociclib are a new class of specific CDK4/6 inhibitors that are more effective and have fewer side effects [38]. Imatinib is a c-Kit inhibitor found to be effective against c-Kit-mutated metastatic melanomas [43].

### Immunotherapy options available for malignant melanoma

Substantial advances have been made in immunotherapy treatments for metastatic melanoma over the last three decades. Cancer vaccines, adoptive cell therapies, and immunomodulatory approaches are the primary three types of immunotherapy options [34]. Interleukin-2 treatment was one of the first immune therapies for metastatic melanoma [35, 44]. Unfortunately, it was found to be highly toxic [34]. Cancer vaccines are therapeutic vaccines designed to stimulate the immune system against cancer cells. Due to the various evasion mechanisms cancer cells have, creating these vaccines has been challenging, so the early vaccines were not effective, and none have been approved for clinical application yet [45–47].

Up to date, the most effective treatment is immune checkpoint inhibitors [44, 48, 49]. Antibodies against the immune checkpoint receptors, such as programmed cell death protein 1 (PD-1), PD-1 ligand (PD-L1/2), and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), can be used to counteract the immune checkpoint modulation in melanoma. These antibodies disrupt binding to the corresponding ligands and tolerance signals, ultimately leading to the activation of the immune system [49–52]. The anti-CTLA-4 antibody ipilimumab and the anti-PD-1 antibodies nivolumab and pembrolizumab are currently the approved immune checkpoint inhibitor drugs for melanoma treatment [51]. Despite the benefits of checkpoint inhibitors, they have serious side effects mainly related to immunity because they inhibit the tolerance of immune mechanisms [53, 54]. Corticosteroids can neutralise their toxicity in some cases, but others continue to struggle with these side effects. In addition, a majority of patients still show no response, and others may even acquire secondary resistance [34, 55]. Overview of malignant melanoma with its newer therapeutic targets is summarised in Fig. 1.

## Mutanome-based individualised immunotherapy for malignant melanoma

Individualisation of melanoma immunotherapy represents a shifting paradigm in the field of oncology towards personalised medicine [7, 56, 57]. This transformation relies on various factors such as biomarker expression [58–64], immune system profiling [65], tumour microenvironment [66], patients' well-being [67, 68], and preferences [69]. However, tumour characteristics, which encompass the patient's mutanome and respective molecular profile, are the most important factor. The role of mutanomes in immunotherapy for malignant melanoma is summarised in Fig. 2. This holds a promising and powerful tool, as most melanoma mutations are unique and rarely shared, even among the same type [9, 70].

The "mutanome" or "mutation-genome" reflects the tumour genetic mutational signature [71], while the molecular profile includes the ribonucleic acids (RNAs) [72], encoded neoantigens [73, 74], and neo-epitopes [15]. This concept emerged thanks to sequencing technologies, especially after publishing the first complete set of mutations in *Saccharomyces cerevisiae* yeast in 2002 [75]. One of the pioneering studies, which was done by Krauthammer and his team, was the first to unveil melanomas' mutational landscape using exosome sequencing [76].

As time progressed, significant advancements in sequencing technologies propelled us from traditional and exosome-only sequencing to embracing more sophisticated approaches, such as whole genome and next-generation sequencing [77]. These advancements have allowed for a more comprehensive exploration of all types of mutations, ranging from single nucleotide polymorphisms (SNPs) and insertions to deletions and frameshifts, regardless of their effect as driver or passenger mutations and irrespective of whether they occur in coding or non-coding regions [77, 78]. This way, we can catch mutations even with low mutational burden melanomas [79, 80].

Moreover, the integration of additional fields such as transcriptomics, immunogenicity testing [81], and computational biology pushed the concept to its extreme limits [82–84]. This enabled us to leverage individualisation by decoding the patient's tumour mutanome using NGS according to the health human genome atlas, predicting neoantigens [85], and identifying epitopes with strong

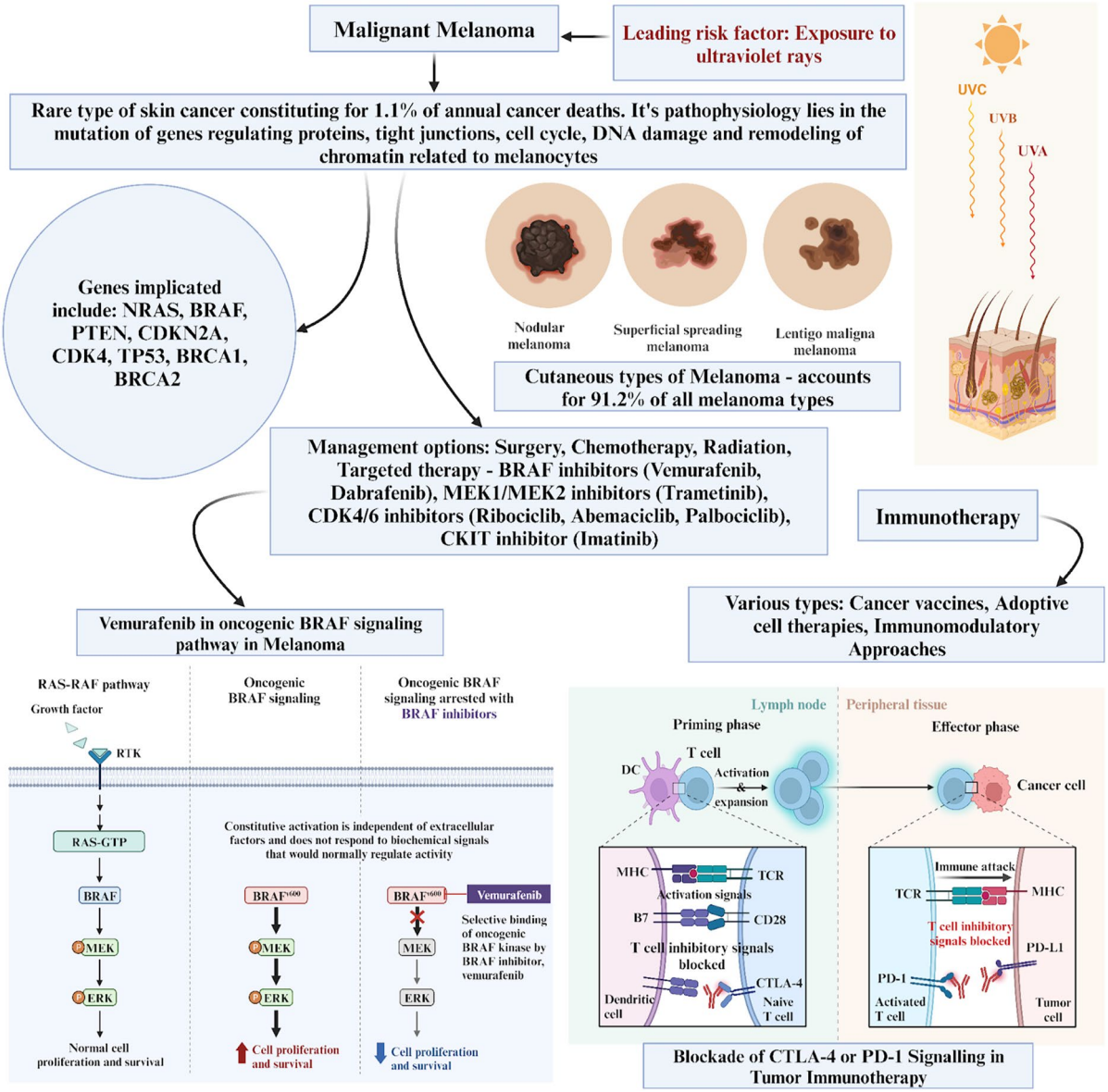


**Fig. 1** Overview of malignant melanoma along with its new therapeutic targets. CTLA-4, cytotoxic T-lymphocyte associated protein-4; PD-1, programmed cell death protein 1; TCR, T cell receptor; PDL-1, programmed death ligand 1; MHC, major histocompatibility complex; DC, dendritic cell; BRAF, v-Raf murine sarcoma viral oncogene homolog B1; MEK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; RAF, rapidly activated fibrosarcoma; RAS, rat sarcoma; RTK, receptor tyrosine kinase; GTP, guanosine triphosphate; NRAS, neuroblastoma RAS viral oncogene homolog; PTEN, phosphatase and tensin homolog; TP53, tumour protein 53; BRCA, breast cancer gene; CDK, Cyclin dependent kinase

human leukocyte antigen (HLA) binding affinity [83, 86]. That precious information can later be used in different types of immunotherapies.

In the context of adoptive cell therapy, research utilising this knowledge showed that tumour-infiltrating lymphocytes (TIL) prepared based on predicted neo-antigens and neo-epitopes exhibited enhanced T cell expansion and response [87, 88]. But like other passive immunotherapies, despite their potential benefits, they lack long-term effectiveness due to challenges like T cell specificity loss [89] and research still trying to solve them [90].

A multimodal immunotherapy that makes use of both passive and active approaches is oncolytic virus therapy. Studies demonstrated that genetically modified viruses, like herpes [91], adenoma, and vaccinia, have the ability to directly lyse virus-infected melanoma cells and release tumour neoantigens, stimulating anti-tumour immunity

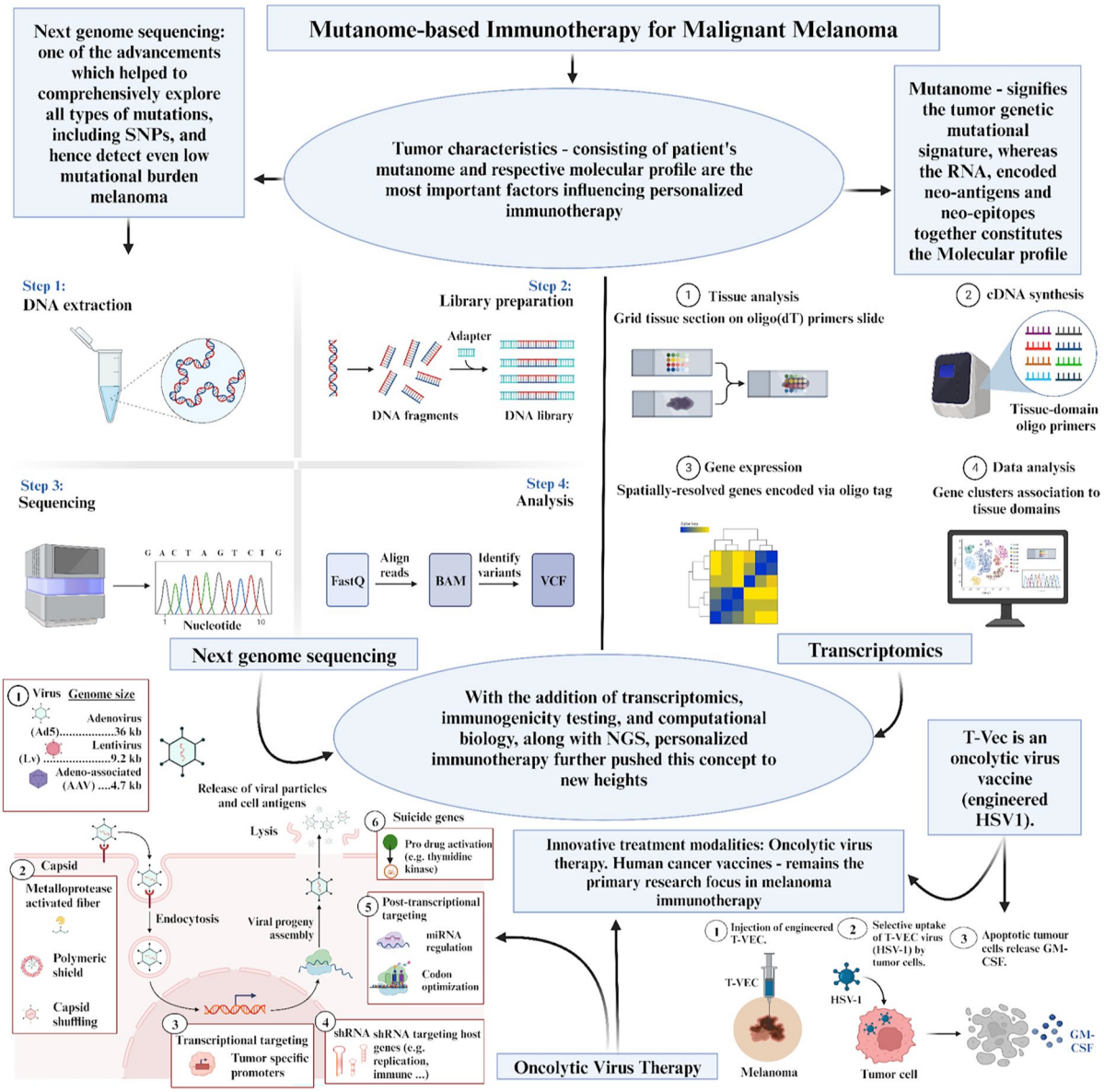


**Fig. 2** Overview of mutanome-based immunotherapy for malignant melanoma. DNA, deoxyribonucleic acid; RNA, ribonucleic acid; T-VEC, talimogene laherparepvec; GM-CSF, granulocyte macrophage colony stimulating factor; HSV-1, herpes simplex virus-1; NGS, Next Genome Sequencing; BAM, binary alignment map; VCF, variant cell format; SNP, single nucleotide polymorphism; shRNA, small hairpin RNA; cDNA, complementary DNA

[2, 93]. In recent studies, scientists have further enhanced active immunotherapy by coating viruses with predicted tumour neoantigens, Peptide-coated Conditionally Replicating Adenovirus (PeptiCRAd) [94]. This innovative technique holds great promise for future research.

However, vaccines continue to remain the primary research focus of active melanoma immunotherapy [95–97]. Mutanome-based individualisation approaches have been employed to develop on-demand vaccine manufacturing pipelines and conduct thorough testing. Various vaccine types, including peptide, RNA, and dendritic cell vaccines, have been studied.

For instance, autologous dendritic cells loaded ex vivo with patient-specific neoantigens demonstrated good tolerance and an increase in the breadth and diversity of T cell responses [98–100]. Subsequently, custom messenger ribonucleic acid (mRNA) liposomal vaccines capable of neoantigen encoding were developed and tested, resulting in the expansion of preexisting T cells and the induction of new T cell responses against the neo-epitopes

[101–104]. Other studies explored a custom peptide vaccine synthesis approach using patients' neoantigen structures [105, 106].

This approach to melanoma treatment ensures that the treatment is tailored to the individual profile, maximising the chances of a successful immune response and reducing the risk of treatment resistance. This can also directly or indirectly target cancer cells and kill them. Overall, the integration of mutanome knowledge in individualised immunotherapy holds promise for revolutionising melanoma treatment, offering patients the potential for better responses, prolonged remissions, and a step closer to achieving the goal of precision oncology.

Despite our advancing knowledge of the mutanome, several limitations remain when implementing this research for individualised immunotherapy of malignant melanoma. One of the biggest limitations is the impact physiological differences in the body have on the absorption, distribution, metabolism, and elimination of drugs [107–109]. Immune checkpoint inhibitors (ICI) have revolutionised the treatment of malignant melanoma; however, the response rate is approximately one-third [110–112]. A lack of research into the pharmacokinetic responses of ethnicity, age, sex, and disease stage, however, limits the effectiveness of individualised immunotherapy [113]. Targeting this area of research remains challenging due to the large genetic variations that exist within these subpopulations [114]. Effectively targeting and utilising such data could allow individualised immunotherapy for malignant melanoma to reach its full potential [70].

## AI and cancer immunotherapy

### AI techniques of importance in cancer immunotherapy

In the field of cancer treatment, immunotherapy has made significant advancements and is now widely used. However, a challenge that has arisen is the identification of suitable individuals who can benefit from this therapy and who should receive it. To address this challenge, AI has been developed to aid in performing tasks that typically require human intelligence. These tasks include interpretation of language, perception of visual materials, and decision-making [115]. The utilisation of AI technologies has resulted in enhanced precision and effectiveness in the diagnosis and prediction of cancer treatment responses. AI has enabled the classification of patients into two groups: those who will respond positively to cancer immunotherapy and those who will not, thereby ensuring that only suitable patients receive the treatment [116]. With the aid of neural-based models, the tumour immune microenvironment of solid tumours such as colorectal, breast, lung, and pancreatic cancer, which plays a crucial role in patients' responses to cancer immunotherapy, has been accurately characterised by integrating RNA sequencing (RNA-Seq) and imaging data in a clinical setting [117].

Currently, numerous research groups and companies are dedicated to creating programmes that can enhance the efficiency, precision, and affordability of cancer screening. By acting as a supplementary visual aid, AI can aid medical professionals in identifying and diagnosing cancer in images with greater precision than would be possible otherwise. This results in improved accuracy and, consequently, insight for patients [117]. The application of deep learning (DL) methods enables the precise and automated identification of changes in tumour size and gene status, which can serve as an assisting tool for monitoring the efficacy of immunotherapy [115].

As biotechnology continues to develop and our understanding of the molecular mechanisms of tumours expands, immunotherapy has become an effective method of training the immune system to recognise and target specific cancer cells. This treatment modality can enhance the immune cells' ability to identify and eliminate cancer cells while also providing the body with supplementary components to augment the immune response. There are different types of cancer immunotherapy available, including targeted antibodies, cancer vaccines, adoptive cell transfer, tumour-infecting viruses, checkpoint inhibitors, cytokines, and adjuvants. In the prediction of immunotherapy responses, AI has been employed in the evaluation of immune signatures, medical imaging, and histologic analysis [117].

### Current application of AI in the individualisation of cancer immunotherapy

The utilisation of AI, a cutting-edge technology, has made it possible to provide personalised treatment to patients with tumours by automating the prediction of the effects of tumour immunotherapy through the construction of models [118]. The use of AI in immunotherapy is concentrated on three main themes. The first theme concerns tumour neoantigens, which form the foundation of immunotherapy. A key unresolved issue in this area is the rapid and precise prediction of immunogenic tumour antigens using AI, which would minimise the need for experimental screening and validation [119]. Machine learning (ML) techniques have the potential to identify the factors that determine tumour immunogenicity and the peptides presented by major histocompatibility complex class I (MHC-I), which can be utilised to assess neoantigen binding and/or treatment response predictions in cancer immunotherapy [115]. Artificial neural networks enable the observation of tumour antigen T cell epitopes in patients with melanoma, which can be utilised for personalised cancer immunotherapy [117]. The second

theme of AI application in immunotherapy pertains to the scope for improvement in tumour therapeutic monoclonal antibodies, despite their notable success. This has spurred much innovation in antibody design, with AI-augmented antibodies holding immense potential for further advancements in cancer treatment. The advent of DL has opened up new avenues for therapeutic antibody design, including the prediction of structure, screening for target binding, affinity maturation, and pharmaceutical property prediction.

The third theme pertains to the challenges associated with predicting the response to immunotherapy. This includes the identification of patients who are most likely to respond to immunotherapy using multimodal and multi-scale biomarkers, as well as the characterisation of the tumour immune microenvironment [119]. AI-based techniques like imaging and histopathology analysis both ML-based and DL-based approaches have demonstrated efficacy in interpreting tumour microenvironment (TME) in combination with immunohistochemistry. These methods reveal disparities in the expression and localisation of biomarkers among various histological subtypes, which can be leveraged to predict responses to immunotherapies or other targeted therapies [115].

To predict the effectiveness of immunotherapy using AI, a general approach involves creating a training cohort and a validation cohort. The multi-scale medical data from the training cohort are collected, filtered, segmented, and features extracted and selected. This data is then used to train and model AI. The validation cohort is used to verify the results of the AI's learning. The multi-scale medical data may include genomics, proteomics, pathological tissue, computed tomography / magnetic resonance (CT/MR) imaging, and more. The goal is for the AI to predict whether a patient will benefit from immunotherapy or suggest further evaluation, such as whole genome sequencing. Additionally, AI can predict which immunotherapy drug will be most effective for the patient. This approach can improve the accuracy of immunotherapy treatment and potentially lead to better patient outcomes [118].

Radiomics is an emerging AI technique that is gaining increasing attention in cancer management. It is an algorithm-based method that extracts patterns from images obtained from computed tomography, magnetic resonance imaging, positron emission tomography or a combination of two of these [120, 121]. These patterns serve as the basis for response rate monitoring [122], individualisation of therapy [122], risk stratification [121, 123], survival analysis [123], metastatic capability predictions [121, 124] and patient monitoring [122]. In the individualisation of therapy, this is especially useful as it can discern little differences in obtained images, thereby forming patterns that can be used in correlation generation, thus influencing therapy choices. One of such is its application as a predictive signature generator for better correlation with immune markers. $CD8^+$ expression in melanoma was found to be inversely proportional to the mean of positive pixel (MPP) and standard deviation (SD) using radiomics which also correlates with prognostic outcomes in patients [125]. It has similarly been applied in signature–immune marker correlations in other types of cancers like non-small-cell lung [126] and renal cancers [127]. Furthermore, signature correlations have also been used in evaluating survival in melanoma patients treated with pembrolizumab [123].

#### Advantages and limitations of the use of AI in cancer immunotherapy

AI has emerged as a highly advanced tool in the field of computer-assisted cancer immunotherapy. As clinical data and AI methodologies continue to advance, AI has the potential to play an even greater role in predicting immunotherapy responses. One of the greatest strengths of AI is its ability to learn from large sets of data and identify patterns that can be applied to specific tasks, such as mutation annotation or diagnosis [128].

The incorporation of AI in cancer immunotherapy has been recognised as a developing computer-assisted approach that can enhance the predictive abilities and functional roles of personalised therapy. Nonetheless, there are discrepancies in the application of AI techniques for widespread use in clinical practice. AI-based algorithms have the potential to be a promising strategy for optimising individualised immunotherapy and ultimately improving the healthcare quality and prognosis of patients [115].

The application of AI in cancer immunotherapy has demonstrated some limitations. These include a shortage of available data, data biases, insufficient data sharing, a lack of code sharing, and difficulties in interpreting the models. Also, there is a gap between the ease of gathering data from various platforms and the ease of access by external agencies for independent use, especially for private or controlled-access datasets. The absence of data sharing hinders the effective validation of AI models across multiple medical centres. Additionally, the variability of data presents a significant challenge in implementing DL for immunotherapy, whereby incongruities in data batches and quality issues often lead to unsuccessful external validation [119].

The intricate nature of predicting immunotherapy outcomes necessitates collaboration between scientific researchers, enterprises, and clinicians to construct databases and establish industry standards. This collaborative effort should aim to eliminate technical obstacles

and foster the development of AI-assisted systems that can precisely identify the target population for immunotherapy, accurately forecast treatment efficacy and prognosis, and promote the implementation of AI-assisted treatment while earning the trust of both physicians and patients [118].

## AI in refining mutanome-based immunotherapy of malignant melanoma

AI is a tool that can potentially change outcomes in malignant melanoma. With advances in AI, the sequencing of melanoma mutations quickly, the development of individualised vaccines, the determination of the response rate to individualised immunotherapy, patient stratification based on predicted outcomes, and modifying the use of adoptive cell therapy can be refined to meet the increasing needs of melanoma patients. The use of AI in refining mutanome-based immunotherapy is summarised in Fig. 3.

### AI in understanding melanoma mutanome

AI has the potential to advance comprehension of the melanoma mutanome and its significance for immunotherapy. Melanoma harbours an exceptionally high

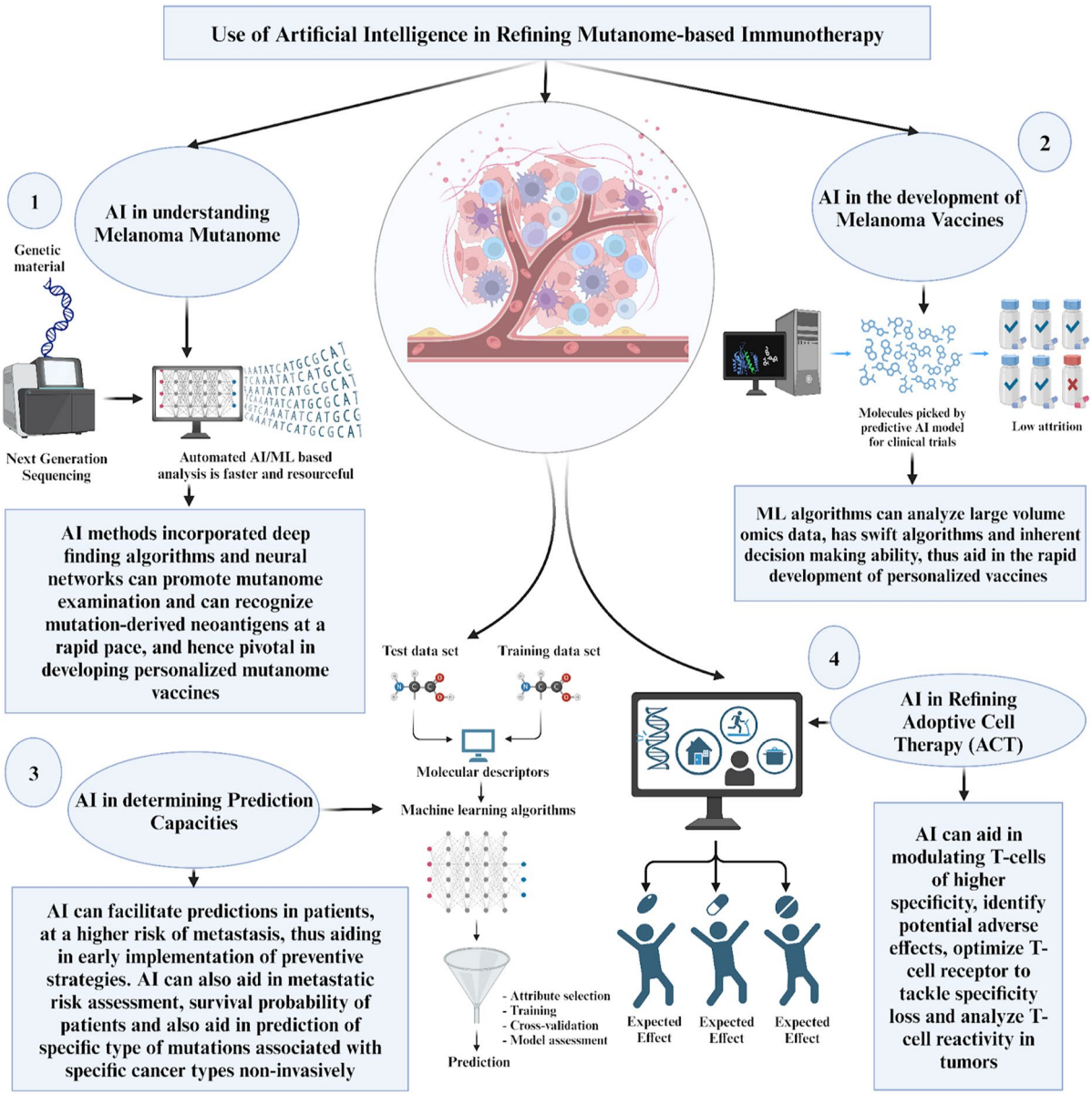


**Fig. 3** Application of AI refining in mutanome-based immunotherapy. ACT, adoptive cell therapy; AI, artificial intelligence; ML, machine learning

mutational burden, which produces tumour-particular neoantigens that can be targeted by the immune system [21, 130]. Nevertheless, completely exploiting the mutanome necessitates the identification of immunogenic mutations from whole genome and transcriptome data [131]. AI methods employing deep finding algorithms can promote mutanome examination, and this has been used to advance rapid technology-based identification and validation of individual mutanomes by individualised vaccines against cancer (IVAC) in the individualisation of immunotherapy for malignant melanoma [132]. Also, neural networks can recognise mutation-derived neoantigens by incorporating genomic, epigenomic, and immunogenicity information at an unprecedented scale and swiftness [133]. This will empower exhaustive mining of the melanoma mutanome to develop personalised mutanome vaccines [134]. AI can also uncover mutations related to immunotherapy response or resistance, guiding individual categorisation and combination tactics [129].

By accelerating mutanome profiling, AI has the potential to boost comprehension of how the mutational landscape influences immunotherapy efficacy in melanoma. This may reveal new pathways to conquer resistance by targeting special mutational signatures [135]. AI-driven multi-omic relationships with clinical outcomes could also supply insights into optimising mutanome-focused methods through rational drug combinations impacting ribosome biogenesis or epigenetics [136, 137]. Thus, AI is well-positioned to revolutionise understanding of the melanoma mutanome's benefits for immunotherapy through thorough assessment of its tumour-particular abnormalities.

#### AI in the development of melanoma vaccines

Personalising melanoma vaccines based on mutanomes is an up-and-coming application of AI [95–97]. With machine learning algorithms able to learn from large amounts of omics data and make inferences that can be applied to new situations, the identification of neoantigens can be optimised, leading to the development of individualised vaccines for different mutational variants [128]. Aside from this, machine learning can streamline vaccines suited to individual immune profiles and hasten the development of large amounts of vaccines for different individuals in a short period of time due to swift algorithms and inherent decision-making capabilities [128]. An mRNA vaccine, mRNA-4157, in a phase 3 clinical trial for melanoma by Moderna and Merck utilises proprietary algorithms in the identification of mutanomes as targets of the vaccine [138]. Advancements in these algorithms are also predicted to shorten the production time from 6 weeks to 30 days, thus increasing the turnaround time, which is one of the major issues identified with the individualisation of immunotherapy [138]. As is known, neoantigens result from mutations in tumours, which can vary among melanoma patients [56]. The identification of immunogenic neoantigens has been challenging so far [139]. However, AI advancements in next-generation sequencing (NGS) have made it possible to identify neoantigens, which are ideal vaccine targets [56]. An AI tool developed by Evaxion (EVX) named Pioneer Technology has been used to identify specific neoantigens for individualised melanoma vaccines like EVX-01 and EVX-02, which are novel molecules at various stages of clinical trials [140].

#### AI in refining adoptive cell therapy immunotherapy option

In addition to vaccines, AI can refine the adoptive cell therapy (ACT) immunotherapy option. It is known that melanoma mutations are unique and rarely shared [9, 70]. Thus, AI can build on this knowledge to enhance the modulations of T cells, having greater specificity for individual mutations. Also, with deep learning algorithms, AI can simulate what happens when ACT is used, thus limiting resource waste and identifying major lapses and potential adverse effects early on in the drug discovery process [141]. A major problem with ACT is T cell specificity loss, which can be optimised by T cell receptor (TCR) deep sequencing. However, TCRs of significance are rare to come across. With AI, TCR can easily be identified compared to previous experiences via machine learning algorithms that can predict TCR–target interactions specific to every individual [89]. Another issue with ACT is that T cells cannot recognise all mutanomes in tumours. Rather than using peptide-binding algorithms to identify immunogenic mutations, advancements in predictive algorithms have made it possible for minigenes to analyse T cell reactivity in tumours, thus making it possible to develop novel ACTs that recognise individual neoantigens [142].

#### AI in determining prediction capacities

AI presents an advancing approach that can achieve things that were previously deemed resource-intensive in melanoma. This can help improve prediction capacities, thus increasing the drug discovery pipeline efficiency [143]. In particular, AI can improve predictions in patients that are at a higher risk of metastasis based on their mutanome [141], thus allowing for early preventive measures that can increase patient survival rates. Different melanoma mutanomes are associated with varying levels of serum biomarkers [144]. Some predictive biomarkers, like dermcidin, interferon-gamma, interleukin-4, and granulocyte macrophage colony stimulating factor (GM-CSF), are associated with metastatic

melanoma in early-stage patients [141]. Using an AI algorithm to streamline metastatic risk assessment can help improve immunotherapy options that will best reduce the risk of metastasis at an early stage. Machine learning can also increase the speed of determining the probability of survival in melanoma patients. This was demonstrated in research where a combination of machine learning and radiomics was used to assess the survival rates of advanced melanoma patients treated with the immune checkpoint blocker pembrolizumab [123]. This approach can benefit from machine learning's ability to automate how lesions are identified and segmented in melanoma. AI has also been used to predict the specific type of mutations that initiated a particular cancer in an individual via a noninvasive method [145]. The detailing of the *BRAF* mutation underlying the melanoma brain metastasis using machine learning-assisted radiomics technique was achieved in contrast to the norm where tissue biopsy is required to determine the genetic aspect of brain metastasis [145]. This noninvasive approach presents a novel technique that can be utilised to predict the exact mutanome in melanoma, thus facilitating better immunotherapy selection [145]. However, this method cannot predict the development of metastasis in specific patients. Table 2 provides a summary of the potential impact of AI on the enhancement of mutanome-based immunotherapy for malignant melanoma.

### Future prospects and potential limitations of AI in advancing and refining mutanome-based immunotherapy for malignant melanoma

AI is a powerful tool that can change the future management and outcomes associated with malignant melanoma. In light of rising concerns about the development of resistance to available immunotherapy options, exploring the mutanome-based immunotherapy approach refined by AI is gaining traction. Limited research has been carried out on how understanding individual mutations can benefit therapy outcomes due to the diverse nature of the mutations underlying the development of melanomas [9, 70]. Also, the use of AI in melanoma management is not without drawbacks. Notably, imprecisions in AI's ability to adequately detect lesions in people outside the dataset used in developing the AI algorithm have been cited [146], thus raising concerns about AI's inference applicability in a larger population [146]. However, AI still remains a game changer that can effectively turn the tide on melanoma management.

A futuristic utility of AI is its ability to swiftly through large sets of mutanomes in a short time. One major problem often cited in the development of individualised immunotherapy is the time and resource intensiveness of sequencing individual mutanomes and modulating immunotherapy options specific to the mutanomes. ML can process large amounts of data in a relatively short time, carry out gene-treatment pairing for best fit, determine the chances of toxicity and efficacy, and also use this data as a pattern for future predictions [143].

Exploring AI to improve individualised immunotherapy options based on mutanomes remains an aspect of the cancer drug discovery process requiring much attention. The growing resistance to multiple immunotherapies available for melanoma continues to dash the hopes of discovering immunotherapy ignited in the scientific world. Worse still, other therapy options like chemotherapy are ineffective in achieving the cure rates obtained from immunotherapies. Thus, it is important to improve and facilitate research that seeks to enhance the application of AI in individualising therapy best suited for the specific genetic mutations in every patient. With improvements in technologies and newer AI algorithms developing, individualised immunotherapy is becoming a possibility. This will help increase the efficiency of the drug discovery process, reduce adverse drug events, and increase survival rates in melanoma patients.

While AI shows promise for optimising mutanome-based immunotherapy, certain limitations must be addressed. Accurately predicting immunogenic neoantigens from tumour sequencing data remains challenging due to tumour heterogeneity and the complexity of antigen presentation [21, 137]. DL models require vast amounts of high-quality immunogenomic training data, which are difficult to obtain, potentially limiting generalisability [131, 133].

Additional barriers include the dynamic interplay between mutations, epigenetic modifications, and cellular signalling pathways influencing immunogenicity, which are challenging to fully incorporate into static AI models [135, 137]. Mutational signatures associated with endogenous and exogenous DNA damage involve complex biological processes not easily defined by current machine learning algorithms [135]. There are also ethical concerns around explaining "black box" AI predictions to patients and difficulties validating models using prospective clinical trial data [129, 131].

Overcoming these limitations requires multidisciplinary collaborations between clinicians, immunologists, geneticists, and AI specialists. Larger pan-cancer immunogenomic databases with linked multi-omic profiles and treatment outcomes could improve generalisability but represent a major undertaking [133]. Combining unsupervised and supervised machine learning with mechanistic modelling may help capture tumour biology dynamics not evident from bulk sequencing alone [133, 137]. With refinements, AI has the potential to optimise mutanome-based therapies if technical challenges

**Table 2** Summary of the role of AI in refining mutanome-based immunotherapy of malignant melanoma

| Advantages | Description |
|---|---|
| Enhance understanding of melanoma mutanome [120–124, 129, 132, 133, 135–137] | • Deep finding algorithms can promote mutanome examination, that is used to advance rapid technology-based identification and validation of individual mutanomes by IVAC |
| | • Neural networks recognise mutation-derived neoantigens by incorporating genomic, epigenomic, and immunogenicity information at an unprecedented scale and swiftness |
| | • Uncover mutations related to immunotherapy response or resistance, guiding individual categorisation and combination tactics |
| | • Potential to reveal new pathways to conquer resistance by targeting special mutational signatures |
| | • Supply insights into optimising mutanome-focused methods through rational drug combinations impacting ribosome biogenesis or epigenetics |
| | • Radiomics extract patterns from imaging modalities like CT, MRI, and PET |
| | • Patterns derived from radiomics serve as a basis for response rate monitoring, risk stratification, survival analysis, metastatic capability predictions, and patient monitoring |
| | • In individualised therapy, radiomics discerns subtle differences in images, forming patterns influencing therapy choices |
| Facilitate the development of melanoma vaccines [95–97, 125, 128] | • Personalised melanoma vaccines |
| | • Radiomics contributes to individualised therapy by generating predictive signatures |
| | • Optimised identification of neoantigens, leading to the development of individualised vaccines for different mutational variants |
| | • Streamline vaccines suited to individual immune profiles |
| | • Hasten the development of large amounts of vaccines for individuals in a short period of time |
| Refining adoptive cell therapy immunotherapy option [9, 70, 89, 125–127, 141, 142] | • Refine ACT |
| | • Enhance the modulation of T cells, having greater specificity for individual mutations |
| | • Limit resource waste and identify major lapses and potential adverse effects early through simulation |
| | • Mitigate T cell specificity loss, optimised by TCR deep sequencing |
| | • Development of novel ACTs that recognise individual neoantigens, enabled by advancements in predictive algorithms for minigenes to analyse T cell reactivity in tumours |
| | • Application in signature-immune marker correlations extends to other cancers like non-small-cell lung and renal cancers |
| Determine prediction capacities [123, 141, 143, 145] | • Improve prediction capacity, thus increasing drug discovery pipeline efficiency |
| | • Predict specific type of mutations that initiate cancer in an individual via a noninvasive method (machine learning-assisted radiomics technique) |
| | • Improve predictions in patients at higher risk of metastasis based on their mutanome |
| | • Streamline metastatic risk assessment |
| | • Allows for early preventive measures that can increase patient survival rates |
| | • Automate the identification and segmentation of lesions in melanoma |
| | • Radiomics serve as a predictive signature generator, aiding in better correlation with immune markers |
| | • Signature correlations have been utilised in evaluating survival in melanoma patients treated with pembrolizumab |

ACT, adoptive cell therapy; AI, artificial intelligence; IVAC, Individualised vaccines against cancer; TCR, T cell receptor

around data, modelling complexity, and clinical integration are addressed.

## Conclusion

AI is a tool with vast potential in melanoma, as demonstrated by numerous studies on how to optimise its use to simplify management approaches. Although it is not without lapses, its application in rapidly sequencing mutanomes to enhance the ease of individualising therapy in all stages of melanoma is revolutionary. Thus, exploring AI to refine mutanome-based individualisation of therapy can strengthen current predictions of response and toxicity in melanoma patients at all stages. Owing to its robustness, it can also be used to predict the kind of mutation underlying a cancer type, thus easing the ease of patient stratification for immunotherapy and helping future prevention of metastasis. However, more research is required to address the shortcomings of AI in its multiple distinguishing capabilities, large-scale application, and data porosity in order to aid its future outcomes in melanoma.

**Abbreviations**

| | |
|---|---|
| CTLA-4 | Cytotoxic T-lymphocyte associated protein-4 |
| PD-1 | Programmed cell death protein 1 |
| TCR | T cell receptor |
| PDL-1 | Programmed death ligand 1 |
| MHC | Major histocompatibility complex |
| DC | Dendritic cell |
| BRAF | V-raf murine sarcoma viral oncogene homolog B1 |
| MEK | Mitogen-activated protein kinase |
| ERK | Extracellular signal-regulated kinase |
| RAF | Rapidly activated fibrosarcoma |
| RAS | Rat sarcoma |
| RTK | Receptor tyrosine kinase |
| GTP | Guanosine triphosphate |
| NRAS | Neuroblastoma ras viral oncogene homolog |
| PTEN | Phosphatase and tensin homolog |
| TP53 | Tumour protein 53 |
| BRCA | Breast cancer gene |
| CDK | Cyclin dependent kinase |
| DNA | Deoxyribonucleic acid |
| RNA | Ribonucleic acid |
| T-VEC | Talimogene laherparepvec |
| GM-CSF | Granulocyte macrophage colony stimulating factor |
| HSV-1 | Herpes simplex virus-1; NGS: Next Genome Sequencing |
| BAM | Binary alignment map |
| VCF | Variant cell format |
| c-Kit | Tyrosine-protein kinase kit |
| SNP | Single nucleotide polymorphism |
| shRNA | Small hairpin RNA |
| cDNA | Complementary DNA |
| ACT | Adoptive cell therapy |
| AI | Artificial Intelligence |
| ML | Machine Learning |
| IVAC | Individualised vaccines against cancer |
| CDKN2A | Cyclin dependent kinase inhibitor 2A |
| mRNA | Messenger RNA; UV: Ultra violet |
| AIDS | Acquired immunodeficiency syndrome |
| NCCN | National Comprehensive Cancer Network |
| CSD | Chronic sun damage |
| SSM | Superficial spreading melanoma |
| NM | Nodular melanoma |
| ABCDE | Asymmetry, border, colour, diameter, and evolving |
| AM | Acral melanoma |
| HLA | Human leukocyte antigen |
| TIL | Tumour-infiltrating lymphocyte |
| EVX | Vaxion |
| PeptiCRAD | Peptide-coated Conditionally Replicating Adenovirus |
| ICI | Immune checkpoint inhibitors |
| RNA Seq | RNA sequencing |
| DL | Deep learning |
| TME | Tumour microenvironment |
| CT | Computed tomography |
| MR | Magnetic resonance |
| MPP | Mean of positive pixel |
| SD | Standard deviation |

**Acknowledgements**
We acknowledge the Icormed Research Collaborative for facilitating this project.

**Author contributions**
Conceptualisation of topic and coordination of reading, writing, and editing: FZ; reading, writing, and editing of the original draft: FZ, FKS, AAA, ZGB, JKT, VS, MH, RH; critical revision of the manuscript: FZ, HH, WAA; figures and tables: VS, JKT, FZ; final approval of manuscript: all authors.

**Funding**
Authors have no funding to declare.

**Availability of data and materials**
No data available.

**Declarations**
Ethics approval and consent to participate.
Not applicable.

**Competing interests**
Authors have no competing interests to declare.

Received: 17 November 2023 Accepted: 25 December 2023
Published online: 05 January 2024

**References**

1. Kalkan Z. Evaluation of Immunotherapy and Targeted Therapies in the Treatment of Metastatic Malignant Melanoma. Eurasian J Med Invest. 2022. https://doi.org/10.14744/ejmi.2022.79013.
2. Ali Z, Yousaf N, Larkin J. Melanoma epidemiology, biology and prognosis. EJC Suppl. 2013;11(2):81–91. https://doi.org/10.1016/j.ejcsup.2013.07.012.
3. Islami F, Ward EM, Sung H, et al. Annual report to the nation on the status of cancer, part 1: national cancer statistics. J Natl Cancer Inst. 2021;113(12):1648–69. https://doi.org/10.1093/jnci/djab131.
4. Leonardi GC, Falzone L, Salemi R, et al. Cutaneous melanoma: from pathogenesis to therapy (review). Int J Oncol. 2018;52(4):1071–80. https://doi.org/10.3892/ijo.2018.4287.
5. Ticha I, Hojny J, Michalkova R, et al. A comprehensive evaluation of pathogenic mutations in primary cutaneous melanomas, including the identification of novel loss-of-function variants. Sci Rep. 2019;9(1):17050. https://doi.org/10.1038/s41598-019-53636-x.
6. Rastrelli M, Tropea S, Rossi CR, Alaibac M. Melanoma: epidemiology, risk factors, pathogenesis, diagnosis and classification. In Vivo. 2014;28(6):1005–11.
7. Knight A, Karapetyan L, Kirkwood JM. Immunotherapy in melanoma: recent advances and future directions. Cancers. 2023. https://doi.org/10.3390/cancers15041106.
8. Overwijk WW, Wang E, Marincola FM, Rammensee HG, Restifo NP. Mining the mutanome: developing highly personalized Immunotherapies

based on mutational analysis of tumors. J Immunother Cancer. 2013;1:11. https://doi.org/10.1186/2051-1426-1-11.
9. Vormehr M, Tureci O, Sahin U. Harnessing Tumor Mutations for Truly Individualized Cancer Vaccines. Annu Rev Med. 2019;70:395–407. https://doi.org/10.1146/annurev-med-042617-101816.
10. Lim SY, Shklovskaya E, Lee JH, et al. The molecular and functional landscape of resistance to immune checkpoint blockade in melanoma. Nat Commun. 2023;14(1):1516. https://doi.org/10.1038/s41467-023-36979-y.
11. Strashilov S, Yordanov A. Aetiology and pathogenesis of cutaneous melanoma: current concepts and advances. Int J Mol Sci. 2021. https://doi.org/10.3390/ijms22126395.
12. Ko JM, Velez NF, Tsao H. Pathways to melanoma. Semin Cutan Med Surg. 2010;29(4):210–7. https://doi.org/10.1016/j.sder.2010.10.004.
13. Munoz-Couselo E, Adelantado EZ, Ortiz C, Garcia JS, Perez-Garcia J. NRAS-mutant melanoma: current challenges and future prospect. Onco Targets Ther. 2017;10:3941–7. https://doi.org/10.2147/OTT.S117121.
14. Pons M, Quintanilla M. Molecular biology of malignant melanoma and other cutaneous tumors. Clin Transl Oncol. 2006;8(7):466–74. https://doi.org/10.1007/s12094-006-0046-4.
15. Alcazer V, Bonaventura P, Tonon L, Wittmann S, Caux C, Depil S. Neoepitopes-based vaccines: challenges and perspectives. Eur J Cancer. 2019;108:55–60. https://doi.org/10.1016/j.ejca.2018.12.011.
16. Kim M. Cooperative interactions of PTEN deficiency and RAS activation in melanoma metastasis. Small GTPases. 2010;1(3):161–4. https://doi.org/10.4161/sgtp.1.3.14344.
17. Romano C, Schepis C. PTEN gene: a model for genetic diseases in dermatology. ScientificWorldJournal. 2012;2012: 252457. https://doi.org/10.1100/2012/252457.
18. Abdo JF, Sharma A, Sharma R. Role of heredity in melanoma susceptibility: a primer for the practicing surgeon. Surg Clin North Am. 2020;100(1):13–28. https://doi.org/10.1016/j.suc.2019.09.006.
19. Kozmin S, Slezak G, Reynaud-Angelin A, et al. UVA radiation is highly mutagenic in cells that are unable to repair 7,8-dihydro-8-oxoguanine in Saccharomyces cerevisiae. Proc Natl Acad Sci U S A. 2005;102(38):13538–43. https://doi.org/10.1073/pnas.0504497102.
20. Obrador E, Liu-Smith F, Dellinger RW, Salvador R, Meyskens FL, Estrela JM. Oxidative stress and antioxidants in the pathophysiology of malignant melanoma. Biol Chem. 2019;400(5):589–612. https://doi.org/10.1515/hsz-2018-0327.
21. Douki T. Oxidative stress and genotoxicity in melanoma induction: impact on repair rather than formation of dna damage? Photochem Photobiol. 2020;96(5):962–72. https://doi.org/10.1111/php.13278.
22. Khan AQ, Travers JB, Kemp MG. Roles of UVA radiation and DNA damage responses in melanoma pathogenesis. Environ Mol Mutagen. 2018;59(5):438–60. https://doi.org/10.1002/em.22176.
23. Trucco LD, Mundra PA, Hogan K, et al. Ultraviolet radiation-induced DNA damage is prognostic for outcome in melanoma. Nat Med. 2019;25(2):221–4. https://doi.org/10.1038/s41591-018-0265-6.
24. Hausauer AK, Swetter SM, Cockburn MG, Clarke CA. Increases in melanoma among adolescent girls and young women in California: trends by socioeconomic status and UV radiation exposure. Arch Dermatol. 2011;147(7):783–9. https://doi.org/10.1001/archdermatol.2011.44.
25. Raimondi S, Suppa M, Gandini S. Melanoma Epidemiology and Sun Exposure. Acta Derm Venereol. 2020;100(11):adv00136. https://doi.org/10.2340/00015555-3491.
26. Trakatelli M, Bylaite-Bucinskiene M, Correia O, et al. Clinical assessment of skin phototypes: watch your words! Eur J Dermatol. 2017;27(6):615–9. https://doi.org/10.1684/ejd.2017.3129.
27. Karimkhani C, Green AC, Nijsten T, et al. The global burden of melanoma: results from the Global Burden of Disease Study 2015. Br J Dermatol. 2017;177(1):134–40. https://doi.org/10.1111/bjd.15510.
28. Stanganelli I, De Felici MB, Mandel VD, et al. The association between pesticide use and cutaneous melanoma: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2020;34(4):691–708. https://doi.org/10.1111/jdv.15964.
29. Kubica AW, Brewer JD. Melanoma in immunosuppressed patients. Mayo Clin Proc. 2012;87(10):991–1003. https://doi.org/10.1016/j.mayocp.2012.04.018.
30. Konsoulova A. Principles of cancer immunobiology and immunotherapy of solid tumors. Intech Open. 2015. https://doi.org/10.5772/61211.
31. Varrone F, Mandrich L, Caputo E. Melanoma immunotherapy and precision medicine in the era of tumor micro-tissue engineering: where are we now and where are we going? Cancer. 2021. https://doi.org/10.3390/cancers13225788.
32. Liu J, Zou X. Melanoma. In: Liu J, Zou X, editors. Practical Dermoscopy. Singapore: Springer; 2022. p. 57–69.
33. Lee C, Collichio F, Ollila D, Moschos S. Historical review of melanoma treatment and outcomes. Clin Dermatol Mar-Apr. 2013;31(2):141–7. https://doi.org/10.1016/j.clindermatol.2012.08.015.
34. Davis LE, Shalin SC, Tackett AJ. Current state of melanoma diagnosis and treatment. Cancer Biol Ther. 2019;20(11):1366–79. https://doi.org/10.1080/15384047.2019.1640032.
35. Rebecca VW, Sondak VK, Smalley KS. A brief history of melanoma: from mummies to mutations. Melanoma Res. 2012;22(2):114–22. https://doi.org/10.1097/CMR.0b013e328351fa4d.
36. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med. 2011;364(26):2507–16. https://doi.org/10.1056/NEJMoa1103782.
37. Scolyer RA, Long GV, Thompson JF. Evolving concepts in melanoma classification and their relevance to multidisciplinary melanoma patient care. Mol Oncol. 2011;5(2):124–36. https://doi.org/10.1016/j.molonc.2011.03.002.
38. Rahimi A, Esmaeili Y, Dana N, et al. A comprehensive review on novel targeted therapy methods and nanotechnology-based gene delivery systems in melanoma. Eur J Pharm Sci. 2023;187:106476. https://doi.org/10.1016/j.ejps.2023.106476.
39. Liu Y, Sheikh MS. Melanoma: molecular pathogenesis and therapeutic management. Mol Cell Pharmacol. 2014;6(3):228.
40. Swaika A, Crozier JA, Joseph RW. Vemurafenib: an evidence-based review of its clinical utility in the treatment of metastatic melanoma. Drug Des Devel Ther. 2014;8:775–87. https://doi.org/10.2147/DDDT.S31143.
41. Ballantyne AD, Garnock-Jones KP. Dabrafenib: first global approval. Drugs. 2013;73(12):1367–76. https://doi.org/10.1007/s40265-013-0095-2.
42. Livingstone E, Zimmer L, Vaubel J, Schadendorf D. BRAF, MEK and KIT inhibitors for melanoma: adverse events and their management. Chin Clin Oncol. 2014;3(3):29. https://doi.org/10.3978/j.issn.2304-3865.2014.03.03.
43. Hodi FS, Corless CL, Giobbie-Hurder A, et al. Imatinib for melanomas harboring mutationally activated or amplified KIT arising on mucosal, acral, and chronically sun-damaged skin. J Clin Oncol. 2013;31(26):3182–90. https://doi.org/10.1200/JCO.2012.47.7836.
44. Byrne EH, Fisher DE. Immune and molecular correlates in melanoma treated with immune checkpoint blockade. Cancer. 2017;123(S11):2143–53. https://doi.org/10.1002/cncr.30444.
45. Berd D, Sato T, Cohn H, Maguire HC Jr, Mastrangelo MJ. Treatment of metastatic melanoma with autologous, hapten-modified melanoma vaccine: regression of pulmonary metastases. Int J Cancer. 2001;94(4):531–9. https://doi.org/10.1002/ijc.1506.abs.
46. Guo C, Manjili MH, Subjeck JR, Sarkar D, Fisher PB, Wang XY. Therapeutic cancer vaccines: past, present, and future. Adv Cancer Res. 2013;119:421–75. https://doi.org/10.1016/B978-0-12-407190-2.00007-1.
47. Baars A, van Riel JM, Cuesta MA, Jaspars EH, Pinedo HM, van den Eertwegh AJ. Metastasectomy and active specific immunotherapy for a large single melanoma metastasis. Hepatogastroenterology May-Jun. 2002;49(45):691–3.
48. Weber J. Immunotherapy for melanoma. Curr Opin Oncol. 2011;23(2):163–9. https://doi.org/10.1097/CCO.0b013e3283436e79.
49. Lee N, Zakka LR, Mihm MC Jr, Schatton T. Tumour-infiltrating lymphocytes in melanoma prognosis and cancer immunotherapy. Pathology. 2016;48(2):177–87. https://doi.org/10.1016/j.pathol.2015.12.006.
50. Koller KM, Wang W, Schell TD, et al. Malignant melanoma-The cradle of anti-neoplastic immunotherapy. Crit Rev Oncol Hematol. 2016;106:25–54. https://doi.org/10.1016/j.critrevonc.2016.04.010.
51. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell. 2015;27(4):450–61. https://doi.org/10.1016/j.ccell.2015.03.001.

52. Prieto PA, Yang JC, Sherry RM, et al. CTLA-4 blockade with ipilimumab: long-term follow-up of 177 patients with metastatic melanoma. Clin Cancer Res. 2012;18(7):2039–47. https://doi.org/10.1158/1078-0432.CCR-11-1823.
53. Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. Cell. 2015;161(2):205–14. https://doi.org/10.1016/j.cell.2015.03.030.
54. Fellner C. Ipilimumab (yervoy) prolongs survival in advanced melanoma: serious side effects and a hefty price tag may limit its use. P T. 2012;37(9):503–30.
55. Brahmer JR, Lacchetti C, Schneider BJ, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American society of clinical oncology clinical practice guideline. J Clin Oncol. 2018;36(17):1714–68. https://doi.org/10.1200/JCO.2017.77.6385.
56. D'Alise AM, Scarselli E. Getting personal in metastatic melanoma: neoantigen-based vaccines as a new therapeutic strategy. Curr Opin Oncol. 2023;35(2):94–9. https://doi.org/10.1097/CCO.0000000000000923.
57. Spiliopoulou P, Vornicova O, Genta S, Spreafico A. Shaping the future of immunotherapy targets and biomarkers in melanoma and non-melanoma cutaneous cancers. Int J Mol Sci. 2023. https://doi.org/10.3390/ijms24021294.
58. Friedman CF, Postow MA. Emerging tissue and blood-based biomarkers that may predict response to immune checkpoint inhibition. Curr Oncol Rep. 2016;18(4):21. https://doi.org/10.1007/s11912-016-0509-x.
59. Cristescu R, Mogg R, Ayers M, et al. Pan-tumor genomic biomarkers for PD-1 checkpoint blockade-based immunotherapy. Science. 2018. https://doi.org/10.1126/science.aar3593.
60. Namikawa K, Mori T, Muto Y, et al. 346O - PD-L1 expression and clinical outcome after nivolumab monotherapy in various subtypes of melanoma: A single-institutional retrospective study. Ann Oncol. 2018;29:ix105. https://doi.org/10.1093/annonc/mdy439.001.
61. Nebhan CA, Johnson DB. Predictive biomarkers of response to immune checkpoint inhibitors in melanoma. Expert Rev Anticancer Ther. 2020;20(2):137–45. https://doi.org/10.1080/14737140.2020.1724539.
62. Doroshow DB, Bhalla S, Beasley MB, et al. PD-L1 as a biomarker of response to immune-checkpoint inhibitors. Nat Rev Clin Oncol. 2021;18(6):345–62. https://doi.org/10.1038/s41571-021-00473-5.
63. Wang C, Wang HN, Wang L. Biomarkers for predicting the efficacy of immune checkpoint inhibitors. J Cancer. 2022;13(2):481–95. https://doi.org/10.7150/jca.65012.
64. Sorroche BP, Teixeira RJ, Pereira CAD, et al. PD-L1 tumor expression as a predictive biomarker of immune checkpoint inhibitors' response and survival in advanced melanoma patients in Brazil. Diagnostics. 2023. https://doi.org/10.3390/diagnostics13061041.
65. Huang L, Chen H, Xu Y, Chen J, Liu Z, Xu Q. Correlation of tumor-infiltrating immune cells of melanoma with overall survival by immunogenomic analysis. Cancer Med. 2020;9(22):8444–56. https://doi.org/10.1002/cam4.3466.
66. Bai X, Quek C. Unravelling tumour microenvironment in melanoma at single-cell level and challenges to checkpoint immunotherapy. Genes. 2022. https://doi.org/10.3390/genes13101757.
67. Balch CM. Decreased survival rates of older-aged patients with melanoma: biological differences or undertreatment? Ann Surg Oncol. 2015;22(7):2101–3. https://doi.org/10.1245/s10434-015-4540-1.
68. Gulati N, Celen A, Johannet P, et al. Preexisting immune-mediated inflammatory disease is associated with improved survival and increased toxicity in melanoma patients who receive immune checkpoint inhibitors. Cancer Med. 2021;10(21):7457–65. https://doi.org/10.1002/cam4.4239.
69. Garrett SB, Abramson CM, Rendle KA, Dohan D. Approaches to decision-making among late-stage melanoma patients: a multifactorial investigation. Support Care Cancer. 2019;27(3):1059–70. https://doi.org/10.1007/s00520-018-4395-7.
70. Krzyszczyk P, Acevedo A, Davidoff EJ, et al. The growing role of precision and personalized medicine for cancer treatment. Technology. 2018;6(3–4):79–100. https://doi.org/10.1142/S2339547818300020.
71. Yang TT, Yu S, Ke CK, Cheng ST. The genomic landscape of melanoma and its therapeutic implications. Genes. 2023. https://doi.org/10.3390/genes14051021.
72. Raimondo TM, Reed K, Shi D, Langer R, Anderson DG. Delivering the next generation of cancer immunotherapies with RNA. Cell. 2023;186(8):1535–40. https://doi.org/10.1016/j.cell.2023.02.031.
73. Verdegaal EM, de Miranda NF, Visser M, et al. Neoantigen landscape dynamics during human melanoma-T cell interactions. Nature. 2016;536(7614):91–5. https://doi.org/10.1038/nature18945.
74. Lang F, Schrors B, Lower M, Tureci O, Sahin U. Identification of neoantigens for individualized therapeutic cancer vaccines. Nat Rev Drug Discov. 2022;21(4):261–82. https://doi.org/10.1038/s41573-021-00387-y.
75. Giaever G, Chu AM, Ni L, et al. Functional profiling of the Saccharomyces cerevisiae genome. Nature. 2002;418(6896):387–91. https://doi.org/10.1038/nature00935.
76. Krauthammer M, Kong Y, Ha BH, et al. Exome sequencing identifies recurrent somatic RAC1 mutations in melanoma. Nat Genet. 2012;44(9):1006–14. https://doi.org/10.1038/ng.2359.
77. Scatena C, Murtas D, Tomei S. Cutaneous Melanoma Classification: The Importance of High-Throughput Genomic Technologies. Front Oncol. 2021;11: 635488. https://doi.org/10.3389/fonc.2021.635488.
78. Timar J, Ladanyi A. Molecular pathology of skin melanoma: epidemiology, differential diagnostics, prognosis and therapy prediction. Int J Mol Sci. 2022. https://doi.org/10.3390/ijms23105384.
79. Kang K, Xie F, Mao J, Bai Y, Wang X. Significance of tumor mutation burden in immune infiltration and prognosis in cutaneous melanoma. Front Oncol. 2020;10: 573141. https://doi.org/10.3389/fonc.2020.573141.
80. Ning B, Liu Y, Wang M, Li Y, Xu T, Wei Y. The predictive value of tumor mutation burden on clinical efficacy of immune checkpoint inhibitors in melanoma: a systematic review and meta-analysis. Front Pharmacol. 2022;13: 748674. https://doi.org/10.3389/fphar.2022.748674.
81. Xu S, Wang X, Fei C. A highly effective system for predicting MHC-II epitopes with immunogenicity. Front Oncol. 2022;12: 888556. https://doi.org/10.3389/fonc.2022.888556.
82. Kiyotani K, Chan HT, Nakamura Y. Immunopharmacogenomics towards personalized cancer immunotherapy targeting neoantigens. Cancer Sci. 2018;109(3):542–9. https://doi.org/10.1111/cas.13498.
83. Sahin U, Tureci O. Personalized vaccines for cancer immunotherapy. Science. 2018;359(6382):1355–60. https://doi.org/10.1126/science.aar7112.
84. Ping H, Yu W, Gong X, et al. Analysis of melanoma tumor antigens and immune subtypes for the development of mRNA vaccine. Invest New Drugs. 2022;40(6):1173–84. https://doi.org/10.1007/s10637-022-01290-y.
85. Lazdun Y, Si H, Creasy T, et al. A new pipeline to predict and confirm tumor neoantigens predict better response to immune checkpoint blockade. Mol Cancer Res. 2021;19(3):498–506. https://doi.org/10.1158/1541-7786.MCR-19-1118.
86. Sahin U, Derhovanessian E, Miller M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature. 2017;547(7662):222–6. https://doi.org/10.1038/nature23003.
87. van den Berg JH, Heemskerk B, van Rooij N, et al. Tumor infiltrating lymphocytes (TIL) therapy in metastatic melanoma: boosting of neoantigen-specific T cell reactivity and long-term follow-up. J Immunother Cancer. 2020. https://doi.org/10.1136/jitc-2020-000848.
88. Kristensen NP, Heeke C, Tvingsholm SA, et al. Neoantigen-reactive CD8+ T cells affect clinical outcome of adoptive cell therapy with tumor-infiltrating lymphocytes in melanoma. J Clin Invest. 2022. https://doi.org/10.1172/JCI150535.
89. Poschke IC, Hassel JC, Rodriguez-Ehrenfried A, et al. The outcome of ex vivo TIL expansion is highly influenced by spatial heterogeneity of the tumor T-cell repertoire and differences in intrinsic in vitro growth capacity between T-cell clones. Clin Cancer Res. 2020;26(16):4289–301. https://doi.org/10.1158/1078-0432.CCR-19-3845.
90. Tas L, Jedema I, Haanen J. Novel strategies to improve efficacy of treatment with tumor-infiltrating lymphocytes (TILs) for patients with solid cancers. Curr Opin Oncol. 2023;35(2):107–13. https://doi.org/10.1097/CCO.0000000000000925.
91. Chesney JA, Ribas A, Long GV, et al. Randomized, double-blind, placebo-controlled, global phase III trial of talimogene laherparepvec combined with pembrolizumab for advanced melanoma. J Clin Oncol. 2023;41(3):528–40. https://doi.org/10.1200/JCO.22.00343.

92. Cui C, Wang X, Lian B, et al. OrienX010, an oncolytic virus, in patients with unresectable stage IIIC-IV melanoma: a phase Ib study. J Immunother Cancer. 2022. https://doi.org/10.1136/jitc-2021-004307.
93. Robinson C, Xu MM, Nair SK, Beasley GM, Rhodin KE. Oncolytic viruses in melanoma. Front Biosci. 2022;27(2):63. https://doi.org/10.31083/j.fbl2702063.
94. Feola S, Russo S, Martins B, et al. Peptides-coated oncolytic vaccines for cancer personalized medicine. Front Immunol. 2022;13: 826164. https://doi.org/10.3389/fimmu.2022.826164.
95. Maurer DM, Butterfield LH, Vujanovic L. Melanoma vaccines: clinical status and immune endpoints. Melanoma Res. 2019;29(2):109–18. https://doi.org/10.1097/CMR.0000000000000535.
96. Fritah H, Rovelli R, Chiang CL, Kandalaft LE. The current clinical landscape of personalized cancer vaccines. Cancer Treat Rev. 2022;106: 102383. https://doi.org/10.1016/j.ctrv.2022.102383.
97. Chang R, Gulley JL, Fong L. Vaccinating against cancer: getting to prime time. J Immunother Cancer. 2023. https://doi.org/10.1136/jitc-2022-006628.
98. Carreno BM, Magrini V, Becker-Hapak M, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science. 2015;348(6236):803–8. https://doi.org/10.1126/science.aaa3828.
99. Geskin LJ, Damiano JJ, Patrone CC, Butterfield LH, Kirkwood JM, Falo LD. Three antigen-loading methods in dendritic cell vaccines for metastatic melanoma. Melanoma Res. 2018;28(3):211–21. https://doi.org/10.1097/CMR.0000000000000441.
100. Dillman RO, Nistor GI, Keirstead HS. Autologous dendritic cells loaded with antigens from self-renewing autologous tumor cells as patient-specific therapeutic cancer vaccines. Hum Vaccin Immunother. 2023;19(1):2198467. https://doi.org/10.1080/21645515.2023.2198467.
101. Miller M, Sahin U, Derhovanessian E, et al. 6O - IVAC MUTANOME: A first-in-human phase I clinical trial targeting individual mutant neoantigens for the treatment of melanoma. Ann Oncol. 2017;28:xi1–2. https://doi.org/10.1093/annonc/mdx712.003.
102. Lopez JS, Camidge R, Iafolla M, et al. Abstract CT301: A phase Ib study to evaluate RO7198457, an individualized Neoantigen Specific immunoTherapy (iNeST), in combination with atezolizumab in patients with locally advanced or metastatic solid tumors. Cancer Res. 2020;80(16_Supplement):CT-301-CT–301. https://doi.org/10.1158/1538-7445.Am2020-ct301.
103. Sahin U, Oehm P, Derhovanessian E, et al. An RNA vaccine drives immunity in checkpoint-inhibitor-treated melanoma. Nature. 2020;585(7823):107–12. https://doi.org/10.1038/s41586-020-2537-9.
104. Khattak A, Carlino M, Meniawy T, et al. Abstract CT001: a personalized cancer vaccine, mRNA-4157, combined with pembrolizumab versus pembrolizumab in patients with resected high-risk melanoma: efficacy and safety results from the randomized, open-label Phase 2 mRNA-4157-P201/Keynote-942 trial. Cancer Res. 2023;83(8_Supplemen):CT-001-CT–001. https://doi.org/10.1158/1538-7445.Am2023-ct001.
105. Ott PA, Hu-Lieskovan S, Chmielowski B, et al. A phase Ib trial of personalized neoantigen therapy plus anti-PD-1 in patients with advanced melanoma, non-small cell lung cancer, or bladder cancer. Cell. 2020;183(2):347-362 e24. https://doi.org/10.1016/j.cell.2020.08.053.
106. Hu Z, Leet DE, Allesoe RL, et al. Personal neoantigen vaccines induce persistent memory T cell responses and epitope spreading in patients with melanoma. Nat Med. 2021;27(3):515–25. https://doi.org/10.1038/s41591-020-01206-4.
107. Kesisoglou F, Chung J, van Asperen J, Heimbach T. Physiologically based absorption modeling to impact biopharmaceutics and formulation strategies in drug development—industry case studies. J Pharm Sci. 2016;105(9):2723–34.
108. Kesisoglou F, Mitra A. Application of absorption modeling in rational design of drug product under quality-by-design paradigm. AAPS J. 2015;17:1224–36.
109. Rowland M, Peck C, Tucker G. Physiologically-based pharmacokinetics in drug development and regulatory science. Annu Rev Pharmacol Toxicol. 2011;51:45–73.
110. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012;366(26):2455–65. https://doi.org/10.1056/NEJMoa1200694.
111. Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med. 2013;369(2):134–44. https://doi.org/10.1056/NEJMoa1305133.
112. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012;366(26):2443–54. https://doi.org/10.1056/NEJMoa1200690.
113. Hartmanshenn C, Scherholz M, Androulakis IP. Physiologically-based pharmacokinetic models: approaches for enabling personalized medicine. J Pharmacokinet Pharmacodyn. 2016;43(5):481–504. https://doi.org/10.1007/s10928-016-9492-y.
114. Khalil F, Laer S. Physiologically based pharmacokinetic modeling: methodology, applications, and limitations with a focus on its role in pediatric drug development. J Biomed Biotechnol. 2011;2011: 907461. https://doi.org/10.1155/2011/907461.
115. Yang Y, Zhao Y, Liu X, Huang J. Artificial intelligence for prediction of response to cancer immunotherapy. Semin Cancer Biol. 2022;87:137–47. https://doi.org/10.1016/j.semcancer.2022.11.008.
116. Damane BP, Mkhize-Kwitshana ZL, Kgokolo MC, Luvhengo T, Dlamini Z. Applying artificial intelligence prediction tools for advancing precision oncology in immunotherapy: future perspectives in personalized care. In: Dlamini Z, editor. Artificial intelligence and precision oncology: bridging cancer research and clinical decision support. Springer: Berlin; 2023. p. 239–58.
117. Afkham SA, Khormali E, Dorigo T. A new look at cancer immunotherapy via artificial intelligence. In: Rezaei N, editor. Handbook of Cancer and Immunology. Springer International Publishing; 2022. p. 1–18.
118. Xie J, Luo X, Deng X, et al. Advances in artificial intelligence to predict cancer immunotherapy efficacy. Front Immunol. 2022;13:1076883. https://doi.org/10.3389/fimmu.2022.1076883.
119. Li T, Li Y, Zhu X, et al. Artificial intelligence in cancer immunotherapy: Applications in neoantigen recognition, antibody design and immunotherapy response prediction. Semin Cancer Biol. 2023;91:50–69. https://doi.org/10.1016/j.semcancer.2023.02.007.
120. Amorim BJ, Torrado-Carvajal A, Esfahani SA, et al. PET/MRI radiomics in rectal cancer: a pilot study on the correlation between PET- and MRI-derived image features with a clinical interpretation. Mol Imag Biol. 2020;22(5):1438–45. https://doi.org/10.1007/s11307-020-01484-x.
121. Ferro M, Crocetto F, Barone B, Del Giudice F, Maggi M, Lucarelli G, Busetto GM, Autorino R, Marchioni M, Cantiello F, Crocerossa F, Luzzago S, Piccinelli M, Mistretta FA, Tozzi M, Schips L, Falagario UG, Veccia A, Vartolomei MD, Musi G, Tătaru OS. Artificial intelligence and radiomics in evaluation of kidney lesions: a comprehensive literature review. Ther Adv Urol. 2023;15:17562872231164804. https://doi.org/10.1177/17562872231164803.
122. Cook GJR, Siddique M, Taylor BP, Yip C, Chicklore S, Goh V. Radiomics in PET: principles and applications. Clin Transl Imag. 2014;2(3):269–76. https://doi.org/10.1007/s40336-014-0064-0.
123. Dercle L, Zhao B, Gonen M, et al. Early readout on overall survival of patients with melanoma treated with immunotherapy using a novel imaging analysis. JAMA Oncol. 2022;8(3):385–92. https://doi.org/10.1001/jamaoncol.2021.6818.
124. Coroller TP, Grossmann P, Hou Y, et al. CT-based radiomic signature predicts distant metastasis in lung adenocarcinoma. Radiother Oncol. 2015;114(3):345–50. https://doi.org/10.1016/j.radonc.2015.02.015.
125. Aoude LG, Wong BZY, Bonazzi VF, et al. Radiomics Biomarkers Correlate with CD8 Expression and Predict Immune Signatures in Melanoma Patients. Mol Cancer Res. 2021;19(6):950–6. https://doi.org/10.1158/1541-7786.Mcr-20-1038.
126. Miles KA, Ganeshan B, Rodriguez-Justo M, et al. Multifunctional imaging signature for V-KI-RAS2 Kirsten rat sarcoma viral oncogene homolog (KRAS) mutations in colorectal cancer. J Nucl Med. 2014;55(3):386–91. https://doi.org/10.2967/jnumed.113.120485.
127. Ferro M, Musi G, Marchioni M, et al. Radiogenomics in Renal Cancer Management—Current Evidence and Future Prospects. Int J Mol Sci. 2023;24(5):4615.
128. Xu Z, Wang X, Zeng S, Ren X, Yan Y, Gong Z. Applying artificial intelligence for cancer immunotherapy. Acta Pharm Sin B. 2021;11(11):3393–405. https://doi.org/10.1016/j.apsb.2021.02.007.
129. Schumacher TN, Schreiber RD. Neoantigens in cancer immunotherapy. Science. 2015;348(6230):69–74. https://doi.org/10.1126/science.aaa4971.

130. Samstein RM, Lee CH, Shoushtari AN, et al. Tumor mutational load predicts survival after immunotherapy across multiple cancer types. Nat Genet. 2019;51(2):202–6. https://doi.org/10.1038/s41588-018-0312-8.
131. Robbins PF, Lu YC, El-Gamil M, et al. Mining exomic sequencing data to identify mutated antigens recognized by adoptively transferred tumor-reactive T cells. Nat Med. 2013;19(6):747–52. https://doi.org/10.1038/nm.3161.
132. Kloke B-P, Britten CM, Loquai C, et al. Abstract CT202: IVAC MUTANOME: individualized vaccines for the treatment of cancer. Cancer Res. 2015;75(15_Supplement):CT202–CT202. https://doi.org/10.1158/1538-7445.Am2015-ct202.
133. Hartmaier RJ, Charo J, Fabrizio D, et al. Genomic analysis of 63,220 tumors reveals insights into tumor uniqueness and targeted cancer immunotherapy strategies. Genome Med. 2017;9(1):16. https://doi.org/10.1186/s13073-017-0408-2.
134. Zhang X, Sharma PK, Peter Goedegebuure S, Gillanders WE. Personalized cancer vaccines: targeting the cancer mutanome. Vaccine. 2017;35(7):1094–100. https://doi.org/10.1016/j.vaccine.2016.05.073.
135. Alexandrov LB, Nik-Zainal S, Wedge DC, et al. Signatures of mutational processes in human cancer. Nature. 2013;500(7463):415–21. https://doi.org/10.1038/nature12477.
136. Xue S, Barna M. Specialized ribosomes: a new frontier in gene regulation and organismal biology. Nat Rev Mol Cell Biol. 2012;13(6):355–69. https://doi.org/10.1038/nrm3359.
137. Pelletier J, Thomas G, Volarevic S. Ribosome biogenesis in cancer: new players and therapeutic avenues. Nat Rev Cancer. 2018;18(1):51–63. https://doi.org/10.1038/nrc.2017.104.
138. Carvalho T. Personalized anti-cancer vaccine combining mRNA and immunotherapy tested in melanoma trial. New York: Nature News; 2023.
139. Bidram M, Zhao Y, Shebardina NG, et al. mRNA-based cancer vaccines: a therapeutic strategy for the treatment of melanoma patients. Vaccines. 2021. https://doi.org/10.3390/vaccines9101060.
140. Evaxion. Using AI to create a vaccine revolution. New York: Nature; 2023.
141. Mancuso F, Lage S, Rasero J, et al. Serum markers improve current prediction of metastasis development in early-stage melanoma patients: a machine learning-based study. Mol Oncol. 2020;14(8):1705–18. https://doi.org/10.1002/1878-0261.12732.
142. Lu YC, Yao X, Crystal JS, et al. Efficient identification of mutated cancer antigens recognized by T cells associated with durable tumor regressions. Clin Cancer Res. 2014;20(13):3401–10. https://doi.org/10.1158/1078-0432.CCR-14-0433.
143. Goussault R, Frénard C, Maubec E, et al. Machine learning models to predict the response to anti-cancer therapy in metastatic melanoma patients. J Clin Oncol. 2020;38:e4071–e4071. https://doi.org/10.1200/JCO.2020.38.15_suppl.e14071.
144. Wang X, Montoyo-Pujol YG, Bermudez S, et al. Serum cytokine profiles of melanoma patients and their association with tumor progression and metastasis. J Oncol. 2021;2021:6610769. https://doi.org/10.1155/2021/6610769.
145. Shofty B, Artzi M, Shtrozberg S, et al. Virtual biopsy using MRI radiomics for prediction of BRAF status in melanoma brain metastasis. Sci Rep. 2020;10(1):6623. https://doi.org/10.1038/s41598-020-63821-y.
146. Wen D, Khan SM, Ji XuA, et al. Characteristics of publicly available skin cancer image datasets: a systematic review. Lancet Digit Health. 2022;4(1):e64–74. https://doi.org/10.1016/S2589-7500(21)00252-1.


## Publisher's Note