Individualized Immunotherapy Approaches in Precision Medicine

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Abstract

Individualized immunotherapy represents a paradigm shift in precision medicine, offering tailored therapeutic strategies based on a patient's unique immunological profile. Recognizing the inherent variability in immune responses, this approach moves beyond conventional one-size-fits-all treatments, particularly in managing cancer and autoimmune diseases. A key pillar of personalized immunotherapy is the identification of predictive biomarkers that help forecast a patient's response to specific treatments. By analyzing molecular and genetic signatures within an individual's immune system, clinicians can optimize therapy selection, minimizing trial-and-error approaches and reducing potential adverse effects. Advances in high-throughput technologies and genomic research have significantly propelled this field forward. The identification of neoantigens—tumor-specific antigens arising from mutations—has enabled the development of personalized cancer vaccines. Additionally, CRISPR-based gene-editing techniques have facilitated precise modifications of immune cells, enhancing their ability to target specific diseases. As individualized immunotherapy continues to evolve, its successful integration into precision medicine will rely on overcoming technological and biological challenges, ultimately unlocking new possibilities for highly effective, patient-specific treatments.

Keywords: Cancer Vaccines,Biomarkers, Precision Medicine, Personalized Treatments.

Significance | This study highlights the transformative potential of personalized immunotherapy in precision medicine by optimizing treatments through individual immunological profiling.

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Introduction

Precision medicine, also known as personalized medicine or genomic medicine, represents a paradigm shift in healthcare, offering immense potential to revolutionize patient care. This innovative approach customizes medical interventions based on an individual's unique genetic makeup, lifestyle, and environmental factors (De Leon, 2009). By integrating genomic data, data science, and clinical expertise, precision medicine aims to optimize disease prevention, diagnosis, and treatment, ultimately enhancing patient outcomes (Manolopoulos, 2012).

The foundation of precision medicine lies in the understanding that individuals respond differently to treatments due to genetic variations, environmental exposures, and diverse physiological factors. Traditionally, medicine followed a "one-size-fits-all" approach, where treatments were determined based on population averages and clinical trial results (Bakker et al., 2015). However, this method often failed to account for the significant variations observed among individuals, leading to suboptimal treatment outcomes and, in some cases, adverse reactions.

The advent of high-throughput genomic sequencing, powerful computational analytics, and artificial intelligence has propelled precision medicine to the forefront of medical innovation (Madad et al., 2014). The decreasing cost and increasing accessibility of genomic profiling have made it possible to identify specific genetic alterations associated with various diseases. Moreover, the

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integration of advanced machine learning algorithms enables the extraction of critical insights from vast biomedical datasets, facilitating the development of targeted therapies.

Precision medicine has found applications across a wide range of disease domains, including cancer, cardiovascular disorders, and rare genetic diseases. In oncology, it has revolutionized cancer diagnosis and treatment by enabling the identification of genetic mutations that drive tumor progression (Flockhart et al., 2018). This knowledge has paved the way for the development of targeted therapies, such as monoclonal antibodies and small-molecule inhibitors, which selectively attack cancer cells while sparing healthy tissues.

In cardiovascular medicine, precision medicine has enabled genetic risk assessments to identify individuals predisposed to heart diseases. This has allowed for the implementation of personalized preventive strategies, including tailored dietary modifications, customized medication regimens, and specific lifestyle interventions to mitigate cardiovascular risk. Additionally, pharmacogenomics—the study of how genetic variations influence drug responses—plays a crucial role in optimizing drug selection and dosage for each patient, thereby minimizing adverse effects and maximizing therapeutic efficacy (Seidman & Furst, 2012).

For rare genetic disorders, precision medicine has been a game changer, addressing significant diagnostic and therapeutic challenges. The use of whole-genome sequencing has facilitated the early and accurate identification of disease-causing genetic mutations, leading to timely interventions. Gene therapy and genome-editing technologies, such as CRISPR-Cas9, offer promising therapeutic avenues by correcting genetic defects at the molecular level. For patients who previously had limited or no treatment options, these advancements have provided renewed hope.

Despite its transformative potential, several challenges and ethical concerns must be addressed before precision medicine can be widely implemented (Deverka et al., 2018). One of the primary concerns is the handling of vast amounts of genetic and health data, raising issues related to data privacy, security, and consent. Ensuring equitable access to precision medicine is another significant challenge, as disparities in healthcare infrastructure and costs may limit its availability to certain populations. Additionally, the interpretation of genetic data remains complex, requiring continuous advancements in bioinformatics and clinical expertise.

According to the National Cancer Institute (NCI), approximately 1,685,210 new cancer cases were diagnosed in 2016 (Siegel et al., 2018). Given this high incidence, developing effective treatments that either halt disease progression or achieve a cure is of utmost importance. Traditionally, cancer patients have been assigned standardized treatment protocols based on the type and stage of their malignancy. However, as our understanding of tumor heterogeneity deepens, the limitations of this "one-size-fits-all" approach are becoming increasingly evident.

The future of cancer treatment hinges on a highly individualized approach that integrates multi-dimensional tumor profiling and biomarker-driven therapy selection (Collins et al., 2015). Advanced molecular diagnostics enable comprehensive biochemical characterization of tumors, allowing for precise treatment decisions that improve overall response rates (ORR) and overall survival (OS).

A major breakthrough in precision oncology has been the resurgence of immunotherapy, driven by the discovery that tumors exploit immune checkpoints to evade immune surveillance (Mellman et al., 2016). Emerging evidence suggests that treatment responses in immunotherapy are influenced by each patient's unique immune system rather than solely by tumor biology (Kakimi et al., 2017). Consequently, novel technologies are needed to accurately predict which patients will benefit from immunotherapy.

Although immunotherapy has led to remarkable cures in some patients with terminal cancer, clinical outcomes vary significantly (Ferris et al., 2016). Therefore, ongoing research efforts are focused on refining precision medicine strategies to improve treatment efficacy and expand its applications. This includes developing robust predictive biomarkers, enhancing patient stratification methods, and leveraging artificial intelligence to tailor therapies with unprecedented accuracy.

Precision medicine represents a transformative shift in modern healthcare, offering personalized treatment strategies that optimize clinical outcomes. By leveraging genomic data, advanced analytics, and targeted therapies, precision medicine has significantly impacted the management of cancer, cardiovascular diseases, and rare genetic disorders. However, overcoming challenges related to data security, accessibility, and ethical considerations remains essential for its broader implementation. As research continues to evolve, precision medicine is poised to redefine the future of disease treatment, moving beyond the conventional "one-size-fits-all" model toward truly individualized care.

2. Classic Biomarker-Based Approaches for Precision Diagnostics

The first generation of individualized medicine has been enabled by the discovery of molecular cancer biomarkers, often referred to as "addictive" oncogenes. These tumor-specific overexpressed proteins or genetic abnormalities can provide cancer cells with mechanisms of therapeutic resistance, which have been identified using genomic screening techniques (Sethi et al., 2013). Targeting these biomarkers therapeutically has led to improved clinical outcomes.

For instance, the development of diagnostic tools like HercepTest has been facilitated by antibodies and small-molecule inhibitors targeting specific proteins, such as Human Epidermal Growth Factor Receptor 2 (HER2) (Barrett et al., 2007). The overexpression of HER2 in multiple cancer types led to the FDA's approval of trastuzumab for stomach and gastroesophageal junction cancer in 2010 (Gunturu et al., 2013). Similarly, repurposing existing drugs is a growing trend in oncology, exemplified by the approval of thalidomide for multiple myeloma (Barlogie et al., 2023).

Another key discovery in precision oncology was the overexpression of Epidermal Growth Factor Receptor (EGFR) in certain cancers, identified as early as 1997 (Rusch et al., 1997). This finding led to the development of EGFR tyrosine kinase inhibitors (EGFR-TKIs) like gefitinib and afatinib. However, approximately 60% of patients treated with first-line EGFR-TKIs eventually develop resistance (Yu et al., 2013). Subsequent research identified the T790M mutation as the primary driver of this resistance, leading to the development of osimertinib (Tagrisso), a next-generation EGFR-TKI specifically designed to target this mutation (Sgambato et al., 2012).

Beyond EGFR-targeted therapies, individualized medicine has expanded into hematologic malignancies. For example, patients with FMS-like tyrosine kinase 3 (FLT3) mutations in acute myeloid leukemia (AML) have been approved for treatment with midostaurin (Rydapt), a small-molecule inhibitor of vascular endothelial growth factor (VEGF) (Levis, 2017). Since FLT3 mutations occur in only 10% of leukemia cases and 25% of AML cases, biomarker-driven treatment selection has become crucial (Walker et al., 2016). In April 2017, the FDA approved the LeukoStrat CDx FLT3 Mutation Assay alongside midostaurin, with a Phase III trial demonstrating a 23% increase in overall survival (Gupta et al., 2013).

Despite the success of biomarker-guided therapies, only 16 out of more than 200 FDA-approved cancer drugs currently require or benefit from companion diagnostic tests (Myers, 2016). The evolving landscape of oncology suggests that new approaches in precision medicine must integrate immunotherapy and other novel strategies to further enhance treatment outcomes.

3. Targeting the Immune Compartment

3.1 Cytokine Stimulation

The foundation of cancer immunotherapy can be traced back to William Coley, who, in 1890, observed a connection between a patient's complete remission from sarcoma and an infection caused by Streptococcus pyogenes (Coley et al., 2018). Based on this finding, he initiated cancer treatments using bacterial infections post-surgery, aiming to stimulate the immune response and prevent tumor recurrence. However, due to the adverse effects associated with infections, this approach proved largely ineffective. Despite its limitations, Coley's work laid the groundwork for immune system-based cancer therapies.

It was not until 1992 that the FDA approved high-dose interleukin-2 (HD IL-2) as an immunotherapy for renal cell carcinoma (RCC) (Klapper et al., 2008). Between 1986 and 2006, the National Cancer Institute (NCI) treated 259 patients with metastatic RCC using HD IL-2, achieving an objective response rate of 20%, with 23 patients experiencing complete remission and 30 achieving partial responses (Klapper et al., 2008). In 1998, HD IL-2 therapy was also approved for melanoma, yielding similar response rates (Bhatia et al., 2012). Although only a small subset of patients respond favorably, this non-specific immunotherapeutic approach remains one of the few capable of inducing complete remission in select individuals.

3.2 Immune Checkpoint Inhibitors

Immune checkpoints act as regulatory mechanisms that prevent excessive T cell activation and maintain immune homeostasis. The primary goal of immune checkpoint inhibition is to prevent T cell exhaustion and reduce the activity of regulatory T cells (Tregs). Among the most well-characterized immune cells in cancer biology are CD4+ helper T cells, which can promote tumor progression, and cytotoxic CD8+ T cells, which exhibit tumor-suppressive effects (Alderton, 2012).

Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), one of the earliest identified immune checkpoint receptors, was discovered in 1987. By competitively binding to B7 proteins—molecules essential for T cell activation—CTLA-4 downregulates immune responses. However, it was not until 1996 that targeting CTLA-4 was demonstrated to have anti-cancer effects in mice (Leach et al., 2016). This breakthrough led to the development of ipilimumab (Yervoy), an anti-CTLA-4 monoclonal antibody, which became the first immune checkpoint inhibitor approved for metastatic melanoma in 2011.

The success of ipilimumab paved the way for more advanced immune checkpoint inhibitors, including pembrolizumab (Keytruda), nivolumab (Opdivo), and atezolizumab (Tecentriq), which target the programmed cell death-1 (PD-1) and programmed death-ligand 1 (PD-L1) pathways. Notably, pembrolizumab has received FDA approval for multiple indications, including refractory Hodgkin's lymphoma, metastatic non-small cell lung cancer (NSCLC), and metastatic melanoma. A pivotal Phase III trial reported a progression-free survival of 10.3 months in advanced NSCLC patients treated with pembrolizumab, compared to 6 months with platinum-based chemotherapy (Reck et al., 2016).

A landmark moment in precision medicine occurred in May 2017 when the FDA approved pembrolizumab for solid tumors based solely on the presence of mismatch repair deficiencies or high microsatellite instability, rather than tumor location. This shift highlights the growing role of biomarker-driven therapy in

Table 1. Types of cancer immunotherapies

Type of Immunotherapy	Examples
Cancer Vaccines	Provenge, Vigil
Immune modulators	Checkpoint inhibitors Immune regulatory cytokines
Adoptive cell therapy	Monoclonal antibodies
Targeted antibodies	CAR-T therapy in leukemia and lymphoma

Table 2. Clinical trials utilizing biomarker stratification analysis

Trail name	Short Description	Experiment Arms/Cohorts	Biomarker Stratification
KEYNOTE-158	Phase II, two arm, open-label trial investigating pembrolizumab and evaluating predictive biomarkers in subjects with advanced solid tumors	Arm 1: Pembrolizumab 200 mg Arm 2: Participants failed at least one line of therapy and have TMB high.	TMB high
NCT03428802	Phase II, single-arm, open-label trial studying the use of pembrolizumab in patients with metastatic, recurrent, or locally advanced solid tumors and genomic instability	Arm 1: Pembrolizumab and lab biomarker analysis	Response rate will be stratified by mutation type (POLE and POLD1 versus BRCA1/2) Patient/clinical outcomes will be stratified by PD-L1 expression and presence of PD-1/PDL-1 polymorphisms and presence of immunoregulatory gene mutations (via deep sequencing) Response will be stratified by presence of immunogenic neoantigens (via exome sequencing) and expression of checkpoint genes, Immune regulatory modules, or non-coding RNAs including repetitive RNAs and retroelements (via RNA sequencing)
V3-OVA	Phase II, single-arm, open-label trial studying the use of vaccine V3-OVA in ovarian cancer	Arm 1: V3-OVA vaccine (containing ovarian cancer antigens)	Secondary outcomes will assess the effect on level of serum tumor markers compared to baseline (including CA-125)
AdORN	Phase I/II, single-arm, open-label trial studying the use of atezolizumab with neoadjuvant chemotherapy in interval cytoreductive surgery in patients with newly diagnosed advanced-stage epithelial ovarian cancer	Arm 1: Atezolizumab, carboplatin, and paclitaxel (and optional bevacizumab)	PFS will be stratified based on the expression of PD-L1,tumor-infiltrating lymphocytes, immune checkpoint receptors,and cytokines and gene expression profiles Each of those subsets will be further stratified by BRCA mutation status and tumor mutation profile

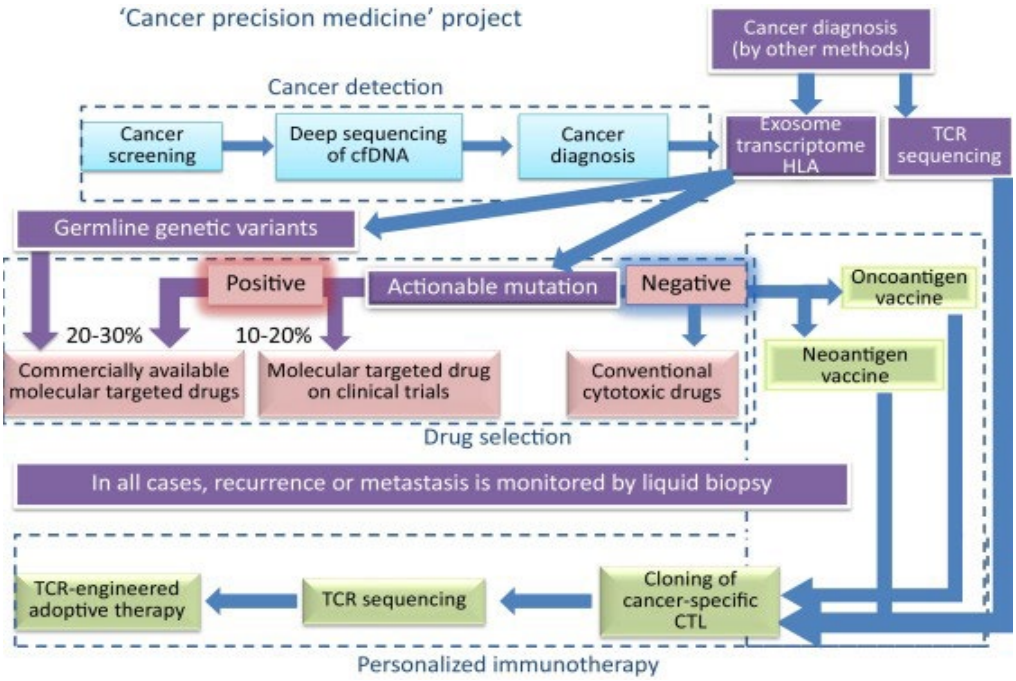

Figure 1. Percision Medicine

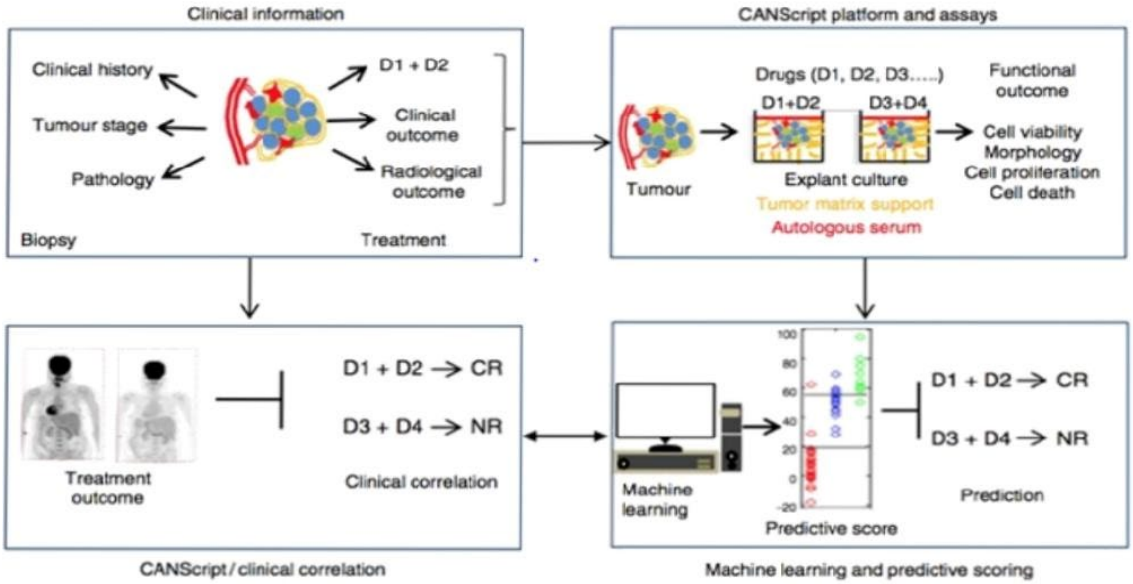

Figure 2. CANscript® platform technology

oncology. The full potential of immune checkpoint inhibitors remains untapped, with 734 ongoing clinical trials investigating their efficacy in combination with other therapies.

4. Adoptive cell transfer: Personalized T-cell therapy

Chimeric antigen receptor (CAR)-T cells represent a specialized form of adoptive cell transfer (ACT). In this approach, T cells are harvested from a patient (or donor), genetically modified ex vivo to express cancer-specific antigens, and then reinfused into the patient. CAR-T cell therapy has demonstrated remarkable success in treating B cell malignancies, particularly B cell acute lymphoblastic leukemia (B-ALL). In a study involving 50 children and young adults with CD19+ ALL, all patients achieved complete remission following CAR-T cell treatment (Onea, 2016).

Despite these promising results in liquid tumors, CAR-T therapy faces challenges in treating solid tumors due to physical and biochemical barriers. For instance, a Phase I clinical trial evaluating EGFR-targeted CAR-T cells in patients with EGFR-positive relapsed/refractory non-small cell lung cancer (NSCLC) reported only two partial responses among 11 evaluable patients, while five patients maintained stable disease for two to eight months (Feng et al., 2016). To enhance CAR-T efficacy, researchers have proposed improving CAR specificity and combining CAR-T therapy with immune checkpoint inhibitors (Jin et al., 2016).

However, CAR-T therapy is associated with significant adverse effects, such as the potentially life-threatening cytokine release syndrome, which must be carefully managed before wider clinical application. Another ACT approach involves expanding tumor-infiltrating lymphocytes (TILs) ex vivo with IL-2 and reinfusing them directly into the tumor site. This strategy has shown promising overall survival rates in clinical settings. It has been successfully used in a subset of patients with melanoma and B cell cancers. Additionally, a recent study reported that three out of nine patients with metastatic cervical cancer who received human papillomavirus (HPV)-targeted TIL therapy responded, with two achieving complete remission lasting up to 22 months (Stevanović et al., 2015).

4.1 Biomarkers for Personalized Cancer Immunotherapy

While tumor-related biomarkers have been successfully utilized to tailor kinase-targeted therapies for individual patients, applying similar methodologies to personalized cancer immunotherapy has proven more challenging (Table 1, Figure 1). The complexity of the tumor microenvironment and its diverse cellular landscape necessitate an expansion of traditional biomarker-based approaches to encompass the entire tumor ecosystem and tumor-immune interactions (Kakimi et al., 2017). In the context of immunotherapy, improved treatment outcomes are often linked to the ability of T cells to mount a response against invasive tumor growth (Fridman et al., 2012). Several studies have demonstrated that lymphocyte infiltration and spatial distribution within tumors can serve as predictors of overall or progression-free survival (Galon et al., 2016).

Specifically, different lymphocyte subtypes—such as CD3+/CD8+, CD3+/CD45RO+, or CD8+/CD45RO+—exhibit distinct infiltration patterns that correlate with varying prognostic outcomes (Galon et al., 2016). One of the first standardized immune-based assays for measuring the spatial heterogeneity of infiltrating immune cells is Immunoscore® Colon, developed by the French cancer diagnostics company HalioDx (Hermitte et al., 2016). This assay, specific to colon cancer, assesses the tumor core and invasive margin to quantify the density and distribution of CD8+ cytotoxic T cells and CD3+ T lymphocytes. An algorithm generates an Immunoscore®, ranging from I0 (lowest immune infiltration) to I4 (highest immune infiltration) (Hermitte et al., 2016).

Patients with Immunoscores of I3 or I4 exhibited significantly longer overall survival (OS) and disease-specific survival (DSS), regardless of microsatellite instability status. Conversely, those with Immunoscores in the I0–I2 range had shorter OS and DSS, with a higher likelihood of relapse (Mlecnik et al., 2016). While this method of assessing lymphocyte infiltration has proven superior to conventional response metrics, the expression profile of immune-related genes also plays a crucial role in predicting therapeutic response. For instance, in clinical trials involving ipilimumab, melanoma patients with elevated expression of immune function-related genes (e.g., CD8A, CD27, CD38, CD3, CD40, GZMB, PRF1, CCL4) were more likely to respond positively to treatment (Ji et al., 2012). However, emerging evidence suggests that dynamic resistance mechanisms may impact immunotherapy efficacy, further driving research into personalized approaches (Mellman et al., 2016).

One such personalized approach is CANscript®, an ex vivo tumor model developed by MitraRxDx Inc., a Boston-based company specializing in individualized cancer therapy. CANscript® utilizes freshly obtained tumor biopsies and surgical specimens to assess drug responses in a fully humanized, autologous setting (Majumder et al., 2015). By maintaining tumor tissue within culture wells coated with tumor-type and grade-matched tumor matrix proteins (TMPs) alongside peripheral blood nucleated cells (PBNCs), CANscript® preserves the heterogeneity of both the tumor and its microenvironment. This system effectively replicates the tumor's 3D architecture, including its immune compartment, providing a robust platform for assessing the functional effects of targeted therapies and immunotherapies (Figure 2).

Drug responses are evaluated based on various functional parameters following drug exposure. These data are then used to train a machine learning algorithm, which generates an M-score

predicting drug efficacy. The CANscript® system integrates four critical modules for development and validation.

The first module, Sample Collection, involves obtaining tumor core or surgical biopsy specimens along with detailed information on tumor staging, pathology, and patient clinical history. In the second module, Ex Vivo Culture, the collected tumor biopsies are rapidly processed into thin explants and cultured with tumor- and grade-matched tumor matrix proteins (TMPs), autologous serum (AS), and selected drug regimens. Although multiple drug regimens can be tested, the one prescribed by the patient's oncologist is always included in the tumor explant culture.

The third module, Drug Response Evaluation, assesses the functional effects of drug treatment by measuring key parameters such as cell viability, pathological and morphological analysis, cell proliferation, and apoptosis. A machine learning algorithm then aggregates these quantitative scores to classify responses into one of three categories: complete response (CR), partial response (PR), or no response (NR).

Finally, in the fourth module, Clinical Correlation, the predictive models generated through the system are validated against real-world clinical outcomes. This comprehensive approach ensures that CANscript® provides a highly personalized and clinically relevant prediction of drug efficacy, thereby improving treatment decision-making for cancer patients.

By bridging the gap between preclinical models and patient-specific responses, CANscript® provides an innovative framework for precision cancer immunotherapy (Image Courtesy of MitraRxDx).

4.2 Ongoing Clinical Trials

Despite extensive research, the integration of immunotherapies into ovarian cancer treatment has yet to demonstrate consistent efficacy. However, ongoing studies aim to identify biomarkers that can predict patient responses to immune-based therapies. Additionally, trials are investigating combinations of immune checkpoint inhibitors, vaccines, and adoptive cell therapies to enhance treatment efficacy in specific ovarian cancer subgroups.

Numerous clinical trials are currently evaluating the impact of various immunotherapeutic strategies on ovarian cancer. A subset of these trials incorporates biomarker-driven patient stratification, allowing researchers to refine treatment selection and optimize therapeutic responses. The results of these investigations are summarized in Table 2, which outlines key trials and their findings.

5. Discussion

Individualized immunotherapy, within the scope of precision medicine, represents a groundbreaking approach to revolutionizing medical treatments. This strategy is predicated on understanding the unique genetic and immunological profiles of individual patients. In cancer therapy, precision medicine enables comprehensive molecular analysis of tumors, identifying patient-specific antigens or neoantigens that drive treatment decisions.

Schumacher and Schreiber (2015) underscore the importance of neoantigens as ideal targets for immunotherapy. These neoantigens, arising from somatic mutations in cancer cells, are pivotal in shaping personalized immunotherapeutic strategies. For instance, cancer vaccines and adoptive T-cell therapies are designed to target these specific neoantigens, enhancing the immune system's ability to precisely eradicate tumor cells.

Beyond cancer, individualized immunotherapy is increasingly applied to autoimmune diseases and allergies. By tailoring treatments based on a patient's distinct immune profile, this approach optimizes therapeutic efficacy while reducing potential side effects.

Nevertheless, challenges remain. Torga and Pienta (2018) highlight obstacles such as the need for advanced molecular profiling and the financial burden of personalized therapies. Emerging technologies, particularly next-generation sequencing, are addressing these barriers, gradually making precision medicine more accessible and practical.

Individualized immunotherapy, as emphasized by Schumacher and Schreiber (2015) and Torga and Pienta (2018), signifies a transformative shift towards patient-specific treatments. As advancements in genomics and immunology continue to evolve, integrating individualized immunotherapy into clinical practice holds the potential to redefine therapeutic strategies across various medical fields.

6. Conclusion and Perspective

The ongoing challenge of selecting the most effective cancer treatments underscores the complexity of the disease and the limitations of current therapeutic strategies. Despite significant advances in identifying biomarkers, oncogenes, and mutations, clinical progress has plateaued, as only a small percentage of patients have tumor characteristics that align with a specific therapeutic target. This is especially true in the era of cancer immunotherapy, where immune-related side effects, particularly when combined with CTLA-4 inhibitors, can significantly impact patient outcomes. A significant portion of patients experiences these side effects, emphasizing the critical importance of patient selection and the need for personalized treatment approaches.

Currently, treatment choices often rely on an understanding of growth factor receptors and key immunological checkpoint proteins, rather than taking a comprehensive patient-specific approach. Tumors present a complex array of overexpressed, mutant, and malfunctioning proteins, and focusing on just one target may not yield the optimal therapeutic response. To improve patient outcomes, we need a robust method for evaluating and

selecting the most effective treatment based on the patient's unique tumor profile.

With the rapid advancements in technologies such as high-throughput sequencing, we are entering an exciting era of truly individualized cancer medicine. These technologies allow for a more objective approach to drug selection by identifying mutations across the entire genome. However, there remains a gap between identifying mutations and selecting the appropriate therapy.

The future of cancer treatment lies in developing new platform technologies that go beyond molecular biomarkers. These platforms could explore the dynamic and heterogeneous nature of tumors, ensuring that patients receive the most effective care tailored to their specific cancer type. Moreover, they offer opportunities for discovering new drug efficacies, including the potential for repurposing immunotherapies alongside traditional drugs. Ultimately, these advancements have the potential to revolutionize cancer care, significantly improving patient survival rates and contributing to the eradication of cancer.

Author contributions

K.H.C. contributed to the conceptualization, methodology, and initial drafting of the manuscript. S.S.K. participated in data analysis, interpretation, and critical revision of the manuscript. Both authors reviewed and approved the final version of the manuscript.

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Competing financial interests

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