



## Review article

# Elucidating the nexus between onco-immunology and kidney transplantation: An insight from precision medicine perspective

Athaya Febriantyo Purnomo<sup>a,b</sup>, Fahrul Nurkolis<sup>c</sup>, Rony Abdi Syahputra<sup>d</sup>,  
 Seungjoon Moon<sup>e,f</sup>, Dain Lee<sup>e,j</sup>, Nurpudji Astuti Taslim<sup>g</sup>, Moon Nyeo Park<sup>e,j</sup>,  
 Besut Daryanto<sup>b</sup>, Kurnia Penta Seputra<sup>b</sup>, Paksi Satyagraha<sup>b</sup>,  
 Nurul Cholifah Lutfiana<sup>h</sup>, Pande Made Wisnu Tirtayasa<sup>i</sup>, Bonglee Kim<sup>e,j,\*</sup>

<sup>a</sup> Department of Oncology, University of Oxford, Oxford, OX3 7DQ, United Kingdom

<sup>b</sup> Department of Urology, Faculty of Medicine Universitas Brawijaya–Saiful Anwar General Hospital, Malang, 65142, Indonesia

<sup>c</sup> Department of Biological Sciences, State Islamic University of Sunan Kalijaga (UIN Sunan Kalijaga), Yogyakarta, 55281, Indonesia

<sup>d</sup> Department of Pharmacology, Faculty of Pharmacy, Universitas Sumatera Utara, Medan, Indonesia

<sup>e</sup> Department of Pathology, College of Korean Medicine, Kyung Hee University, Hoegidong Dongdaemun-gu, Seoul, 02447, Republic of Korea

<sup>f</sup> Chansol Hospital of Korean Medicine, 290, Buheung-ro, Bupyeong-gu, Incheon, South Korea, 21390, Republic of Korea

<sup>g</sup> Division of Clinical Nutrition, Department of Nutrition, Faculty of Medicine, Hasanuddin University, Makassar, 90245, Indonesia

<sup>h</sup> Department of Biochemistry and Biomedicine, Faculty of Medicine, Universitas Muhammadiyah Surabaya, Surabaya, Indonesia

<sup>i</sup> Department of Urology, Faculty of Medicine, Universitas Udayana, Universitas Udayana Teaching Hospital, Bali, 80361, Indonesia

<sup>j</sup> Korean Medicine-Based Drug Repositioning Cancer Research Center, College of Korean Medicine, Kyung Hee University, Seoul, 02447, Republic of Korea

## ARTICLE INFO

## Keywords:

Oncology  
 Immunology  
 Malignancies  
 Transplantation  
 Personalized therapeutic  
 Genetic

## ABSTRACT

The interplay of onco-immunology and kidney transplantation heralds a transformative era in medical science. This integration, while promising, presents significant challenges. Chief among these is the dichotomy of immunosuppression—boosting immunity against malignancies while suppressing it for graft survival. Additionally, limited clinical data on novel therapies, genetic variations influencing responses, economic concerns, and the narrow therapeutic window for post-transplant malignancies necessitate strategic addressal. Conversely, opportunities abound, including personalized immune monitoring, targeted therapies, minimized immunosuppression, and improved patient quality of life. Emphasizing collaborative research and interdisciplinary cooperation, the merging of these fields offers the potential for enhanced graft survival and reduced post-transplant malignancy risks. As we harness modern technology and promote patient-centric care, the vision for the future of kidney transplantation becomes increasingly hopeful, paving the way for more personalized and effective treatments. The article aims to elucidate the critical challenge of balancing immunosuppression to simultaneously combat malignancies and ensure graft survival. It addresses the scarcity of clinical data on novel therapies, the impact of genetic variations on treatment responses, and the economic and therapeutic concerns in managing post-transplant malignancies. Furthermore, it explores the opportunities precision medicine offers, such as personalized immune monitoring, targeted therapies, and reduced immunosuppression, which could significantly improve patient outcomes. Highlighting the importance of collaborative research and interdisciplinary efforts, the article seeks to demonstrate the potential for enhanced graft survival and reduced post-transplant malignancy.

\* Corresponding author.

E-mail address: [bongleekim@khu.ac.kr](mailto:bongleekim@khu.ac.kr) (B. Kim).

<https://doi.org/10.1016/j.heliyon.2024.e33751>

Received 4 April 2024; Received in revised form 12 June 2024; Accepted 26 June 2024

Available online 26 June 2024

2405-8440/© 2024 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

risks. By leveraging modern technology and prioritizing patient-centric care, it envisions a future where kidney transplantation is more personalized and effective, offering hope for advancements in this field.

### 1. Introduction

Onco-Immunology bridges oncology and immunology, fundamentally altering our understanding of the immune system’s role in cancer. This field explores the complex interactions between cancer cells and the body’s defenses, building on the foundational work of Thomas and Burnett in 1957, who suggested the immune system could target tumor cells [1].

In transplantation, the immune system’s tendency to reject foreign entities necessitated immunosuppression to prevent organ rejection. However, this approach increased patients’ susceptibility to infections and post-transplant malignancies [2]. Onco-Immunology offers a refined perspective, advocating for a balanced immune response that supports graft acceptance while monitoring for malignancies and infections [3].

Adopting Onco-Immunology in transplantation promotes precision medicine, tailoring interventions based on individual genetic and immunological profiles. This personalized care enhances graft acceptance and reduces complications [3]. Innovations like liquid biopsies, effective in cancer detection, could be adapted for early identification of graft issues or malignancies in transplant recipients, improving outcomes [4].

Integrating Onco-Immunology fosters collaboration among oncologists, immunologists, and transplant surgeons, enabling a holistic treatment approach. This reframing of the immune system as an ally, combined with personalized strategies, promises better patient outcomes, fewer complications, and enhanced graft longevity. As this article will elaborate, the holistic integration of Onco-Immunology has the potential not only to redefine transplantation practices but also to set a gold standard for patient care in the realm of organ transplantation.

### 2. The concept of precision medicine

Precision medicine involves personalizing healthcare, where medical choices, therapies, methodologies, or items are adjusted to suit each unique patient. Rather than adopting a universal approach, precision medicine acknowledges the differences in an individual’s genetic makeup, environmental surroundings, and lifestyle, allowing for more accurate prevention and treatment strategies for particular diseases (Fig. 1) [5].

Precision medicine marks a significant evolution in healthcare, moving away from the traditional “one-size-fits-all” approach to one that tailors prevention and treatment strategies to the individual’s unique genetic makeup and lifestyle factors [5]. This

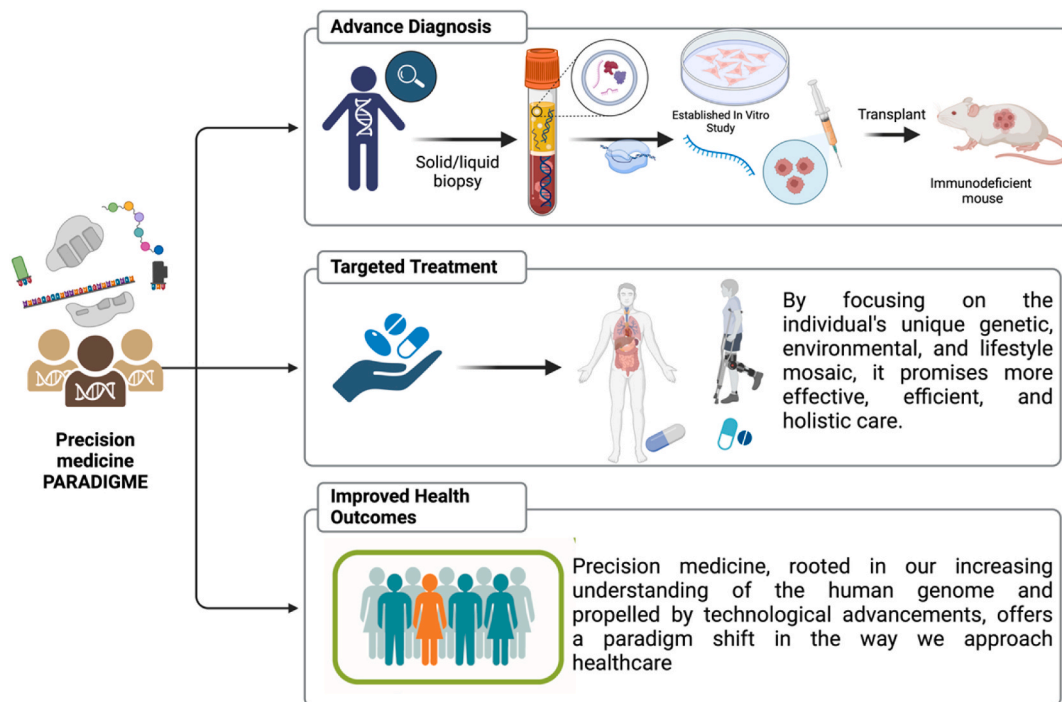


Fig. 1. The concept of precision medicine.

personalized approach has its roots in historical practices where treatments were based on individual symptoms and responses. The advent of genomic medicine, fueled by the completion of the Human Genome Project, has significantly advanced our ability to offer personalized care, highlighting the role of genetics in disease and treatment [6,7]. Fig. 1 illustrates this shift towards a more nuanced understanding of patient care.

The scope of precision medicine extends beyond genomics to include proteomics, metabolomics, and an understanding of environmental and lifestyle factors, offering a comprehensive view of patient health [8,9]. Its application in oncology has been particularly impactful, allowing for targeted treatments based on the genetic profile of tumors, which improves patient outcomes and minimizes side effects [10,11]. Precision medicine's potential is also being explored in treating cardiovascular diseases and in kidney transplantation, showcasing its wide-ranging implications for various medical fields [12].

The integration of big data analytics, including Electronic Health Records (EHRs) and machine learning, plays a crucial role in the development of precision medicine [13,14]. These technologies enable the analysis of vast datasets to identify patterns and correlations that can lead to more informed decision-making and earlier disease detection. However, the reliance on such detailed personal information introduces ethical concerns related to privacy, data access, and the potential for misuse, underscoring the need for careful consideration of these issues as precision medicine continues to evolve [15].

As precision medicine progresses, it promises to revolutionize healthcare by offering more effective, efficient, and personalized treatment options [15]. This shift requires ongoing collaboration among clinicians, researchers, technologists, and ethicists to ensure that its implementation maximizes benefits while addressing ethical and logistical challenges. By focusing on the unique characteristics of each patient, precision medicine aims to not only improve outcomes but also to usher in a new era of holistic and patient-centric care. Fig. 1 encapsulates this transformative approach, symbolizing the future of individualized healthcare strategies.

### 3. Onco-immunology and kidney transplantation in the precision medicine approach

The integration of onco-immunology within the precision medicine approach to kidney transplantation represents a critical advancement in addressing the dual challenges of graft survival and post-transplant malignancies [16]. This interdisciplinary field, focusing on the interactions between cancer cells and the immune system, is particularly relevant for transplant recipients, who face a heightened risk of developing cancers due to the immunosuppressive therapy necessary to prevent organ rejection [17].

Kidney transplantation, a life-saving intervention for individuals with end-stage renal disease, introduces complex post-operative challenges, notably the increased risk of cancer. Onco-immunology provides essential insights into how the immune system, suppressed by necessary medication, interacts with cancer cells. This interaction is crucial since the immunosuppressive drugs, while essential for the graft's survival, compromise the body's cancer surveillance capabilities [18]. Understanding the evasion strategies of cancer cells within this unique immune-modulated environment enables the development of targeted surveillance and treatment strategies for transplant recipients, addressing the heightened incidence of cancers such as skin cancers, lymphomas, and Kaposi's sarcoma [19].

One key aspect of precision medicine in kidney transplantation is genetic risk stratification. Genetic modifiers play a significant role in the immune response and can impact transplant outcomes. While human leukocyte antigen (HLA) matching is crucial in transplantation, other genetic variations beyond HLA genes can also influence graft survival [20,21]. For example, variants in genes like Apolipoprotein L1 (ApoL1), MHC class I-related chain A (MICA), ATP binding cassette subfamily B member 1 (ABC1), caveolin-1 (CAV1), and Ficolin-2 have been linked to graft failure and other complications [22]. By considering these genetic variants, along with HLA matching, a more comprehensive genetic risk assessment can be achieved, allowing for personalized treatment strategies [23]. The approach of precision medicine in this context emphasizes the significance of genetic risk stratification and the identification of individual genetic factors influencing the immune response and transplant outcomes. Beyond traditional HLA matching, the exploration of additional genetic markers could enhance graft longevity and optimize patient management by allowing for tailored immunosuppressive therapies [21–23]. Moreover, the potential application of immunotherapies in this setting illustrates the complex balance between treating malignancies and maintaining transplant tolerance, highlighting the need for strategies that mitigate rejection risks while targeting cancer cells [24].

Incorporating onco-immunology principles into the routine care of kidney transplant recipients, through the use of biomarkers for early detection of malignancies and the application of precision medicine techniques, offers a promising path forward. This approach not only aims to improve graft survival but also to reduce the burden of post-transplant cancers, ensuring a better quality of life for recipients [25]. The confluence of onco-immunology and kidney transplantation under the umbrella of precision medicine brings into focus the importance of personalized care strategies, aligning with the overarching goal of enhancing patient outcomes while navigating the complexities of immune system manipulation.

### 4. Understanding the role of onco-immunology in transplantation

Transplantation, the process of transferring organs or tissues from one individual to another, has emerged as a beacon of hope for countless patients suffering from organ failure. However, the relationship between transplantation, the immune system, and cancer is intricate and multi-dimensional. Transplant recipients, due to immunosuppressive therapy, are at a heightened risk of developing various cancers. Thus, understanding how tumor cells evade the host immune system and potentially induce tolerance is pivotal. This knowledge can be applied to mitigate cancer risks after transplantation [26]. Onco-immunology, a thriving sub-discipline, seeks to elucidate this nexus, laying the foundation for improved transplantation outcomes.

After transplantation, a patient's immune system naturally identifies the transplanted organ as "foreign." To prevent organ

rejection, patients are placed on a regimen of immunosuppressive medications, which reduce the immune system's activity. While this is vital for transplant survival, it also inadvertently suppresses the immune system's natural tumor surveillance mechanisms, elevating the risk of malignancies [18]. A salient feature of many tumors is their ability to evade detection and destruction by the immune system. This can be achieved through various mechanisms, such as expressing immune-inhibitory molecules or inducing an immune-tolerant microenvironment (Fig. 2). In the context of transplantation, the immune system is already suppressed, providing an even more conducive environment for cancers to thrive.

Apart from direct suppression of tumor surveillance, immunosuppressive medications can also increase the susceptibility to certain viral infections. Many of these viruses, like the Epstein-Barr virus and Human Herpesvirus 8, have oncogenic potential. The interplay between viral infections and malignancy in the setting of transplantation is a vivid demonstration of onco-immunology in action [27]. A less common but highly intriguing aspect of onco-immunology in transplantation is the phenomenon of donor-derived malignancies. In these cases, the transplanted organ harbors malignant or pre-malignant cells, which then proliferate in the recipient's immunosuppressed environment. Understanding the immunological dynamics in these situations offers unique insights into tumor biology [28].

Onco-immunological studies have highlighted potential strategies to reduce post-transplant cancer risks [29]. One approach involves modulating the immunosuppressive regimen, either by reducing doses or shifting to agents with a lower malignancy risk [30]. Another avenue is the prophylactic use of antiviral agents in patients who are at heightened risk of viral-associated tumors [31]. When a transplant recipient does develop cancer, therapeutic decisions become complex. Standard oncological treatments might compromise the transplanted organ. Here, onco-immunology presents novel solutions. Immune checkpoint inhibitors, for instance, have revolutionized cancer care by reactivating the immune response against tumors. However, their use in transplant patients needs careful balancing, as reactivating the immune system might jeopardize the graft [32].

The realm of onco-immunology in transplantation is a testament to the intricate dance between the immune system, malignancies, and transplantation medicine. With every discovery in this field, we move a step closer to ensuring that transplant recipients not only enjoy a renewed lease on life due to their new organ but also remain free from the shadow of malignancies.

## 5. Precision medicine approach in kidney transplantation

With advancements in genomics and personalized medicine, it's now feasible to predict which patients may have heightened risks for post-transplant malignancies. By tailoring immunosuppression and monitoring strategies based on individual genetic markers, better transplantation outcomes might be achieved [33]. In the contemporary era of medical advancements, precision medicine has emerged as a transformative approach, shifting the paradigm from a one-size-fits-all treatment strategy to individualized care (Fig. 3). In the realm of kidney transplantation, integrating precision medicine promises improved outcomes, reduced complications, and

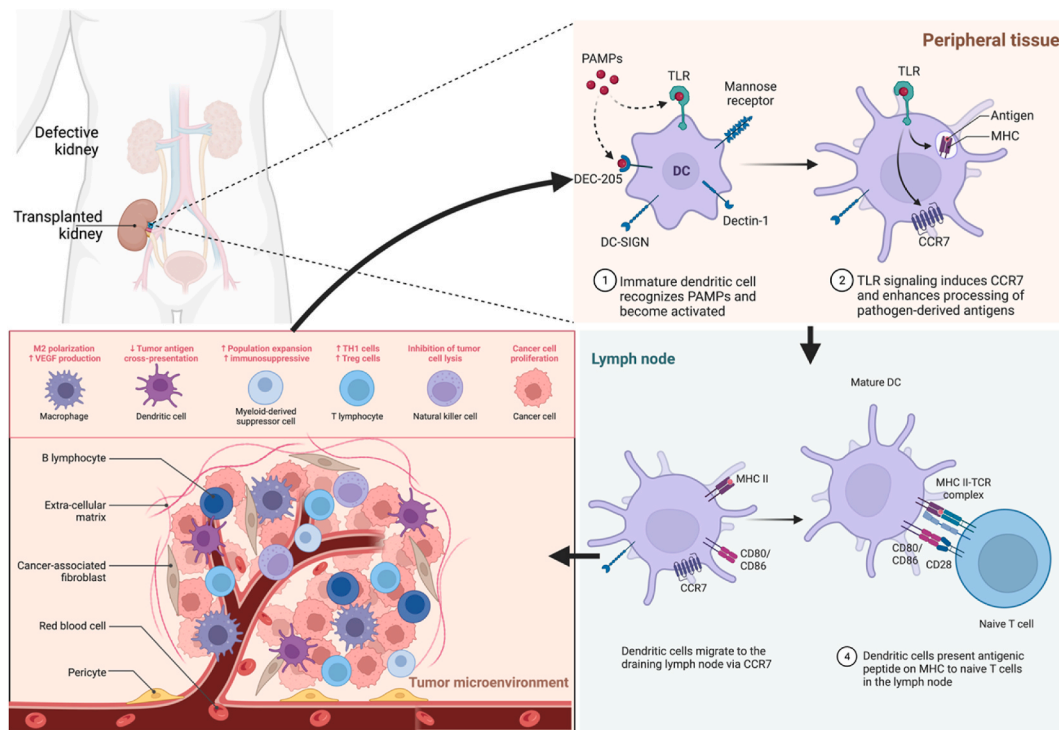


Fig. 2. The prompting of onco-immunology.

tailored patient care (Fig. 3).

At its core, precision medicine endeavors to tailor medical treatment to the individual characteristics of each patient. This includes genetic makeup, environmental factors, and lifestyle. By understanding these unique parameters, interventions can be optimized to offer the most effective, least harmful solutions for each individual [5]. One of the keystones of precision medicine is genomics. In kidney transplantation, donor and recipient genomic compatibility is paramount. Modern tools allow for detailed genomic analysis, ensuring a closer match between donor and recipient (Fig. 3). This translates to reduced chances of graft rejection and improved organ survival [34].

Immunosuppressive drugs are essential post-transplantation. However, their efficacy and side-effect profiles can vary widely among patients. Pharmacogenomics, the study of how genes affect drug response, can guide clinicians in selecting the optimal drug regimen for each patient, minimizing side effects like nephrotoxicity or the heightened risk of malignancies [35]. Beyond genomics, transcriptomics, which deals with RNA sequences in the body, offers insights into the real-time functional status of the transplanted kidney. Variations in RNA sequences can indicate early signs of graft rejection or other complications, allowing for preemptive interventions and reducing potential damage [36].

Precision medicine also reshapes post-transplant surveillance. Traditional follow-ups have largely been uniform. But with individualized data, clinicians can adjust the frequency and nature of follow-ups, tests, and interventions based on each patient's unique risk profile. For instance, a patient with a genomic predisposition for post-transplant lymphoproliferative disorder might undergo more frequent screenings [37]. Understanding a patient's unique genetic, environmental, and lifestyle factors can facilitate personalized risk assessments. This, in turn, can be instrumental in patient education, empowering them to make informed decisions about their health. A patient at higher genetic risk of post-transplant diabetes, for example, can be given targeted nutritional and lifestyle advice [38].

While precision medicine holds great promise, it also brings forth ethical and socio-economic challenges. Ensuring equitable access to genomic testing and personalized care, protecting patient genetic data, and managing potential discrimination based on genetic predispositions are pivotal considerations as we move forward [39].

## 6. The future of kidney transplantation: onco-immunology

There's growing interest in using onco-immunology principles to prevent and treat malignancies in kidney transplant recipients. Approaches such as cancer vaccines or immunotherapies might be integrated into the post-transplant care regimen to boost the immune system against potential malignancies [40].

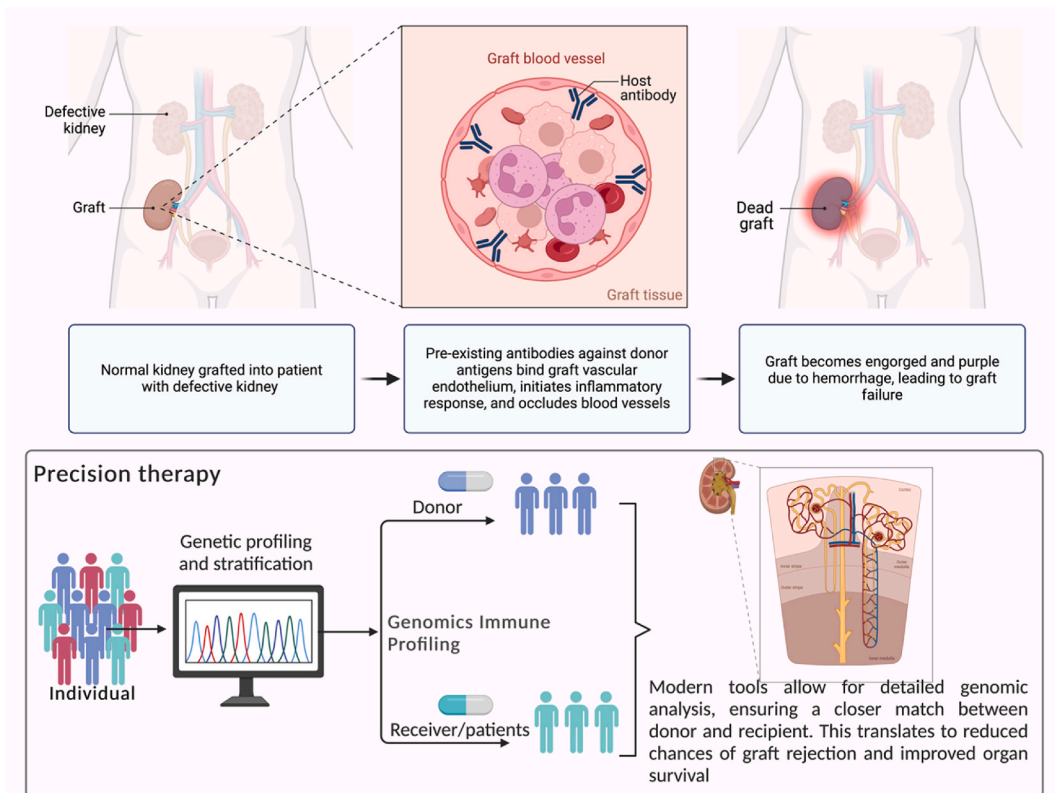


Fig. 3. Precision medicine in kidney transplantation.

The continuous evolution of medical science is an intricate ballet of discovery, application, and refinement. The merging of oncology and immunology into the specialized field of onco-immunology has heralded an era of profound implications for the realm of kidney transplantation. As we gaze into the future, we find that the path forward for kidney transplantation is significantly shaped by the discoveries and innovations from onco-immunology. One of the most distressing challenges in kidney transplantation is the elevated risk of malignancies post-transplant, primarily due to the necessary immunosuppressive regimen that patients undergo. The suppressed immune system not only reduces graft rejection but also diminishes the body's innate defenses against malignancies [18]. Recognizing and mitigating this risk is crucial in optimizing long-term transplant outcomes.

A notable innovation in cancer therapy has been the development of immune checkpoint inhibitors. These drugs target specific proteins that cancer cells use to evade the immune system, like PD-1 and CTLA-4 [12,41]. Their potential application in transplant recipients can be two-fold: enhancing the body's ability to tackle malignancies without escalating graft rejection risk, and potentially modulating the immune response to the graft itself. The future might see the development of vaccines tailored to prevent malignancies in transplant recipients. Onco-immunology has already made headway in therapeutic cancer vaccines. Given the distinct risk profile of transplant recipients, specialized vaccines can be a game-changer in preventing malignancies like post-transplant lymphoproliferative disorder [42].

Beyond generic immunosuppressive regimens, the future will likely embrace personalized immunosuppression. Leveraging insights from onco-immunology, clinicians could tailor regimens to individuals based on their unique genetic, immunologic, and oncologic risk profiles, thereby reducing malignancy risks and optimizing graft survival [43]. Onco-immunology's advancements in the early detection of malignancies, particularly through liquid biopsies that identify circulating tumor DNA, offer immense potential for transplant recipients. Regular monitoring using these minimally invasive techniques can ensure early intervention, better prognosis, and improved survival [44].

As we gain a deeper understanding of the molecular underpinnings of tumors, targeted therapies are coming to the fore. Drugs targeting specific pathways or molecules pivotal for tumor growth and survival, without broadly suppressing the immune system, can provide therapeutic benefits to transplant recipients who develop malignancies [45]. The integration of bioinformatics with onco-immunology holds promise. Advanced algorithms can process vast datasets, from genomic information to clinical outcomes, predicting which transplant recipients are at heightened risk for malignancies and tailoring both preventive and therapeutic interventions accordingly which has already been performed in the field of skin cancer [46].

The future of kidney transplantation, viewed through the lens of onco-immunology, appears vibrant with possibility. While challenges persist, the confluence of these disciplines promises a future where transplant recipients can hope for not just functional grafts but also a life unencumbered by the specter of malignancies.

## 7. Advancements in kidney transplantation through precision medicine

Recent innovations, like organ-specific genomic profiling and immune checkpoint inhibitors, have shown promise in managing transplantation challenges. By harnessing the power of precision medicine, clinicians can optimize organ matching, predict potential complications, and personalize post-transplant care [47].

Onco-immunology, a field that focuses on the interplay between the immune system and cancer, has provided valuable insights into transplant rejection and potential targets for drug development. Metastatic renal cell carcinoma (mRCC), a type of kidney cancer, shares similarities with transplant rejection on both clinical and molecular levels. The treatment approach for mRCC has evolved, with targeted therapies and angiogenic inhibitors playing a significant role in precision medicine. These therapies target pathways involved in tumorigenesis and disease progression. However, some patients with clear-cell renal cell carcinoma (ccRCC), the most common histologic subtype, remain resistant to these treatments, highlighting the need for novel approaches. Precision medicine, with its individualized approach towards treatment and prevention, has transformed various medical disciplines. In the domain of kidney transplantation, precision medicine has the potential to reshape practices, leading to more personalized therapeutic strategies and improved outcomes. In recent years, there's been an exponential growth in understanding the human genome, largely driven by advancements in high-throughput sequencing technologies [47,48]. For kidney transplantation, genomic data has paved the way to assess donor-recipient compatibility at a molecular level beyond traditional HLA-matching [49,50]. This can predict potential alloreactivity, guide immunosuppressive regimens, and even estimate graft longevity.

One of the major challenges in transplantation is tailoring the right immunosuppressive therapy for individual patients. Too little can result in graft rejection, while excessive immunosuppression exposes patients to infections and malignancies. With precision medicine, algorithms using genetic, molecular, and clinical data can tailor regimens to individual needs [51]. The search for non-invasive biomarkers for graft health is a priority. Precision medicine has introduced tools like transcriptomics and proteomics, which analyze patterns of genes or proteins in blood or urine samples. These can identify early signs of graft dysfunction or rejection, enabling timely intervention [52].

The field of regenerative medicine is fast-evolving, with the possibility of 3D printing functional organs using a recipient's own cells. Precision medicine guides the biofabrication process, ensuring compatibility at the cellular and molecular level [53]. Emerging research shows that the gut microbiome can influence transplant outcomes, including rejection episodes and drug metabolism. Precision medicine allows for a detailed analysis of this microbiome, leading to potential therapeutic interventions like tailored probiotics or diet modifications to optimize graft outcomes [54]. The rise of wearable tech and telehealth solutions, backed by precision medicine algorithms, allows clinicians to remotely monitor transplant recipients. This includes tracking vital signs, medication adherence, and potential signs of complications, ensuring rapid responses to any deviations [55]. Artificial Intelligence-driven platforms, trained on vast datasets, can predict patient outcomes, optimize donor-recipient matching, and even guide post-transplant care. As these systems

become more sophisticated, they'll likely become an integral part of the transplant decision-making process [56].

The synergy of kidney transplantation and precision medicine has ushered in a period of rapid evolution in transplant care. As we continue to gather more data and refine our tools, the promise of truly personalized transplantation becomes increasingly tangible. This not only means better survival rates but also improved quality of life for recipients.

## 8. Impact of onco-immunology on patient outcomes in kidney transplantation

The integration of onco-immunology into the field of transplantation is a noteworthy advancement, demonstrating the intertwined nature of cancer and the immune system. Onco-immunology delves deep into the intricate relationship between these two entities, and its implications go far beyond the traditional realms of oncology. Particularly in the context of kidney transplantation, this convergence of disciplines has given rise to a more comprehensive understanding, presenting both novel possibilities and potential pitfalls.

Kidney transplant recipients face a daunting challenge in the form of increased susceptibility to malignancies. This risk is largely attributed to the immunosuppressive regimens that are indispensable for preventing graft rejection. Through the lens of onco-immunology, there is an enriched perspective on the multifaceted interplay between tumors and the surrounding immune environment, which has been articulated by Engels (2008). Such insights lay the foundation for devising strategies that strike a balance between countering malignancies and promoting graft survival [57]. The nuanced understanding from onco-immunology has reshaped the paradigm of immunosuppression in transplant patients. It illuminates the path to more judicious modulation of immune responses, guiding the selection, dosage, and combinations of agents, aiming to diminish the risk of cancer without compromising graft integrity, as suggested by Kasiske (2004) [58].

Immune checkpoint inhibitors, though transformative in cancer therapeutics, present a complex scenario for transplant patients. These agents can be wielded as potent tools against malignancies in these individuals. However, they also carry the potential risk of precipitating graft rejection, a conundrum highlighted by De Bruyn (2019). This delicate balance remains an area of active investigation [59]. In the quest for early cancer detection in transplant patients, onco-immunology stands as a pioneer. Advanced modalities such as liquid biopsies, which identify circulating tumor DNA, are potent heralds for the early identification of malignancies. Such innovations, as pinpointed by Cohen (2017), allow for prompt medical intervention, thereby augmenting the chances of positive clinical outcomes [60].

Furthermore, onco-immunology has shed light on virus-induced malignancies post-transplantation. For instance, the post-transplant lymphoproliferative disorder, often a consequence of viral infections in the backdrop of a compromised immune system, can now be addressed more effectively. Strategies informed by onco-immunology aim to counter these virally-mediated cancers without amplifying the degree of immunosuppression, as elucidated by Opelz (2004) [61]. The realm of onco-immunology also emphasizes the significance of enhancing the quality of life for transplant recipients. By diminishing the cancer-associated morbidity, it enables patients to embrace a healthier, more rewarding existence following their transplant, a sentiment echoed by Sharma (2016) [62].

An era of personalized therapeutic interventions is unfolding, championed by onco-immunology. Integrative approaches that harness genomic and molecular data from both donor and recipient allow for tailored therapeutic strategies. The spectrum of these interventions can span from the discerning choice of immunosuppressants to crafting targeted regimens for diagnosed malignancies, a notion underscored by Jones (2016) [63].

In summation, the confluence of onco-immunology and transplantation science is sculpting a transformative trajectory for kidney transplantation outcomes. Notwithstanding the challenges on the horizon, this synergistic approach is progressively reshaping the landscape of transplantation, paving the way for a more integrated and holistic patient care regimen.

## 9. Challenges and opportunities in applying onco-immunology to kidney transplantation

While promising, implementing onco-immunological principles in transplantation is not without challenges. Balancing immunity against cancer and transplant rejection, understanding the long-term effects of new therapies, and managing costs are areas that require attention (Table 1). Nevertheless, the opportunities for improved patient outcomes are vast [64].

The interplay of onco-immunology and kidney transplantation has shown promising avenues for improving transplant outcomes, primarily by addressing post-transplant malignancies. While the union of these disciplines offers great potential, it also presents challenges that need strategic addressal for its complete realization. The crossroad of onco-immunology and kidney transplantation

**Table 1**  
Challenges and opportunities.

Challenges	Opportunities
1. Balancing immunosuppression to combat malignancies and ensure graft survival.	1. Personalized immune monitoring to tailor treatments to individual needs.
2. Scarcity of clinical data on novel therapies, complicating treatment decisions.	2. Targeted therapies that address specific genetic variations, enhancing treatment efficacy.
3. Genetic variations influencing individual responses to treatments, posing a barrier to standardized care.	3. Minimized immunosuppression, reducing the risk of post-transplant malignancies and other side effects.
4. Economic and therapeutic concerns in managing post-transplant malignancies, including the narrow therapeutic window and cost-effectiveness.	4. Improved quality of life for patients through more effective and less burdens

presents a unique paradigm where the principles of immunology are both an ally and an adversary. The dichotomy of immunosuppression is particularly challenging, as pointed out by Cole (2008). While onco-immunology seeks to empower the immune system to detect and eradicate cancer cells, kidney transplantation hinges on the necessity to suppress immune responses to prevent organ rejection. This precarious balancing act is fundamental in ensuring that the immune system is precisely modulated to thwart malignancies without compromising the graft [65].

Clinical data regarding the intersection of onco-immunology interventions and kidney transplant recipients is scarce and this gap, as Ito (2015) emphasizes, underscores the need for a deeper understanding of how novel therapies like checkpoint inhibitors interact with the complex immunological landscape of these patients. The long-term effects of such treatments are still being unraveled, with a careful eye on how they could influence the overall trajectory of both the recipient's well-being and the graft's integrity [66].

In the era of precision medicine, genetic considerations become ever more prominent. As Rebbeck (2018) notes, genetic variability among individuals can dramatically influence tumor behavior and immune responses. Each kidney transplant recipient carries a unique genetic signature that necessitates personalized therapeutic strategies, thus adding a layer of complexity to treatment planning [67]. Economic implications, as Verma (2012) has observed, are unavoidable when discussing advanced diagnostic and therapeutic approaches inherent to precision medicine and onco-immunology. The financial burden of these sophisticated modalities is non-trivial, casting a shadow on the accessibility and sustainability of such interventions within the healthcare system [68]. Moreover, Chapman (2013) draws attention to the narrow therapeutic window that exists for post-transplant malignancies. The stage at which these cancers present varies, and the opportunity for effective intervention is often fleeting. The challenge lies in ensuring timely diagnosis and treatment without jeopardizing graft health [69].

On the flip side, the field is rife with opportunities. Personalized immune monitoring is a beacon of hope, allowing for the early detection of malignancies. Llinas-Mallol (2022) and Malheiro (2018) have both underscored the potential benefits of such surveillance, which can significantly improve patient outcomes by catching cancers in their nascent stages [70,71]. Targeted therapies are another area of opportunity. Understanding the molecular underpinnings of post-transplant malignancies opens the door to treatments that are more precise, as Hart (2016) suggests, reducing side effects and improving efficacy [72]. Minimizing immunosuppression is a tangible goal, as Bunnapradist (2007) has argued, with the aim of reducing the incidence of post-transplant malignancies and other complications. By refining the understanding of the immune responses to both grafts and tumors, immunosuppression can be tailored more accurately, enhancing patient safety [73]. An improved quality of life is the ultimate pursuit, and Overington (2006) has highlighted that the application of onco-immunology principles could yield a healthier post-transplant existence for patients by mitigating malignancy-related complications [74]. Lastly, the merging of onco-immunology and transplantation heralds an era of collaborative research, which, as evidenced by the comprehensive work by The British Society for Immunology (2017), has the power to drive forward interdisciplinary advancements, unveil novel therapies, and redefine best practices in transplant care, reinforcing the critical role of the immune system in both the success and challenges of organ transplantation [75].

Through this lens, the journey of integrating onco-immunology with kidney transplantation is one of navigating a labyrinth, poised delicately between innovation and caution, a venture fraught with hurdles but illuminated by the potential for transformative patient-centric breakthroughs.

## 10. Closing thoughts: the way forward in kidney transplantation precision medicine approach using onco-immunology

As we move forward, the integration of onco-immunology within the framework of precision medicine stands as a pivotal shift in enhancing patient management in kidney transplantation. This novel approach promises to significantly improve graft longevity and reduce the risk of cancer in transplant recipients, signaling a promising future for patient care [76]. The path to this future is reliant on the concerted efforts of a multidisciplinary team of researchers and clinicians, committed to pioneering breakthroughs in this complex field.

The intersection of onco-immunology and kidney transplantation represents a critical juncture in medical practice. By exploring the intricate relationship between the immune system and cancer within the transplant setting, we unlock new possibilities for advanced treatment protocols that could dramatically improve patient outcomes. Central to this evolution is the application of onco-immunology principles, aiming to strengthen the immune response against cancer while preserving the function of the transplanted kidney [77].

The success of this endeavor is contingent upon fostering interdisciplinary collaborations, drawing together oncologists, immunologists, nephrologists, and transplant surgeons. Such synergistic partnerships are vital for sparking innovation that could lead to the development of novel treatments [78]. Education also plays a crucial role in this process, empowering patients, families, and healthcare professionals with the knowledge needed to navigate the changing landscape of kidney transplantation [79]. Leveraging emerging technologies in genomics and proteomics, alongside advancements in imaging techniques, will accelerate our progress towards personalized patient care, ensuring treatments are both precise and timely [80].

Ethical considerations remain at the forefront of integrating these new therapeutic approaches, with a focus on safeguarding patient interests and upholding the trust in medical research [81]. The research by Renzhi Hu et al. (2024), which explores the intersection of traditional medicine with onco-immunology in kidney transplantation, underscores the potential of integrating traditional remedies with modern scientific methods to modulate immune activity and mitigate transplant rejection [82]. Our collective goal is to achieve a paradigm where kidney transplantation is synonymous with holistic care, significantly reducing the incidence of post-transplant malignancies through precise and targeted interventions. This vision of a future where treatments are customized to each patient's unique profile is rapidly becoming a tangible reality, promising a transformative impact on kidney transplantation care.

In summary, merging onco-immunology with precision medicine in kidney transplantation is a journey fraught with challenges but rich in potential, setting the stage for an era where the fusion of these disciplines redefines the standards of care for transplant



recipients. This journey is not a solitary endeavor but a collaborative mission that invites all stakeholders to contribute towards a future of optimized, patient-centric care in kidney transplantation.

### Funding statement

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education (NRF-2020R111A2066868), the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (No. 2020R1A5A2019413), and a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2020-KH087790).

### Data availability statement

No data was used for the research described in the article.

### CRediT authorship contribution statement

**Athaya Febriantyo Purnomo:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Conceptualization. **Fahrul Nurkolis:** Writing – review & editing, Writing – original draft, Visualization, Software, Formal analysis, Conceptualization. **Rony Abdi Syahputra:** Writing – review & editing, Visualization, Software. **Seungjoon Moon:** Writing – review & editing, Formal analysis. **Dain Lee:** Writing – review & editing, Formal analysis. **Nurpudji Astuti Taslim:** Writing – review & editing, Validation, Supervision. **Moon Nyeo Park:** Writing – review & editing, Validation, Supervision. **Besut Daryanto:** Writing – review & editing, Validation, Supervision. **Kurnia Penta Seputra:** Writing – review & editing, Validation, Supervision. **Paksi Satyagraha:** Writing – review & editing, Validation, Supervision. **Nurul Cholifah Lutfiana:** Writing – review & editing, Validation, Supervision. **Pande Made Wisnu Tirtayasa:** Writing – review & editing, Supervision. **Bonglee Kim:** Writing – review & editing, Writing – original draft, Validation, Supervision, Funding acquisition, Formal analysis, Conceptualization.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

### References

- [1] R.D. Schreiber, L.J. Old, M.J. Smyth, Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion, *Science* 331 (6024) (2011 Mar 25) 1565–1570.
- [2] J.A. Fishman, *Infection in organ transplantation*, *Am. J. Transplant.* 17 (4) (2017 Apr 1) 856–879.
- [3] M.A. Postow, M.K. Callahan, J.D. Wolchok, Immune checkpoint blockade in cancer therapy, *J. Clin. Oncol.* 33 (17) (2015 Jun 6) 1974.
- [4] G. Siravegna, S. Marsoni, S. Siena, A. Bardelli, Integrating liquid biopsies into the management of cancer, *Nat. Rev. Clin. Oncol.* 14 (9) (2017 Sep) 531–548.
- [5] F.S. Collins, H. Varmus, A new initiative on precision medicine, *N. Engl. J. Med.* 372 (9) (2015 Feb 26) 793–795.
- [6] E.S. Lander, L.M. Linton, B. Birren, C. Nusbaum, M.C. Zody, J. Baldwin, K. Devon, K. Dewar, M. Doyle, W. FitzHugh, R. Funke, D. Gage, K. Harris, A. Heaford, J. Howland, L. Kann, J. Lehoczky, R. LeVine, P. McEwan, K. McKernan, International Human Genome Sequencing Consortium, Initial sequencing and analysis of the human genome, *Nature* 409 (6822) (2001) 860–921, <https://doi.org/10.1038/35057062>.
- [7] G.S. Lopes, Y. Sela, Human genome Project, ZEIGLER-HILL, Virgil. *Encyclopedia of Personality and Individual Differences* 1 (2017) 1–4.
- [8] L. Hood, M. Flores, A personal view on systems medicine and the emergence of proactive P4 medicine: predictive, preventive, personalized and participatory, *New biotechnology* 29 (6) (2012 Sep 15) 613–624.
- [9] T.A. Manolio, F.S. Collins, N.J. Cox, D.B. Goldstein, L.A. Hindorf, D.J. Hunter, M.I. McCarthy, E.M. Ramos, L.R. Cardon, A. Chakravarti, J.H. Cho, Finding the missing heritability of complex diseases, *Nature* 461 (7265) (2009 Oct 8) 747–753.
- [10] A. Drilon, T.W. Laetsch, S. Kummar, S.G. DuBois, U.N. Lassen, G.D. Demetri, M. Nathanson, R.C. Doebele, A.F. Farago, A.S. Pappo, B. Turpin, Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children, *N. Engl. J. Med.* 378 (8) (2018 Feb 22) 731–739.
- [11] L.A. Garraway, E.S. Lander, Lessons from the cancer genome, *Cell* 153 (1) (2013 Mar 28) 17–37.
- [12] B. Daryanto, A.F. Purnomo, Cytotoxic T-lymphocyte associated-protein-4+ 49A/G-allele (rs231775) single nucleotide polymorphisms are associated with acute allograft renal transplantation rejection: a multilevel modelling of meta-analysis, *F1000Research* 11 (2022 Aug 5) 904.
- [13] W. Raghupathi, V. Raghupathi, Big data analytics in healthcare: promise and potential, *Health Inf. Sci. Syst.* 2 (2014 Dec) 1, 0.
- [14] T.B. Murdoch, A.S. Detsky, The inevitable application of big data to health care, *JAMA* 309 (13) (2013 Apr 3) 1351–1352.
- [15] E. Juengst, M.L. McGowan, J.R. Fishman, Jr RA. Settersten, From “personalized” to “precision” medicine: the ethical and social implications of rhetorical reform in genomic medicine, *Hastings Cent. Rep.* 46 (5) (2016 Sep) 21–33.
- [16] I. Rama, J.M. Grinyó, Malignancy after renal transplantation: the role of immunosuppression, *Nat. Rev. Nephrol.* 6 (9) (2010 Sep) 511–519.
- [17] E. Au, G. Wong, J.R. Chapman, Cancer in kidney transplant recipients, *Nat. Rev. Nephrol.* 14 (8) (2018 Aug) 508–520.
- [18] E.A. Engels, R.M. Pfeiffer, J.F. Fraumeni, B.L. Kasiske, A.K. Israni, J.J. Snyder, R.A. Wolfe, N.P. Goodrich, A.R. Bayakly, C.A. Clarke, G. Copeland, Spectrum of cancer risk among US solid organ transplant recipients, *JAMA* 306 (17) (2011 Nov 2) 1891–1901.
- [19] A. Fujimoto, R. Suzuki, Epstein-Barr virus-associated post-transplant lymphoproliferative disorders after hematopoietic stem cell transplantation: pathogenesis, risk factors and clinical outcomes, *Cancers* 12 (2) (2020 Feb 1) 328.
- [20] S.Z. Josefowicz, L.F. Lu, A.Y. Rudensky, Regulatory T cells: mechanisms of differentiation and function, *Annu. Rev. Immunol.* 30 (2012 Apr 23) 531–564.
- [21] Y. Caliskan, B. Lee, A.M. Whelan, F. Abualrub, K.L. Lentine, A. Jittir, Evaluation of genetic kidney diseases in living donor kidney transplantation: towards precision genomic medicine in donor risk assessment, *Current transplantation reports* 9 (2) (2022 Jun) 127–142.
- [22] A. Palanisamy, A.M. Reeves-Daniel, B.I. Freedman, The impact of APOL1, CAV1, and ABCB1 gene variants on outcomes in kidney transplantation: donor and recipient effects, *Pediatr. Nephrol.* 29 (9) (2014 Sep) 1485–1492.

- [23] P. Jethwani, A. Rao, L. Bow, M.C. Menon, Donor–recipient non-HLA variants, Mismatches and renal allograft outcomes: evolving paradigms, *Front. Immunol.* 13 (2022 Apr 1) 822353.
- [24] P. Sharma, J.P. Allison, The future of immune checkpoint therapy, *Science* 348 (6230) (2015 Apr 3) 56–61.
- [25] R. Trappe, S. Oertel, V. Leblond, P. Mollee, M. Sender, P. Reinke, R. Neuhaus, H. Lehmkuhl, H.A. Horst, G. Salles, F. Morschhauser, Sequential treatment with rituximab followed by CHOP chemotherapy in adult B-cell post-transplant lymphoproliferative disorder (PTLD): the prospective international multicentre phase 2 PTLD-1 trial, *Lancet Oncol.* 13 (2) (2012 Feb 1) 196–206.
- [26] P. Pontrelli, F. Rascio, G. Castellano, G. Grandaliano, L. Gesualdo, G. Stallone, The role of natural killer cells in the immune response in kidney transplantation, *Front. Immunol.* 11 (2020 Jul 23) 1454.
- [27] V.R. Dharmidharka, A.H. Tejani, P.L. Ho, W.E. Harmon, Post-transplant lymphoproliferative disorder in the United States: young Caucasian males are at highest risk, *Am. J. Transplant.* 2 (10) (2002 Nov 1) 993–998.
- [28] G.H. Greenhall, M. Ibrahim, U. Dutta, C. Doree, S.J. Brunskill, R.J. Johnson, L.A. Tomlinson, C.J. Callaghan, C.J. Watson, Donor-transmitted cancer in orthotopic solid organ transplant recipients: a systematic review, *Transpl. Int.* 35 (2022) 10092.
- [29] S. Gourishankar, J.C. McDermid, G.S. Jhangri, J.K. Preiksaitis, Herpes zoster infection following solid organ transplantation: incidence, risk factors and outcomes in the current immunosuppressive era, *Am. J. Transplant.* 4 (1) (2004 Jan 1) 108–115.
- [30] A. Sharif, J. Peracha, D. Winter, R. Reulen, M. Hawkins, Exploring the epidemiology of cancer after solid organ transplantation (EpCOT): an observational cohort study, *BMJ Open* 11 (4) (2021 Apr 1) e043731.
- [31] Z. Huo, C. Li, X. Xu, F. Ge, R. Wang, Y. Wen, H. Peng, X. Wu, H. Liang, G. Peng, R. Li, Cancer risks in solid organ transplant recipients: results from a comprehensive analysis of 72 cohort studies, *Oncoimmunology* 9 (1) (2020 Jan 1) 1848068.
- [32] F. Martins, L. Sofiyya, G.P. Sykiotis, F. Lamine, M. Maillard, M. Fraga, K. Shabafrouz, C. Ribí, A. Cairolí, Y. Guex-Crosier, T. Kuntzer, Adverse effects of immune-checkpoint inhibitors: epidemiology, management and surveillance, *Nat. Rev. Clin. Oncol.* 16 (9) (2019 Sep) 563–580.
- [33] T.M. Snyder, K.K. Khush, H.A. Valantine, S.R. Quake, Universal noninvasive detection of solid organ transplant rejection, *Proc. Natl. Acad. Sci. USA* 108 (15) (2011 Apr 12) 6229–6234.
- [34] P.J. Phelan, P.J. Conlon, M.A. Sparks, Genetic determinants of renal transplant outcome: where do we stand? *J. Nephrol.* 27 (2014 Jun) 247–256.
- [35] K.A. Birdwell, B. Decker, J.M. Barbarino, J.F. Peterson, C.M. Stein, W. Sadee, D. Wang, A.A. Vinks, Y. He, J.J. Swen, J.S. Leeder, Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP3A5 genotype and tacrolimus dosing, *Clin. Pharmacol. Therapeut.* 98 (1) (2015 Jul) 19–24.
- [36] D.G. Maluf, V.R. Mas, K.J. Archer, K. Yanek, E.M. Gibney, A.L. King, A. Cotterell, R.A. Fisher, M.P. Posner, Molecular pathways involved in loss of kidney graft function with tubular atrophy and interstitial fibrosis, *Mol. Med.* 14 (2008 May) 276–285.
- [37] M. Naesens, D.R. Kuypers, M. Sarwal, Calcineurin inhibitor nephrotoxicity, *Clin. J. Am. Soc. Nephrol.* 4 (2) (2009 Feb 1) 481–508.
- [38] E. Porrini, J.M. Díaz, F. Moreso, R. Lauzurrica, M. Ibernón, I.S. Torres, R.B. Ruiz, A.E. Rodríguez, P.D. Mallén, B. Bayés-Genís, F.J. Gainza, Prediabetes is a risk factor for cardiovascular disease following renal transplantation, *Kidney Int.* 96 (6) (2019 Dec 1) 1374–1380.
- [39] B. Nordlinger, C. Villani, D. Rus (Eds.), *Healthcare and Artificial Intelligence*, Springer, 2020 Mar 17.
- [40] G. Dranoff, Cytokines in cancer pathogenesis and cancer therapy, *Nat. Rev. Cancer* 4 (1) (2004 Jan 1) 11–22.
- [41] S.L. Topalian, J.M. Taube, R.A. Anders, D.M. Pardoll, Mechanism-driven biomarkers to guide immune checkpoint blockade in cancer therapy, *Nat. Rev. Cancer* 16 (5) (2016 May) 275–287.
- [42] G. Roussey-Kesler, M. Giral, A. Moreau, J.F. Subra, C. Legendre, C. Noël, E. Pillebout, S. Brouard, J.P. Souillou, Clinical operational tolerance after kidney transplantation, *Am. J. Transplant.* 6 (4) (2006 Apr 1) 736–746.
- [43] K.A. Newell, A. Asare, A.D. Kirk, T.D. Gislser, K. Bourcier, M. Suthanthiran, W.J. Burlingham, W.H. Marks, I. Sanz, R.I. Lechler, M.P. Hernandez-Fuentes, Identification of a B cell signature associated with renal transplant tolerance in humans, *J. Clin. Invest.* 120 (6) (2010 Jun 1) 1836–1847.
- [44] J. Phallen, M. Sausen, V. Adleff, A. Leal, C. Hruban, J. White, V. Anagnostou, J. Fiksel, S. Cristiano, E. Papp, S. Speir, Direct detection of early-stage cancers using circulating tumor DNA, *Sci. Transl. Med.* 9 (403) (2017 Aug 16) ean2415.
- [45] M. Gerlinger, A.J. Rowan, S. Horswell, J. Larkin, D. Endesfelder, E. Gronroos, P. Martinez, N. Matthews, A. Stewart, P. Tarpey, I. Varela, Intratumor heterogeneity and branched evolution revealed by multiregion sequencing, *N. Engl. J. Med.* 366 (10) (2012 Mar 8) 883–892.
- [46] A. Esteve, B. Kuprel, R.A. Novoa, J. Ko, S.M. Swetter, H.M. Blau, S. Thrun, Dermatologist-level classification of skin cancer with deep neural networks, *Nature* 542 (7639) (2017 Feb) 115–118.
- [47] W.S. Oetting, C. Dorr, R.P. Rimmel, A.J. Matas, A.K. Israni, P.A. Jacobson, Concepts of genomics in kidney transplantation, *Current transplantation reports* 4 (2017 Jun) 116–123.
- [48] J.C. Venter, M.D. Adams, E.W. Myers, P.W. Li, R.J. Mural, G.G. Sutton, H.O. Smith, M. Yandell, C.A. Evans, R.A. Holt, J.D. Gocayne, The sequence of the human genome, *Science* 291 (5507) (2001 Feb 16) 1304–1351.
- [49] J.G. Lunz, *Immunology of kidney transplantation*, in: C. Ramirez, J. McCauley (Eds.), *Contemporary Kidney Transplantation*, Springer, 2017, pp. 1–10, [https://doi.org/10.1007/978-3-319-14779-6\\_17-1](https://doi.org/10.1007/978-3-319-14779-6_17-1).
- [50] P. Pontrelli, G. Grandaliano, C. Van Kooten, Kidney transplantation and innate immunity, *Front. Immunol.* 11 (2020 Oct 14) 603982.
- [51] W.S. Oetting, D.P. Schladt, W. Guan, M.B. Miller, R.P. Rimmel, C. Dorr, K. Sanghavi, R.B. Mannon, B. Herrera, A.J. Matas, D.R. Salomon, Genomewide association study of tacrolimus concentrations in African American kidney transplant recipients identifies multiple CYP3A5 alleles, *Am. J. Transplant.* 16 (2) (2016 Feb 1) 574–582.
- [52] T.K. Sigdel, M.M. Sarwal, The proteogenomic path towards biomarker discovery, *Pediatr. Transplant.* 12 (7) (2008 Nov) 737–747.
- [53] S.V. Murphy, A. Atala, 3D bioprinting of tissues and organs, *Nat. Biotechnol.* 32 (8) (2014 Aug) 773–785.
- [54] J.R. Lee, T. Muthukumar, D. Dadhania, N.C. Toussaint, L. Ling, E. Pamer, M. Suthanthiran, Gut microbial community structure and complications following kidney transplantation: a pilot study, *Transplantation* 98 (7) (2014 Oct 10) 697.
- [55] J.W. McGillicuddy, A.K. Weiland, R.M. Frenzel, M. Mueller, B.M. Brunner-Jackson, D.J. Taber, P.K. Baliga, F.A. Treiber, Patient attitudes toward mobile phone-based health monitoring: questionnaire study among kidney transplant recipients, *J. Med. Internet Res.* 15 (1) (2013 Jan 8) e2284.
- [56] S. Goto, M. Kimura, Y. Katsumata, S. Goto, T. Kamatani, G. Ichihara, S. Ko, J. Sasaki, K. Fukuda, M. Sano, Artificial intelligence to predict needs for urgent revascularization from 12-lead electrocardiography in emergency patients, *PLoS One* 14 (1) (2019 Jan 9) e0210103.
- [57] E.A. Engels, R.J. Biggar, H.I. Hall, H. Cross, A. Crutchfield, J.L. Finch, R. Grigg, T. Hylton, K.S. Pawlish, T.S. McNeel, J.J. Goedert, Cancer risk in people infected with human immunodeficiency virus in the United States, *Int. J. Cancer* 123 (1) (2008 Jul 1) 187–194.
- [58] B.L. Kasiske, J.J. Snyder, D.T. Gilbertson, C. Wang, Cancer after kidney transplantation in the United States, *Am. J. Transplant.* 4 (6) (2004 Jun 1) 905–913.
- [59] P. De Bruyn, D. Van Gestel, P. Ost, V. Kruse, L. Brochez, H. Van Vierbergh, A. Devresse, V. Del Marmol, A. Le Moine, S. Aspeslagh, Immune checkpoint blockade for organ transplant patients with advanced cancer: how far can we go? *Curr. Opin. Oncol.* 31 (2) (2019 Mar 1) 54–64.
- [60] J.D. Cohen, A.A. Javed, C. Thoburn, F. Wong, J. Tie, P. Gibbs, C.M. Schmidt, M.T. Yip-Schneider, P.J. Allen, M. Schattner, R.E. Brand, Combined circulating tumor DNA and protein biomarker-based liquid biopsy for the earlier detection of pancreatic cancers, *Proc. Natl. Acad. Sci. USA* 114 (38) (2017 Sep 19) 10202–10207.
- [61] G. Opelz, B. Döhler, Lymphomas after solid organ transplantation: a collaborative transplant study report, *Am. J. Transplant.* 4 (2) (2004 Feb 1) 222–230.
- [62] P. Sharma, M.K. Callahan, P. Bono, J. Kim, P. Spiliopoulou, E. Calvo, R.N. Pillai, P.A. Ott, F. de Braud, M. Morse, D.T. Le, Nivolumab monotherapy in recurrent metastatic urothelial carcinoma (CheckMate 032): a multicentre, open-label, two-stage, multi-arm, phase 1/2 trial, *Lancet Oncol.* 17 (11) (2016 Nov 1) 1590–1598.
- [63] P.A. Jones, J.P. Issa, S. Baylin, Targeting the cancer epigenome for therapy, *Nat. Rev. Genet.* 17 (10) (2016 Oct) 630–641.
- [64] J. Hou, H. Zhang, B. Sun, M. Karin, The immunobiology of hepatocellular carcinoma in humans and mice: Basic concepts and therapeutic implications, *J. Hepatol.* 72 (1) (2020 Jan 1) 167–182.
- [65] E.H. Cole, O. Johnston, C.L. Rose, J.S. Gill, Impact of acute rejection and new-onset diabetes on long-term transplant graft and patient survival, *Clin. J. Am. Soc. Nephrol.: CJASN* 3 (3) (2008 May) 814.

- [66] A. Ito, S. Kondo, K. Tada, S. Kitano, Clinical development of immune checkpoint inhibitors, *BioMed Res. Int.* (2015 Oct).
- [67] T.R. Rebbeck, K. Burns-White, A.T. Chan, K. Emmons, M. Freedman, D.J. Hunter, P. Kraft, F. Laden, L. Mucci, G. Parmigiani, D. Schrag, Precision prevention and early detection of cancer: fundamental principles, *Cancer Discov.* 8 (7) (2018 Jul 1) 803–811.
- [68] S. Verma, D. Miles, L. Gianni, I.E. Krop, M. Welslau, J. Baselga, M. Pegram, D.Y. Oh, V. Diéras, E. Guardino, L. Fang, Trastuzumab emtansine for HER2-positive advanced breast cancer, *N. Engl. J. Med.* 367 (19) (2012 Nov 8) 1783–1791.
- [69] J.R. Chapman, A.C. Webster, G. Wong, Cancer in the transplant recipient, *Cold Spring Harbor perspectives in medicine* 3 (7) (2013 Jul).
- [70] L. Llinàs-Mallol, D. Raich-Regué, J. Pascual, M. Crespo, Alloimmune risk assessment for antibody-mediated rejection in kidney transplantation: a practical proposal, *Transplant. Rev.* 20 (2022 Dec) 100745.
- [71] J. Malheiro, S. Tafulo, Clinical implications of anti-HLA antibodies testing in kidney transplantation, *Portuguese Journal of Nephrology and Hypertension* 32 (1) (2018) 42–251.
- [72] A. Hart, J.M. Smith, M.A. Skeans, S.K. Gustafson, D.E. Stewart, W.S. Cherikh, J.L. Wainright, G. Boyle, J.J. Snyder, B.L. Kasiske, A.K. Israni, OPTN/SRTR 2014 annual data report: kidney, *Am. J. Transplant.: official journal of the American Society of Transplantation and the American Society of Transplant Surgeons* 16 (Suppl 2) (2016 Jan) 11.
- [73] S. Bunnapradist, G.M. Danovitch, Evaluation of adult kidney transplant candidates, *Am. J. Kidney Dis.* 50 (5) (2007 Nov 1) 890–898.
- [74] J.P. Overington, B. Al-Lazikani, A.L. Hopkins, How many drug targets are there? *Nat. Rev. Drug Discov.* 5 (12) (2006 Dec 1) 993–996.
- [75] **The British Society for Immunology, Transplant immunology [online] Available at:** <https://www.immunology.org/policy-and-public-affairs/briefings-and-position-statements/transplant-immunology>, 2017. (Accessed 1 October 2023).
- [76] C.M. Vajdic, M.T. Van Leeuwen, Cancer incidence and risk factors after solid organ transplantation, *Int. J. Cancer* 125 (8) (2009 Oct 15) 1747–1754.
- [77] M.D. Stegall, R.S. Gaston, F.G. Cosio, A. Matas, Through a glass darkly: seeking clarity in preventing late kidney transplant failure, *J. Am. Soc. Nephrol.: JASN (J. Am. Soc. Nephrol.)* 26 (1) (2015 Jan) 20.
- [78] J. Sellarés, D.G. De Freitas, M. Mengel, J. Reeve, G. Einecke, B. Sis, L.G. Hidalgo, K. Famulski, A. Matas, P.F. Halloran, Understanding the causes of kidney transplant failure: the dominant role of antibody-mediated rejection and nonadherence, *Am. J. Transplant.* 12 (2) (2012 Feb 1) 388–399.
- [79] R.A. Wolfe, V.B. Ashby, E.L. Milford, A.O. Ojo, R.E. Ettenger, L.Y. Agodoa, P.J. Held, F.K. Port, Comparison of mortality in all patients on dialysis, patients on dialysis awaiting transplantation, and recipients of a first cadaveric transplant, *N. Engl. J. Med.* 341 (23) (1999 Dec 2) 1725–1730.
- [80] P. Cravedi, P.S. Heeger, Immunologic monitoring in transplantation revisited, *Curr. Opin. Organ Transplant.* 17 (1) (2012 Feb) 26.
- [81] A.R. Jonsen, The ethics of organ transplantation: a brief history, *AMA Journal of Ethics* 14 (3) (2012 Mar 1) 264–268.
- [82] R. Hu, M. Xia, S. Weng, Z. Chen, Z. Wang, X. Zou, Y. Zhang, Y. Chen, S. Tang, Network pharmacology and experimental validation to explore the molecular mechanisms of kidney and blood refreshing recipe for the treatment of intrauterine adhesions, *Advances in Traditional Medicine* 9 (2024 Feb) 1–3.