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Gene Therapy Advancements for Precision Cancer Treatment: Challenges and Opportunities in Sub-Saharan Africa – Nigeria Perspective

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Recent breakthroughs in gene therapy have ushered in a new era in precision cancer treatment, offering a transformative approach to combating malignancy and high mortality rates. The development of cutting-edge techniques in gene therapy for cancer treatment has led to a more precise strategy in cancer treatment by focusing on the genetic architecture of the cancer cells and enhancing the immune response to these malignant cells. This article looks at four (4) basic approaches: gene replacement techniques, gene editing techniques, RNA-based techniques and oncolytic viruses; these strategies have revolutionised oncology and cancer treatment, especially in

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the 21st century, with many of their principles stemming from the 20th century. For example, using the CRISPR-Cas9 technology has revolutionised disease treatment - cancer since its development by Emmanuelle Charpentier and Jennifer Doudnagene by improving genetic expression and correcting mutation editing. Aside from these techniques, there are many emerging gene therapy approaches for cancer treatment, with many in their final clinical trial stage. These emerging techniques involve the utilisation of neoantigens/cancer vaccines, epigenetic modulation and combination therapy with immune checkpoint inhibitors. Although this novel approach offers better prospects than conventional cancer treatment, they still face challenges, such as ethical issues, regulation and enhancement of vectors. Sub-Saharan Africa - Nigeria stands a chance to benefit from these novel strategies for cancer through commitment, building infrastructures and private-public partnerships. The roles played by biomedical scientists and researchers are pivotal to offering better prospects for precision medicine in cancer treatment.

Keywords: Gene therapy; cancer; oncolytic viruses; CAR-T; epigenetics.

1. INTRODUCTION

Cancer's escalating global impact demands innovative solutions, with gene therapy emerging as a beacon of promise; defined by uncontrolled cell growth, cancer, a genetic disorder, ranks as the second leading cause of mortality worldwide [1]. In sub-Saharan Africa, notably Nigeria, the burden is pronounced, accentuated by late-stage diagnoses and limited access to therapy [2]. Gene therapy, a transformative medical intervention, addresses the genetic roots of diseases by introducing, altering, or replacing genetic material within cells [3]. The late 20th century witnessed monumental progress, marked by the first human nuclear gene transfer in 1989 and subsequent regulatory clearances for gene therapy medications like Gendicine and Luxturna [4,5].

Inter-disciplinary approaches when it comes to cancer care have improved, this is seen in the aspect of translational medicine while innovative ideas between researchers and clinicians are shared to help serve the general population. In cancer care, gene therapy offers a multifaceted approach, targeting tumour suppressor genes, activating suicide genes, inhibiting angiogenesis, silencing oncogenes, and editing cancer cell genomes [6]. This holds significant promise for sub-Saharan Africa, where conventional therapies face limitations. By protecting healthy cells from traditional treatment side effects, gene therapy presents a potential avenue for improving survival rates and the quality of life for cancer patients in resource-constrained settings [6]. In navigating this landscape, collaborative efforts, informed initiatives, and a conducive environment are essential to harness gene therapy's transformative potential in the fight against cancer, particularly in regions facing unique challenges like sub-Saharan Africa [7].

2. SIGNIFICANCE OF GENE THERAPY IN CANCER TREATMENT

In the oncology landscape, gene therapy stands as a transformative frontier, offering innovative strategies to confront the intricacies of cancer. The benefits and significance of gene therapy in cancer treatment and management centres on its precision targeting of cancer cells, allowing therapies to selectively impact malignant cells while sparing healthy tissue and minimising collateral damage [7]. Tumours often develop resistance to conventional therapies, but gene therapy like CAR-T cell therapy can rewire the immune system to target cancer cells, circumventing resistance mechanisms [8]. Gene therapy approaches, like Luxturna, correct faulty cancer genes with specific genetic mutations, such as RPE65 gene-related retinal diseases [9]. Immunotherapies and genetic therapies, especially immune checkpoint inhibitors, work together to enhance the immune system's ability to recognise and attack cancer cells, thereby improving clinical outcomes [10].

Personalised cancer treatment using cancer vaccines, developed through gene therapy, targets specific neoantigens in tumour cells, enhancing treatment based on an individual's unique genetic profile and improving outcomes [7]. Another essential benefit is gene therapy's role in reducing toxicity and side effects in conventional chemotherapy agents [11]. The breakthrough in gene therapy heralds a paradigm shift in cancer treatment, promising to enhance patient outcomes. By directly targeting the genetic roots of the disease, boosting the immune system's response, and providing

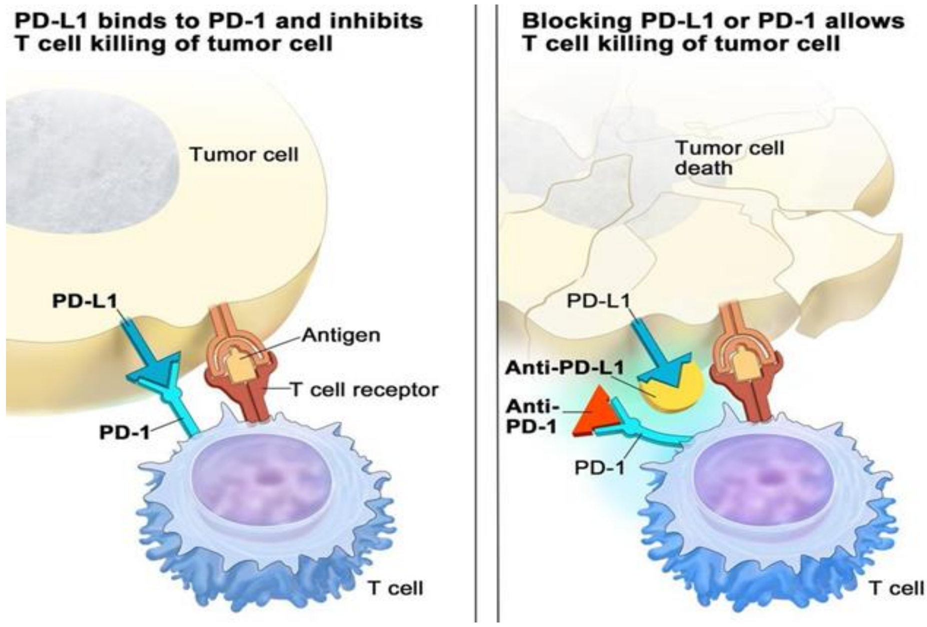

Fig. 1. A schematic representation of an immune checkpoint and the action of immune checkpoint inhibitors [10]

individualised therapy plans, gene therapy reshapes the landscape of cancer care [12]. CAR-T cell therapy, a gene therapy, exemplifies this revolution by genetically altering a patient's T cells to express a specific cancer cell receptor, thereby augmenting the immune system's capacity to identify and combat cancer cells [12].

3. BRIEF OVERVIEW OF TRADITIONAL CANCER TREATMENT

Traditional cancer treatments primarily encompass surgery, chemotherapy, and radiation therapy, each with distinct benefits and drawbacks. Surgery involves the removal of cancerous tissue, particularly effective for localised tumours but less so for preventing metastasis [13]. Chemotherapy utilises drugs to kill or inhibit cancer cells, yet its systemic nature can lead to side effects affecting normal cells.[13] Radiation therapy, on the other hand, damages cancer cells with high-energy rays but may also harm adjacent healthy tissues, causing side effects [13]. The integration of these treatments with therapies like hormone therapy, immunotherapy, targeted therapy, or stem cell transplant is standard, contingent on various factors [13]. Treatment choice depends on cancer type, stage, tumour characteristics, patient health, and availability [14]. Discussions with clinicians regarding diagnosis, prognosis, and treatment options are crucial for informed decisions [14].

Decades of research have produced diverse gene therapy techniques for cancer, including CAR-T cell therapy, CRISPR-Cas9 genome editing, and viral vectors transporting therapeutic genes [15]. Gaining insight about and applying these methods might lead to tailored and effective cancer care [15]. Despite significant progress, gene therapy for cancer faces safety, effectiveness, and scalability challenges [16]. Additionally, addressing immunogenicity and off-target effects is pivotal for viable and enduring gene-based cancer therapy [16].

While developed countries have advanced gene therapy studies, sub-Saharan Africa must catch up due to funding, facilities, and specialist shortages [17]. In the sub-Saharan Africa context, gene therapy has the potential to treat regional diseases like HIV-1, HBV, and Ebola and genetic disorders like sickle cell anaemia [17]. Significant obstacles in resource-scarce African environments include regulatory control, legal complexities, ethics, and cost-effectiveness. Low-income countries or developing nations can overcome these challenges through collaborative efforts among governmental, non-governmental, and educational institutions. By fostering awareness and understanding of gene therapy's potential, particularly among students and researchers, these partnerships can pave the way for overcoming present obstacles.

3.1 Historical Perspective of Gene Therapy in Cancer

The history of gene therapy in cancer reflects a remarkable journey from conceptualisation to sophisticated techniques targeting genetic factors. In the late 1970s and early 1980s, pioneers like Mulligan and Anderson proposed genetic interventions for treating diseases, including cancer [18]. Rosenberg and his team's 1990 gene therapy trial marked a pivotal moment, even though it focused on A.D.A. deficiency [5]. The late 20th century witnessed significant advancements in gene therapy, with transformative breakthroughs in viral vector development and epigenetic strategies [5]. Viral vectors like retroviruses and adenoviruses revolutionised gene delivery, enhancing the efficiency and targeting of therapeutic genes to cancer cells [19]. Notably, the past five years witnessed U.S. Food and Drug Administration (F.D.A.) approvals for viral-vector-based gene therapies, such as Luxturna, Hemegenix and Zolgensma, addressing genetic conditions like Leber's congenital amaurosis, haemophilia B and spinal muscular atrophy respectively [20].

The early 2000s saw the convergence of gene therapy and cancer immunotherapy, leading to the ground-breaking CAR-T therapy. CAR-T cells, genetically modified to target specific cancer antigens, have transformed precision cancer treatment [21]. The first successful CAR-T cells targeting a prostate cancer antigen were created in the 1990s, and subsequent clinical studies, mainly focusing on CD19, demonstrated remarkable results [21]. RNA-based therapeutics, particularly miRNA and siRNA technologies, gained prominence in the 2010s for their ability to alter gene expression in cancer [22]. The revolutionary CRISPR/Cas9 gene editing system, developed in the mid-2010s, offers precise modification of D.N.A. sequences, holding immense potential for correcting genetic mutations in cancer [23].

Recent breakthroughs since 2020 include personalised cancer vaccines and epigenetic modulation, providing novel avenues for cancer treatment [24]. The historical trajectory of gene therapy underscores its transformative role in the fight against cancer, from theoretical foundations to practical applications.

4. TYPES OF GENE THERAPY APPROACHES

Gene therapy offers diverse techniques to address the intricacies of cancer treatment. Each method targets specific genetic or molecular aspects of the disease, utilising genetic engineering to modify cancer cells' genetic material for tumour size reduction, immune response enhancement, or induction of cell death. Several well-known gene therapy strategies used in cancer research will be discussed.

4.1 Gene Replacement Therapy

Gene replacement therapy corrects genetic abnormalities driving tumorigenesis. Targeting p53, microRNA, and tumour suppressor genes such as BRCA1 and BRCA2 shows promise in cancers with specific genetic alterations [25]. Notably, Gendicine, an adenovirus delivering a healthy p53 gene, has shown success in treating head and neck squamous cell carcinoma [25].

4.2 Applications

Gene replacement therapy can restore functional p53, a crucial tumour suppressor, in cancers, enhancing therapeutic effectiveness against cancer due to prevalent mutations in the p53 gene [26]. Gene replacement therapy can be used to target BRCA1 and BRCA2, two genes that are essential for regulating breast cancer [27]. Gene replacement treatment for MLH1 and MSH2 attempts to repair the DNA mismatch repair mechanism, which lowers the risk of colorectal cancer [28].

4.3 Gene Editing Techniques

Gene editing techniques like CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats)/Cas9 (CRISPR-associated protein 9), TALENs, and Zinc-Finger Nucleases enable precise D.N.A. sequence modifications for targeted interventions [29]. CRISPR/Cas9 allows knockout studies, deactivating tumour growth genes by altering genetic [30]. TALENs and Zinc-Finger Nucleases offer alternative tools for cancer therapy and research [30].

4.4 Applications

CRISPR/Cas9 enables targeted gene inactivation, replacement, or repair, providing insight into the roles of specific genes in cancer development [29]. TALENs and Zinc-Finger Nucleases allow for the disruption of oncogenic genes, thereby inhibiting tumour growth and inducing apoptosis in various cancer models [30].

4.5 RNA-Based Therapies

RNA-based therapeutics, including R.N.A. interference and antisense oligonucleotides that precisely regulate gene expression, hampering cancer-associated mRNA translation [32]. R.N.A. Interference targets overexpressed genes crucial in tumourigenesis, enhancing the effectiveness of conventional therapies [32]. Antisense Oligonucleotides (A.S.O.s) modulate gene expression, suppressing the production of malfunctioning proteins and contributing to disease progression [32]. The mRNA vaccines induce an immune response against cancer-specific antigens, offering personalised cancer immunotherapy [32].

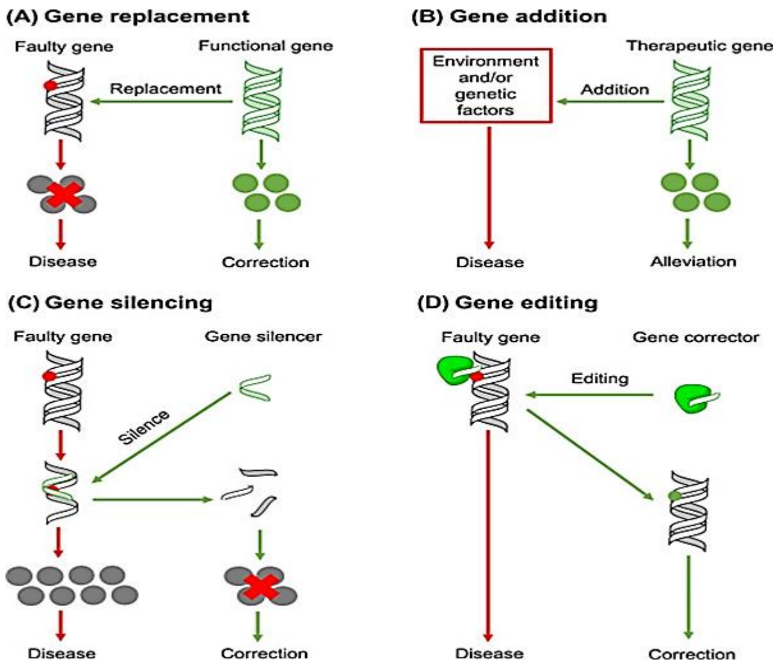

Fig. 2. Schematic representation of various gene therapy strategies. A. gene replacement, B. gene addition, C. gene silencing, and D. gene editing [31]

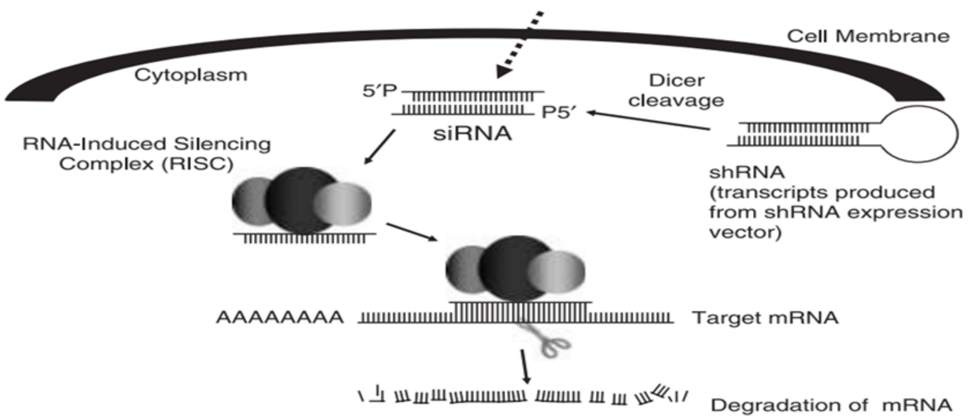

Fig. 3. Dicer, a multienzyme complex, converts shRNA and microRNA into small interfering R.N.A. duplexes. These are added to the R.N.A.-induced silencing complex (RISC), which unravels the duplex, cleaves the complementary mRNA, and destroys the encoding protein [32]

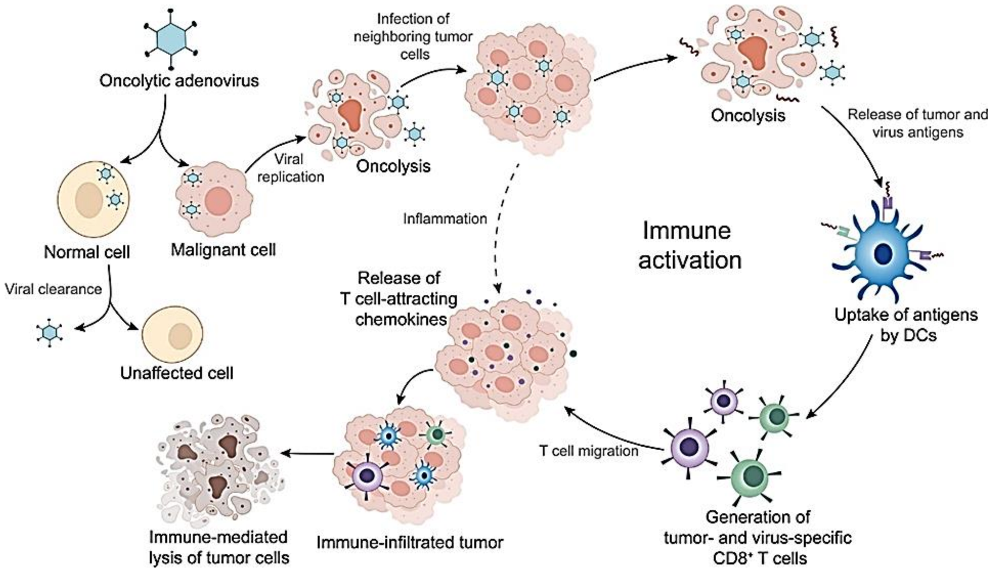

Fig. 4. Oncolysis occurs when oncolytic viruses eradicate cancerous cells and trigger the immune system to develop a targeted response against these malignant cells in the human body [33]

4.6 Oncolytic Viruses

A promising method, oncolytic viruses selectively infect and reproduce in cancer cells, triggering immune responses against tumours [33]. Oncolytic viruses offer diverse mechanisms, inducing tumour cell death, alerting the immune system, and modulating immune checkpoint molecules [33]. This approach, combinable with chemotherapy, radiation therapy, or immunotherapies, enhances overall treatment responses [33].

Gene therapy offers a comprehensive approach to cancer treatment, encompassing gene replacement, RNA-based precision therapies, and oncolytic viruses, showcasing its remarkable evolution and potential.

5. EMERGING GENE THERAPY APPROACHES

In the quest for precision cancer treatment, emerging gene therapy strategies are revolutionising this field with unprecedented efficiency.

5.1 Neoantigens and Tumour Mutations – Personalised Cancer Vaccines

Neoantigens, distinct markers resulting from somatic mutations in cancer cells, offer a highly targeted approach to cancer immunotherapy. The process involves identifying and focusing on immunogenic neoantigens, synthesising peptides, and formulating immunologic adjuvants [31]. Administered based on individual tumour genetic profiles, neoantigen vaccines ensure specificity, tackling the issue of tumour heterogeneity [31].

5.2 Epigenetic Modulations

Epigenetic changes, encompassing D.N.A. and histone modifications, play a pivotal role in cancer progression. Targeting these alterations allows precise interventions to restore normal gene function or silence oncogenic pathways. The use of D.N.A. methylation inhibitors (DNMTis) and Histone Deacetylase inhibitors (HDACis) exhibits promise in treating haematological cancers and various malignancies, showcasing the potential of epigenetic modulation in precision cancer therapy [31].

5.3 Combination Therapies with Immune Checkpoint Inhibitors

Immune checkpoint inhibitors revolutionise cancer therapeutics by enhancing immune responses against cancer cells, especially when combined with conventional treatments like chemotherapy and radiation therapy [34]. Combining these approaches addresses the challenge of cancer cells developing resistance, significantly impacting the overall efficacy of the treatment [34]. These emerging gene therapy approaches are revolutionising cancer treatment by integrating neoantigens, epigenetic modulations, and immune checkpoint inhibitors, transforming precision oncology into personalised, targeted treatments that address the unique genetic makeup of each patient.

6. CHALLENGES AND CONSIDERATIONS IN GENE THERAPY FOR PRECISION CANCER TREATMENT

Gene therapy holds immense promise in revolutionising cancer treatment by targeting the genetic underpinnings of the disease. However, it presents multifaceted challenges that must be systematically addressed to ensure safety, efficacy, and widespread clinical applications.

6.1 Delivery and Targeting

Therapeutic genes targeting cancer cells without affecting healthy ones is challenging, with genetic drift complicating treatment. Delivery systems must effectively treat diverse genetic subpopulations [35].

6.2 Off-Target Effects and Safety Concerns

Therapeutic gene integration into host genomes poses risks, including oncogene activation, necessitating robust procedures for reduced immunogenicity and enhanced immunological tolerance, which is vital [36].

6.3 Regulation of Gene Expression

Implementing conditional expression systems within the tumour microenvironment is crucial for precise cancer treatment, preventing unintended effects like toxicity or ineffectiveness [36].

6.4 Ethical and Social Considerations

Gene therapy's potential raises ethical and societal concerns, necessitating informed decision-making, cost-effectiveness, equal access, and protection of patient privacy and genetic information [36]. When utilizing this technology to promote human health, it is vital to contemplate the ethical consequences. In the wrong hands, this technology could impact the diversity of the human race. Furthermore, military organizations may use it to create enhanced soldiers without discrimination. Although these ethical dilemmas have not arisen yet, it is crucial to oversee and regulate its usage as soon as this technology becomes more accessible and affordable to the public. As a result of these ethical concerns, stringent policies and government regulations will be necessary.

6.5 Long-Term Safety and Manufacturing Challenges

Ensuring the enduring safety of gene therapy involves comprehensive monitoring protocols, including regular follow-ups, genetic monitoring, and immunological assessments [37]. There is much discourse surrounding the safety implications of genetic modifications on germline cells, in contrast to somatic cells. As such, it is imperative to establish rigorous regulations for manufacturing companies and implement efficacious approaches to address any conceivable manufacturing challenges.

6.6 Regulatory and Manufacturing Challenges

Navigating regulatory complexities and establishing scalable manufacturing processes are pivotal for the broader clinical use of gene therapy [37].

6.7 Patient-Specific Considerations

Tailoring gene therapy to individual patients requires addressing intra-tumour genetic diversity, immune system variations, and pre-existing genetic disorders or comorbidities [37].

6.8 Tumour Resistance and Adaptation

The resistance and adaptation of tumour cells pose challenges, demanding dual targeting techniques and combining gene therapy with other modalities for effective resolution [37].

As the landscape of precision cancer treatment evolves, precision cancer treatment requires collaboration among researchers, clinicians, and policymakers to refine gene therapy approaches, ensure ethical practices, and overcome delivery, safety, and regulatory hurdles.

Fig. 5. List of challenges that surround gene therapy for precision cancer treatment

7. GENE THERAPY PROSPECTS AND CHALLENGES IN PRECISION CANCER TREATMENT IN SUB-SAHARAN AFRICA – NIGERIA

Gene therapy is a promising frontier for precision cancer treatment in Sub-Saharan Africa, particularly Nigeria. The region, burdened by infectious and non-communicable diseases, can identify gene therapy strategies as a potential avenue for targeted and curative interventions.

7.1 Prospects in Sub-Saharan Africa

In addressing the substantial disease burden, gene therapy provides a tailored approach. The genetic diversity in sub-Saharan Africa becomes a unique asset, offering opportunities for genetic research to uncover markers and targets for precision cancer therapies [17]. Several challenges are limiting the implementation and scalability of this medical approach in sub-Saharan Africa, focusing on Nigeria. Limited access to medical research and healthcare facilities is central due to the poor economy [17]. The ongoing evolution of regulatory frameworks for gene therapy in Sub-Saharan Africa introduces potential delays in implementation [17]. Again, sub-Saharan Africa needs more dedicated facilities and has been underrepresented in gene therapy research [17]. Gene therapy in Africa extends beyond cancer, promising to address viral infections and inherited diseases.

7.2 Solutions and Recommendations

Prioritising the development of healthcare infrastructure, including specialised treatment centres, research hubs and diagnostic facilities, is imperative [38]. This also comes with international collaborations, governmental support, and policy advocacy [38]. Collaborations between government agencies, private healthcare providers, and research institutions are crucial for mobilising resources for local gene therapy research, investing in manufacturing, and promoting community engagement through educational programs [39]. Sustainable collaborative partnerships with regulatory authorities to develop streamlined frameworks addressing safety, efficacy, and ethical considerations are crucial.

Despite formidable challenges, Sub-Saharan Africa, especially Nigeria, holds the potential to contribute significantly to the growth of gene therapy. Strategic investments, collaborative efforts, and tailored solutions are imperative for successful integration and addressing the unique healthcare landscape.

7.3 Future Perspectives and Potential Applications of Gene Therapy for Precision Cancer Treatment

Gene therapy is a revolutionary cancer treatment that uses advanced viral vectors and non-viral delivery systems to target the genetic roots of cancer [32]. The future envisions personalised therapy, tailoring treatment based on individual genomic, tumoral, and immune characteristics. Safety enhancement focuses on safer vectors and genetically modified immune cells to minimise side effects and increase effectiveness. Combined therapies integrate gene therapy with existing treatments to prevent resistance and enhance tumour regression [32]. The evolution of gene editing technologies, including CRISPR-Cas9, promises more potent and enduring therapies [32]. Novel areas, such as manipulating epigenetic modifications to reprogram gene activity, offer new avenues for precision cancer therapy [32]. Gene therapy aids in personalised cancer vaccines, enhancing immune system recognition and attack. Efforts to make gene therapy globally accessible, particularly in resource-limited regions, are ongoing; however, ethical debates on informed consent and genetic privacy need to be addressed [32]. Furthermore, much of the ongoing cancer gene therapy research is in its final phase. At the same time, those approved by the FDA and other agencies saddled with drug approval in respective countries are not cost-effective. As a result of this, it has created a form of health inequality, preventing low-income people from getting access to such treatment. Making this treatment strategy cost-effective for all people is another area for future research.

8. CONCLUSION

Gene therapy's transformative impact on precision cancer treatment is evident in advanced targeting, multimodal approaches, immunotherapy, and gene editing. Ethical considerations, global accessibility, and psychological support are vital. Nigeria and sub-Saharan countries must align with global trends, fostering political will, collaboration, and research hubs. These strides offer hope for a future where cancer succumbs to genetic innovation, reshaping care for generations. Researchers, clinicians, and advocates stand at the vanguard, knowing genetics can redefine cancer care. The concept of translational medicine has interdisciplinary relationships that have greatly helped evaluate the effectiveness of various gene therapy strategies for cancer patient's treatment and management. Each advancement brings us closer to overcoming this formidable adversary, offering hope to countless individuals.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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