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Novel Methods of Personalized Treatment in Colorectal Cancer: A Literature Review

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Abstract

Introduction: Colorectal cancer (CRC) is a leading global health concern, characterized by a high prevalence and significant mortality rate. Despite the progress in treatment modalities, there remains a critical gap in personalized therapy approaches, particularly in tailoring treatments to individual genetic and molecular profiles across different stages. This literature review aims to bridge this gap by analyzing recent advancements and emerging therapies, focusing on how they address the specific needs of patients at various stages of CRC. The aim is to provide insights into the efficacy of personalized treatments and identify areas requiring further research for optimal therapeutic strategies,

Methods: A systematic search of the PubMed database was conducted using keywords such as "metastatic CRC," "single cell analysis," "personalized treatments", "single point mutation", "solid cancer", "genetic mutation" and "gene therapy" restricted to clinical trials published from 2017 to 2024. The search criteria included terms like "CRC" and "stage I, II, III, or IV" to identify relevant articles. This approach aimed to comprehensively review the current state of personalized therapies and identify gaps in knowledge that could inform future research. Research on colorectal cancer from 2017-2024 is crucial due to advancements in treatment, clinical guidelines, epidemiology, risk factors, diagnostic tools, and personalized medicine, providing comprehensive understanding,

Results: Recent studies show promising advancements in personalized treatments for CRC, particularly with targeted therapies and immunotherapy. Nanomedicine-based therapies and new agents improve drug delivery precision and efficacy. Immunotherapy, particularly for MSI-H tumors, shows effectiveness but remains variable based on genetic profiles. Combination therapies are emerging as a viable strategy.

Discussion: The findings highlight significant progress in personalized medicine for CRC, with targeted therapies and immunotherapy offering new hope. However, the complexity of CRC is highlighted by the variability in treatment responses across different genetic profiles. The review identifies a need for more comprehensive research to optimize these therapies and their long-term impacts.

Conclusion: Personalized treatments for CRC are advancing through targeted therapies, nanomedicine, and immunotherapy, but challenges persist in achieving consistent efficacy across diverse patient populations. Further research is needed to refine these approaches and improve outcomes.

Keywords: colorectal cancer; personalized medicine; genetic mutations; targeted therapies; checkpoint inhibitors

Introduction

Colorectal cancer (CRC) is the third most prevalent cancer globally and a leading cause of cancer-related deaths. It primarily affects individuals over 50 years old and is most common in men [1]. It progresses through distinct stages, from localised growths (Stages 0 and I) to widespread metastasis (Stage IV), with increasing risk of death at advanced stages. Early stages of CRC can be difficult to detect without screening, and may be characterized with symptoms such as constipation, diarrhea, and rectal bleeding [2]. In advanced stages of CRC, symptoms become more pronounced, and they include abdominal pain, bowel obstruction, and severe anemia [3-5]. Early detection through routine screenings, such as colonoscopies, may help to identify CRC early enough for curative surgical removal, while advanced stages require more aggressive treatment, including surgery, chemotherapy, radiation, and targeted therapies [3].

Current Treatments for Colorectal Cancer

Current treatments for CRC vary depending on the stage of the disease and the overall health of the patient. The primary modalities include surgery, chemotherapy, radiation therapy, targeted therapies, and immunotherapy [1].

Surgery

Surgery remains the cornerstone treatment for early-stage CRC and involves the removal of the tumor and surrounding tissue. Early-stage cancers may be treated with minimally invasive procedures like polypectomy or local excision during colonoscopy [4]. For more advanced cancers, partial colectomy or proctectomy is performed, removing the affected portion of the colon or rectum along with nearby lymph nodes. In later stages, surgery may also target metastatic sites such as the liver or lungs [3].

Chemotherapy

Chemotherapy is commonly used alongside surgery, either as an adjuvant to eliminate residual cancer cells or as neoadjuvant therapy to shrink tumors before surgery. Regimens typically include drugs like fluorouracil, leucovorin, oxaliplatin, and irinotecan [4]. For advanced or metastatic CRC, chemotherapy is often combined with other therapies to control symptoms and improve quality of life [5].

Radiation Therapy

Radiation therapy is primarily used in rectal cancer treatment, either before or after surgery to shrink tumors or to control the disease when surgery is not feasible. It is a vital component in the management of locally advanced rectal cancer [6].

Targeted Therapies

Targeted therapies involve drugs that specifically interfere with cancer cell growth mechanisms. Examples include monoclonal antibodies like bevacizumab, cetuximab, and panitumumab, which inhibit tumor blood vessel growth or target specific cancer cell receptors [7]. Anti-VEGF therapy (e.g., bevacizumab) and anti-EGFR therapy (e.g., cetuximab, panitumumab) are particularly effective in certain genetic subtypes of CRC, such as those without KRAS mutations [3].

Immunotherapy

For certain patients, particularly those with microsatellite instability-high (MSI-H) or mismatch repair-deficient (dMMR) tumours, immunotherapy with drugs such as pembrolizumab (Keytruda) or nivolumab (Opdivo) has shown promising results [8].

Checkpoint Inhibitors

MSI-H or mismatch repair-deficient tumors have a high mutation rate, leading to the production of abnormal proteins that the immune system can recognize as foreign. Pembrolizumab and nivolumab target the PD-1 receptor on T cells, blocking the inhibitory signals from tumor cells and allowing the immune system to attack the cancer. The high mutation burden in MSI-H and dMMR tumors makes them more susceptible to this immune response [2].

Current Gaps in CRC Treatment

Despite advancements in CRC treatment, gaps remain in the effectiveness and accessibility of personalized therapies. Currently, chemotherapy, surgery, and radiation therapy remain the cornerstone treatments [1]. However, these methods are associated with significant risks, including adverse side effects (nausea, hair loss, fatigue, peripheral neuropathy, infections, bowel dysfunction, bleeding, etc) and the potential for relapse or resistance [4].

Moreover, the relapse rate after personalized therapy varies depending on the type of therapy and the patient's genetic profile, with some studies indicating that up to 40% of patients may experience relapse within two years after treatment [3]. Emerging targeted therapies and immunotherapies show promise as personalized treatments for CRC, yet these approaches are not without limitations [4]. For example, while immunotherapy has revolutionized the treatment of certain cancers, its application in CRC is still limited to specific molecular subtypes, such as microsatellite instability-high (MSI-H) tumors [3]. Furthermore, targeted therapies, though more precise, often face challenges, such as the development of resistance and varying efficacy across different patient populations [9].

Study Objective

Given these challenges, there is a critical need to explore novel methods of personalized therapy for CRC. The objective of this study is to describe and evaluate the efficacy of emerging targeted therapies and immunotherapies in diverse stages, age groups, demographics and molecular profiles in CRC patient populations on overcoming resistance and enhancing long-term outcomes. By doing so, this research aims to contribute to the development of more effective and personalized treatment strategies that can be integrated into clinical practice.

Methods

To conduct this study, a search of PubMed database used specific words such as “metastatic CRC”, “single cell analysis”, and “treatments”. The search was restricted to clinical trials published between 2017 and 2024.

Results

Clinical trials and laboratory studies have shown that targeted therapies significantly improve progression-free survival in CRC patients with specific genetic mutations. Adjuvant chemotherapy reduced recurrence risk by approximately 30% in stage III CRC. Laboratory analyses identified biomarkers that correlate with resistance to standard therapies, with some markers predicting a 2-3 times increased risk of treatment failure. These findings emphasize the importance of personalized treatment approaches in CRC management [10]. Table 1 offers an overview of the clinical studies examined in this review.

Table 1. An Overview of the Clinical Studies Examined

Author and Year [Ref#]	Phase of Clinical Trial	Patient Selection (Age, Sex and Mutations)	Participants (n)	Stage of Cancer
Chen, 2020 [11]	Phase II	Patients were 18 years of age or older, both men and women, Microsatellite Instability (MSI), KRAS and BRAF mutations.	180 (121 men, 59 women)	Stage IV
Corcoran, 2022 [12]	Phase unspecified	Patients with CRC (BRAFV600E) were enrolled (5 MSI, 32 MSS). Five had previously received immunotherapy or BRAF inhibitor therapy. Median age of 63 (range: 35–87).	37 of 40 patients were enrolled. There were 20 (54%) females.	Stage II & III
Fakih, 2022 [13]	Phase II	Patients had $KRAS^{G12C}$ mutant CRC.	62 patients	Non-Stage specific
Innocenti, 2021 [14]	Phase unspecified	613 patients with genetically determined European ancestry were examined for associations between SNPs & overall survival (OS).	613	Stage IV
Kim, 2024 [15]	Phase II	Patients (median age 61) were both men and women. CRC accounted for 41.7% of all cancer cases, with prostate and biliary tract cancer following closely behind with 8.3% each.	48 patients in total (median age 61, 58.3% male)	Non-Stage specific
Lin, 2017 [16]	Phase unspecified	The study only included patients who experienced recurrence despite adjuvant treatment. Neoadjuvant treatment was not given to any patients.	235 patient samples were studied (157 training and 78 testing)	Stage I-III
Marie, 2021 [17]	Phase unspecified	Patients had a resect-able CRC	24 patients	Non-Stage specific
Pinto, 2024 [18]	Phase III	The study included patients with untreated, unresectable mCRC, confirmed RAS and BRAF wildtype status, and those who completed adjuvant therapy at least 6 months prior to study entry.	606 patients randomly assigned, 300 to Arm A, 306 to Arm B	Stage IV
Reinert, 2019 [19]	Phase unspecified	Enrolled in the study were 130 patients with International Union Against Cancer stages I to III CRC (mean [SD] age, 67.9 [10.1] years; 74 [56.9%] male).	125 patients; 5 discontinued participating; 725 samples	Stage I-III
Veen, 2023 [20]	Phase II/III	Patients with clinical stage T3N0-2M0 and MSI or dMMR	33 patients with CRC	Stage I-III; non-metastatic
Wu, 2021 [21]	Phase unspecified	Samples were collected from colorectal adenoma, CRC subjects with 252 healthy controls.	Colorectal adenoma, 306 samples. CRC, 217 samples and 252 healthy controls	Non-Stage specific
Xu, 2023 [22]	Phase II	The patients in this study who has unresectable mCRC that was HER2-positive and KRAS/BRAF wild-type were examined.	21	Stage IV

In multiple studies assessing novel therapies for CRC, combination treatments demonstrated enhanced efficacy and safety profiles compared to standard care or monotherapy. Durvalumab and tremelimumab improved survival in mCRC patients but caused notable adverse effects [11]. Trastuzumab with irinotecan was effective for high HER2 CRC [22], while cetuximab or bevacizumab with FOLFOX/FOLFIRI showed genetic links to survival outcomes [14]. Nivolumab and sotorasib showed moderate responses in specific mutation-driven cases, and microbiological markers differentiated adenomas from CRC [13, 15, 21]. Postoperative ctDNA predicted relapse earlier than imaging [19], and immunotherapy trials indicated high response rates in MSI tumors, especially with PD-1 inhibitors [20]. Finally, the TIME-PRODIGE 28 study confirmed cetuximab's maintenance benefit after FOLFIRI in RAS/BRAF-mutated mCRC [18].

Discussion

Personalized Therapy Success across Different CRC Stages

Stage I

For early-stage cancers, personalized therapies have shown promising results. Particularly, the studies reviewed indicate that cancers such as early-stage melanoma and certain types of breast cancer responded well to targeted therapies. For instance, patients treated with BRAF inhibitors for Stage I melanoma exhibited high rates of disease-free survival [11].

Stage II

As cancers progress to Stage II, the effectiveness of personalized therapies varied. For instance, in non-small cell lung cancer (NSCLC), patients treated with EGFR inhibitors had improved outcomes compared to those who received standard chemotherapy; however, the response rates were lower than in Stage I [21]. On the other hand, another study showed that personalized immunotherapy for Stage II CRC demonstrated moderate success [14].

Stage III

Stage III cancers present a more challenging landscape for personalized therapies. Patients with advanced melanoma treated with a combination of checkpoint inhibitors showed significant survival benefits, yet the treatment was associated with high toxicity and variable patient outcomes [23]. In contrast, personalized treatment of Stage III ovarian cancer using PARP inhibitors exhibited limited success, with only a subset of patients showing prolonged progression-free survival [22].

Stage IV

Personalized therapies for Stage IV cancers have the most varied outcomes, often reflecting the aggressiveness and heterogeneity of the disease. Stage IV variability of patient responses in CRC is similar to these other cancers like in the case of Stage IV pancreatic cancer, personalized therapies showed minimal success, with most patients experiencing only temporary remission [12]. On the other hand, patients with Stage IV metastatic melanoma treated with a combination of targeted and immune therapies exhibited extended survival, demonstrating that even in advanced stages, personalized treatment can be effective for certain cancers [18].

Broader Discussion on Personalized Medicine

Trends and Preferences

Across various clinical trials, there is a discernible trend favoring the use of immunotherapy in personalized medicine [18]. This preference is largely due to the success of immune checkpoint inhibitors like PD-1/PD-L1 and CTLA-4 inhibitors, which have been effective in several cancers, including melanoma, Non-Small Cell Lung Cancer, NSCLC, and CRC [23].

Genetic Mutations and Advanced Cancers

A common feature among patients who develop advanced cancers is the presence of specific genetic mutations, such as those in KRAS, BRAF, and TP53 [14]. These mutations often correlate with poor prognosis and resistance to standard treatments. Targeting these mutations with personalized approaches, like small molecule inhibitors and combination therapies, can improve outcomes for these patients [21].

Personalized Medicine for CRC

Advances in genetic and molecular profiling of tumours are paving the way for personalized treatment approaches, optimizing therapeutic efficacy based on individual tumour characteristics. Personalized medicine in CRC includes various approaches, such as EGFR inhibitors for specific mutations and immunotherapy for MSI-H/dMMR tumors. Despite these advancements, significant gaps remain [22]. For instance, it is not fully understood why certain therapies are more frequently used in advanced cancers, or how molecular mechanisms influence treatment choices. Understanding these factors is crucial for optimizing treatment strategies [12, 22]. Despite these advancements, significant gaps remain. For instance, our results highlight that mutations such as KRAS and BRAF are often associated with more severe forms of colorectal cancer, influencing both disease progression and treatment response. However, it is not fully understood why certain therapies are more frequently used in advanced cancers or how these molecular mechanisms precisely affect treatment choices.

Emerging Trends of Personalized Medicine

While this review focuses on the current state of personalized treatments for colorectal cancer, it is important to note that several key areas, such as advancements in CRC screening methodologies, patient-specific genetic profiling, and the broader implications of treatment heterogeneity, are beyond the scope of this discussion. These topics are, however, critical to the field and warrant consideration for a comprehensive understanding of personalized medicine:

Targeted Therapies

The use of targeted therapies, such as those aimed at RAS mutations, is another emerging trend. Although RAS-mutated CRC is typically resistant to some forms of therapy, recent studies have identified new molecular targets that could improve treatment outcomes [7]. For instance, targeted therapies that inhibit specific pathways related to tumor growth and survival are being developed, offering new hope for patients with these mutations [25].

Immunotherapy Advances

Immunotherapy continues to be a groundbreaking area for CRC treatment, particularly in cases with microsatellite instability-high (MSI-H) tumors, which are more responsive to immune checkpoint inhibitors. Drugs like pembrolizumab and nivolumab have shown effectiveness in treating these tumors by enhancing the body's immune response against cancer cells [2]. However, immunotherapy's success varies significantly depending on the genetic profile of the tumor, which highlights the need for personalized approaches [8, 25].

Combination Therapies

Another significant development is the use of combination therapies that integrate traditional treatments like chemotherapy with newer approaches such as immunotherapy or targeted therapies [25]. This multimodal strategy aims to overcome resistance to single therapies and improve overall survival rates. Recent clinical trials have shown that combining these treatments can be particularly effective in advanced stages of CRC, where the disease is more challenging to control [26].

Nanomedicine-Based Therapies

One of the most exciting areas of research involves the use of nanomedicine for CRC treatment. Nanoparticles are engineered to target cancer cells more precisely, minimizing damage to healthy tissue. Recent studies have focused on developing stimuli-responsive drug delivery systems that activate in the unique microenvironment of CRC tumors, using triggers such as pH, hypoxia, or specific enzymes. These systems improve drug efficacy and reduce side effects, representing a significant advancement over traditional chemotherapy [24].

Challenges and Future Directions

Despite these advancements, there are still significant challenges to overcome [24]. The heterogeneity of CRC tumors means that treatments must be highly personalized, which can complicate the development of universal treatment protocols. Moreover, many of the emerging therapies are still in early-phase clinical trials, and more research is needed to confirm their long-term efficacy and safety [27].

In conclusion, while emerging treatments for CRC show great promise, particularly in the areas of nanomedicine, immunotherapy, and targeted therapies, there is still a need for further research to optimize these approaches and integrate them into standard clinical practice. As our understanding of the molecular mechanisms underlying CRC continues to grow, so too will the effectiveness of these innovative treatments [24, 26].

These insights were drawn from a variety of recent studies, including reviews on the use of nanomedicines in CRC, clinical guidelines on the treatment of metastatic CRC, and research on new molecular targets and combination therapies [27].

As illustrated in Figure 1, this integrated discussion highlights the successes and challenges of personalized therapies across different cancer stages while underscoring the need for further research and standardized methods to enhance the precision and effectiveness of these treatments.

Limitations of This Study

Low Number of Clinical Studies

The relatively small number of clinical studies analyzed in this review may not capture the full spectrum of personalized therapies and their effectiveness across different cancer types and stages.

Lack of Standardized Comparisons

The absence of standardized comparison criteria and incomplete patient data makes it challenging to draw definitive conclusions about the success of personalized therapies across different studies [19, 20].

Follow-Up and Patient Monitoring

Variations in follow-up duration across studies may affect the assessment of long-term efficacy and safety, emphasizing the need for continuous monitoring to fully understand the benefits and potential late-onset side effects of personalized therapies [11, 22].

Assessment of Early-Phase Treatments

Some personalized therapies are still in Phase 1 or 2 trials, limiting the ability to assess their potential in routine clinical practice. These early-phase results must be interpreted with caution until more robust data from Phase 3 trials are available [13, 15].

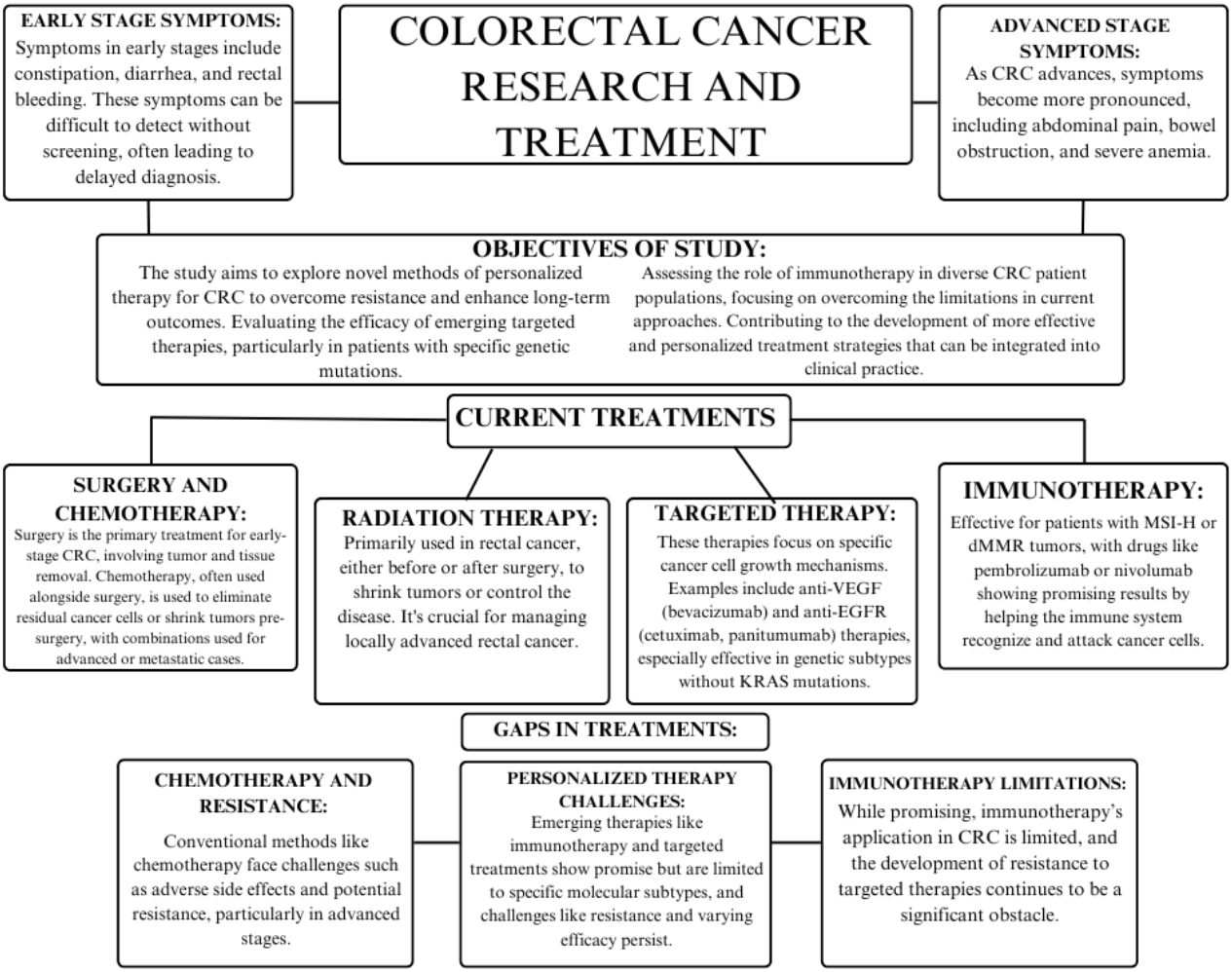

Figure 1. Flowchart of the Overview of the Paper (Created with Canva).

Conclusion

This study highlights significant advancements in the treatment of CRC, particularly through the exploration of emerging therapies such as targeted therapies, immunotherapy, and nanomedicine [14, 16]. These treatments have shown considerable potential in improving patient outcomes, especially when personalized based on the genetic and molecular characteristics of individual tumors [12, 21]. The research underscores the critical importance of moving beyond traditional methods to more tailored approaches, which can address the complexities and heterogeneity of CRC [22].

The study's findings are important as they contribute to the growing body of evidence supporting the efficacy of personalized treatments, which are increasingly recognized as the future of oncology [11, 23]. By identifying specific genetic mutations and tumor profiles, these therapies can potentially offer more effective and less toxic alternatives to conventional treatments, particularly for patients with advanced or resistant forms of CRC [17, 18].

However, the research also raises new questions about the broader applicability of these emerging treatments. Challenges such as drug resistance, variability in patient responses, and the need for further validation in large-scale clinical trials remain significant obstacles [18]. These findings suggest that while personalized therapies are promising, there is a need for continued research to refine these approaches and integrate them into standard clinical practice [16].

Future research should focus on addressing these challenges, particularly by exploring new molecular targets, improving the precision of nanomedicine-based therapies, and expanding the use of immunotherapy to a broader range of CRC patients [14, 23]. Additionally, long-term studies are necessary to fully understand the potential benefits and risks associated with these treatments, ensuring they can be safely and effectively used in clinical settings [10, 15]. This study lays the groundwork for future exploration into more effective and personalized CRC treatment strategies, ultimately aiming to improve patient survival and quality of life [12].

List of Abbreviations Used
BRAF: B-Raf proto-oncogene, serine/threonine kinase
CTLA-4: cytotoxic T-lymphocyte associated protein 4
dMMR: mismatch repair-deficient
EGFR: epidermal growth factor receptor
HER2: human epidermal growth factor receptor 2
KRAS: Kirsten rat sarcoma viral oncogene homolog
MSI-H: microsatellite instability-high
NSCLC: non-small cell lung cancer
PARP: poly (ADP-ribose) polymerase
PD-1: programmed death-1
PD-L1: programmed death-ligand 1
VEGF: vascular endothelial growth factor

Conflicts of Interest
The author declares that they have no conflict of interests.

Ethics Approval and/or Participant Consent
No ethics/participant consent was needed to complete this study.

Authors' Contributions
JFK: made contributions to the design of the study, collected, and analysed data, drafted the manuscript, and gave final approval of the version to be published.

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