CAROL DAVILA UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

DOCTORAL SCHOOL

MEDICINE

Endometrial cancer in the Lynch constellation
SUMMARY OF THE DOCTORAL THESIS

PhD supervisor

PROF. UNIV. DR. NICOLAE SUCIU

PhD student

BOTEA ROBERT

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The doctoral thesis titled "**Endometrial cancer in the Lynch constellation**" is divided into two major sections. The first section comprises two in-depth chapters that review the current understanding of Lynch syndrome and its significant association with endometrial cancer. These chapters lay the groundwork by discussing the genetic and molecular underpinnings of the syndrome, as well as the clinical and therapeutic strategies involved in managing endometrial cancer within this context. The second section, which details personal contributions, includes three chapters that meticulously describe the motivation, objectives, methodology, and results of the original research conducted during the doctoral studies.

THE GENERAL PART

Chapter 1. Overview of Lynch syndrome and endometrial cancer

This chapter provides a comprehensive introduction to Lynch syndrome, a hereditary condition marked by mutations in DNA mismatch repair (MMR) genes. These genetic anomalies predispose individuals to a heightened risk of developing various cancers, notably endometrial cancer, which is the most common extracolonic malignancy associated with the syndrome. The chapter not only talks about the genetic basis and molecular mechanisms driving Lynch syndrome but also connects these factors to the pathogenesis of endometrial cancer, setting the stage for a detailed exploration of the syndrome's clinical implications.

Introduction to Lynch syndrome

This section begins by defining Lynch syndrome and discussing its genetic foundations. Lynch syndrome, also known as hereditary non-polyposis colorectal cancer (HNPCC), is primarily caused by mutations in MMR genes such as MLH1, MSH2, MSH6, PMS2, and EPCAM (Latham, 2019). These mutations lead to microsatellite instability (MSI), a condition where errors that occur during DNA replication are not properly corrected, resulting in increased mutation rates. The section elaborates on the prevalence of Lynch syndrome, highlighting that it is one of the most common hereditary cancer syndromes. Despite its prevalence, Lynch syndrome is often underdiagnosed due to its variable expression and lack of awareness. The section also covers the diagnostic criteria used to identify individuals at high risk for the syndrome, including the Amsterdam II criteria and the revised Bethesda guidelines, which guide the genetic testing and confirmatory diagnosis (Tamura et al., 2019; Trujillo-Rojas et al., 2023).

Endometrial cancer in Lynch syndrome

This section focuses specifically on the risk and characteristics of endometrial cancer in individuals with Lynch syndrome. Women with Lynch syndrome face a significantly elevated risk of developing endometrial cancer, with a lifetime risk ranging from 40% to 60%. The section discusses the distinct pathophysiology of Lynch-associated endometrial cancer, which is primarily driven by the MMR gene mutations leading to high MSI. The higher mutation rates in these tumors contribute to their unique molecular profile, which includes frequent mutations in genes like PTEN and PIK3CA. These molecular changes not only promote tumorigenesis but also have implications for treatment, particularly the potential use of immunotherapy. The section highlights the need for early and aggressive surveillance in Lynch syndrome patients, given the younger age of onset and the hereditary nature of the disease (Capasso, 2023; Møller, 2017).

Genetic and molecular markers

In this section, the focus shifts to the identification and significance of genetic and molecular markers in Lynch syndrome. The discussion begins with an explanation of the key markers used in diagnosing Lynch syndrome, particularly MSI testing and immunohistochemistry (IHC) staining for MMR proteins. These diagnostic tools are essential for identifying the genetic disruptions that characterize Lynch syndrome and for guiding the management of affected individuals. The section also explores the molecular signatures specific to Lynch-associated endometrial cancer, including the role of mutations in the POLE gene, which are associated with a favorable prognosis. These molecular markers not only aid in diagnosis but also provide potential targets for personalized therapy, particularly in the context of emerging treatments like immunotherapy (Roudko et al., 2021; Rosty et al., 2016).

Screening and diagnostic approaches

The final section of this chapter reviews current screening and diagnostic approaches for Lynch syndrome. It discusses the universal screening recommendations for colorectal cancer patients, which include IHC and MSI testing as first-line diagnostic tools. The section also examines the use of clinical criteria in identifying individuals who should undergo genetic testing for Lynch syndrome. The discussion extends to the latest advancements in molecular

diagnostics, particularly next-generation sequencing (NGS), which has enhanced the sensitivity and specificity of Lynch syndrome detection. The integration of these advanced technologies into routine clinical practice is crucial for the early detection and management of Lynch syndrome-associated cancers, including endometrial cancer (Özdemir et al., 2019; Nádorvári et al., 2024).

Chapter 2: Therapeutic strategies and outcomes

This chapter was dedicated to the therapeutic management of endometrial cancer in the context of Lynch syndrome. It provides a thorough analysis of the various treatment strategies available, ranging from surgical interventions to pharmacological treatments and preventive measures. The chapter also explores the outcomes associated with these therapeutic approaches, with a particular focus on survival rates and the prognosis for patients with Lynch-associated endometrial cancer.

Management of endometrial cancer in Lynch syndrome

This section outlines the standard and emerging strategies for managing endometrial cancer in Lynch syndrome patients. Surgical management is emphasized as the cornerstone of treatment, with total hysterectomy and bilateral salpingo-oophorectomy (THBSO) being the most commonly recommended procedures due to the high risk of synchronous ovarian cancer (Ryan et al., 2021). The section also discusses the role of sentinel lymph node (SLN) mapping in reducing the morbidity associated with extensive lymphadenectomy while ensuring accurate staging (Touhami et al., 2017). Additionally, the use of chemotherapy and immunotherapy, particularly PD-1 inhibitors like pembrolizumab, is explored as part of the multimodal treatment approach, especially for advanced or recurrent cases (Bellone et al., 2022). The potential benefits of immunotherapy, given the high MSI status of Lynch-associated tumors, are particularly highlighted.

Preventive measures and surveillance

Given the hereditary nature of Lynch syndrome, preventive measures play a crucial role in managing cancer risk. This section discusses the recommended risk-reducing strategies, such as prophylactic THBSO, which significantly reduces the risk of both endometrial and ovarian cancers in Lynch syndrome patients. The section also covers the importance of regular

surveillance, including endometrial biopsies (Meyer et al., 2009), transvaginal ultrasounds, and colonoscopies, to detect cancers at an early, more treatable stage (Celentano et al., 2011). The discussion also touches on the potential role of chemoprevention, though it notes that more research is needed to establish its efficacy in preventing endometrial cancer in this high-risk population.

Prognosis and survival rates

The prognosis for Lynch syndrome-associated endometrial cancer is explored in this section, with a focus on the factors that influence survival rates. The section compares the survival outcomes of Lynch-associated versus sporadic endometrial cancer, noting that while the overall survival rates are similar, the earlier detection and tailored management strategies in Lynch syndrome patients often lead to better outcomes. I also discussed the impact of specific genetic mutations, tumor characteristics, and treatment modalities on prognosis, emphasizing the importance of personalized treatment plans to optimize patient outcomes (Bounous et al., 2022; Lim et al., 2021).

Future directions and research gaps

The final section of this chapter looks ahead to the future of research and treatment in Lynch syndrome-associated endometrial cancer. It identifies emerging therapies, particularly in the realm of immunotherapy and targeted molecular agents, as promising avenues for improving patient outcomes. The section also outlines the unanswered questions and areas where further research is needed, such as optimizing surveillance protocols, understanding resistance mechanisms to immunotherapy, and exploring fertility preservation options for young women with Lynch syndrome. The chapter concludes by emphasizing the need for continued research to address these gaps and advance the field of hereditary cancer syndromes.

The general part of this thesis provides a detailed foundation for understanding the complex interplay between Lynch syndrome and endometrial cancer. Through an exploration of the genetic, molecular, and clinical aspects of these conditions, the chapters set the stage for the original research contributions that follow. These contributions aim to further elucidate the challenges and opportunities in managing endometrial cancer within the Lynch syndrome context, ultimately striving to improve patient outcomes and guide future research in the field.

PERSONAL CONTRIBUTIONS

Chapter 3. Working hypothesis and general objectives

The central hypothesis driving this doctoral research is that a comprehensive genomic analysis, integrating both germline and somatic mutations, can significantly enhance our understanding of the molecular mechanisms underlying endometrial cancer, particularly in patients with Lynch syndrome. It is hypothesized that by identifying key genetic alterations through whole-exome sequencing (WES), this research will uncover actionable mutations that can be targeted for personalized therapy, thereby improving patient outcomes. Furthermore, it is expected that this integrated approach will reveal common and distinct genetic pathways involved in endometrial and colorectal cancers associated with Lynch syndrome, offering insights that could lead to better risk stratification and management strategies.

General Objectives

1. **Explore the genetic landscape of endometrial cancer in the context of lynch syndrome**

The first objective is to perform a detailed analysis of the genetic alterations in endometrial cancer associated with Lynch syndrome, focusing on both germline and somatic mutations. This involves using WES to identify mutations in key genes, particularly those involved in DNA mismatch repair (MMR) and other pathways implicated in tumorigenesis. The goal is to understand how these genetic changes contribute to cancer development and progression in Lynch Syndrome patients.

2. **Identify pharmacologically relevant mutations in endometrial cancer**

The second objective is to identify and characterize mutations in oncogenes and tumor suppressor genes that are actionable, meaning they can be targeted by existing or investigational therapies. By using WES data, this objective aims to uncover genetic alterations that could guide personalized treatment strategies, thereby enhancing the clinical management of endometrial cancer. Special focus is given to mutations in genes like

PIK3CA, PTEN, KRAS, and ARID1A, which have established roles in cancer biology and potential therapeutic implications.

3. **Compare the genomic profiles of Lynch syndrome-associated endometrial and colorectal cancers**

The third objective is to conduct a comparative analysis of the genomic profiles of endometrial and colorectal cancers in patients with Lynch syndrome. This objective seeks to identify shared and unique genetic pathways that drive tumorigenesis in these two cancer types, which are commonly associated with Lynch syndrome. Understanding these relationships could lead to the development of combined or tailored surveillance and treatment strategies for patients with Lynch syndrome.

These objectives were formulated to guide the research in uncovering new insights into the genetic basis of endometrial cancer, with a particular focus on Lynch syndrome, and to explore the potential for personalized medicine to improve patient care. Through these goals, the research aims to contribute significantly to the field of gynecological oncology and the broader application of precision medicine in cancer treatment.

Chapter 4. Somatic and Germline Mutations in Endometrial Cancer

This study addresses the complex genetic landscape of endometrial cancer, focusing on both somatic and germline mutations. While individual mutations in genes such as PTEN, PIK3CA, and DNA mismatch repair (MMR) system members have been widely studied, comprehensive analyses comparing somatic and germline mutations within the same cohort are limited. Therefore, this study aims to provide a detailed comparison of these mutations using whole-exome sequencing (WES) data from both tumor and blood samples in patients with histologically confirmed endometrial cancer. Endometrial cancer is the most common gynecological malignancy in developed countries, with increasing incidence partly due to the rising prevalence of risk factors such as obesity, hypertension, and diabetes. While most cases are diagnosed at an early stage and have a favorable prognosis, a significant proportion present with advanced disease, which is associated with poor outcomes. Genetic factors play a crucial

role in the development of endometrial cancer, with both germline and somatic mutations contributing to its pathogenesis.

Recent advancements in genomic technologies have facilitated the identification of numerous somatic and germline mutations associated with endometrial cancer. This study utilizes WES to identify and compare these mutations, with the goal of advancing our understanding of the genetic basis of endometrial cancer and informing the development of targeted therapies.

4.2 Material and methods

Thirteen female patients with histologically confirmed endometrial cancer were selected for this study. Inclusion criteria required patients to have a confirmed diagnosis based on histopathological examination, no prior treatment for endometrial cancer, and a strong family history of cancers associated with Lynch syndrome. Exclusion criteria included previous cancer treatments, metastatic disease at diagnosis, and inadequate sample quality.

Ethical considerations were rigorously followed, with study approval from Alessandrescu Rusescu National Institute for Mother and Child Health Ethics Committee, Bucharest, Romania. All patients provided written informed consent for participation, including genetic testing and the use of their samples for research.

Blood and tumor tissue samples were collected, with DNA extracted using standardized protocols. WES was performed on the extracted DNA, and subsequent bioinformatics analysis was conducted to identify and annotate somatic and germline variants. Statistical analysis was used to compare the frequency and type of mutations between the germline and somatic samples.

4.3 Results

The study cohort included 13 women with endometrial cancer. A total of 731 variants were identified, with 329 germline and 402 somatic mutations. Germline mutations were primarily found in DNA repair genes such as MLH1, MSH2, MSH6, PMS2, and BRCA1/2, while somatic mutations were more prevalent in genes involved in cell cycle regulation, signal transduction, and chromatin remodeling, including TP53, PTEN, PIK3CA, ARID1A, and KRAS. The analysis revealed significant differences in the number and types of variants between germline and somatic samples. Somatic samples exhibited a higher mutational burden, reflecting the

genomic instability characteristic of tumor cells. The most frequent germline mutations were found in DNA repair genes, consistent with their role in hereditary cancer predisposition. Somatic mutations were predominantly found in genes associated with tumor progression and metastasis.

4.4 Discussion

This study provides a comprehensive comparison of somatic and germline mutations in endometrial cancer, using WES data from both tumor and blood samples. The higher number of somatic mutations underscores the genomic instability of tumor cells, while the prevalence of germline mutations in DNA repair genes highlights the importance of inherited predisposition in endometrial cancer. The findings suggest that integrating germline and somatic mutation data can enhance our understanding of the genetic basis of endometrial cancer and inform the development of personalized treatment strategies. The identification of new variants, particularly in key oncogenes and tumor suppressor genes, provides potential targets for therapeutic intervention and underscores the need for further research into their functional impact.

4.5 Conclusions

This study advances our understanding of the genetic landscape of endometrial cancer by identifying and comparing somatic and germline mutations. The findings highlight the distinct roles of inherited and acquired mutations in cancer development and progression, with implications for genetic testing, risk stratification, and targeted therapy. Further research is needed to validate these findings and explore their potential clinical applications.

Chapter 5. Identification of pharmacologically relevant mutations in endometrial cancer by whole-exome sequencing of FFPE tumor samples

Endometrial cancer, one of the most common gynecological malignancies, presents a genetically heterogeneous profile, highlighting the need for personalized therapeutic approaches. In this study, we performed WES on formalin-fixed, paraffin-embedded (FFPE) tumor samples from 13 patients with histologically confirmed endometrial cancer. The primary

aim is to identify pharmacologically relevant mutations within key oncogenes and tumor suppressor genes, including PIK3CA, PTEN, KRAS, ARID1A, TP53, as well as MMR genes such as MLH1 and MSH2. By focusing on actionable mutations—those that are either directly targetable by existing drugs or could guide eligibility for clinical trials—this study demonstrates the utility of WES in informing personalized cancer management and underscores the importance of integrating genomic data into routine clinical practice. Endometrial cancer's increasing incidence globally, fueled by rising obesity rates and an aging population, underscores the need for improved management strategies, particularly for advanced and recurrent disease. Recent advances in genomic technologies have revealed distinct molecular subtypes of endometrial cancer, each associated with unique clinical outcomes and therapeutic vulnerabilities. WES, which captures the coding regions of the genome where most disease-causing mutations occur, has become a powerful tool in identifying key mutations driving tumorigenesis and guiding targeted therapy development.

Despite its potential, the application of WES in routine clinical practice remains limited, particularly when using FFPE samples, which are commonly available but present challenges due to DNA degradation. This study seeks to demonstrate that WES is feasible and valuable in this context, offering a pathway to more effective and individualized therapy for endometrial cancer patients.

5.2 Material and methods

This study included 13 female patients with histologically confirmed endometrial cancer, selected based on strict inclusion and exclusion criteria to ensure a clinically relevant and representative sample for WES analysis. The patients varied in age, tumor stage, and histological subtype, with the majority presenting with endometrioid carcinoma, the most common form of endometrial cancer. FFPE tumor samples were collected from these patients and processed according to standard protocols to ensure the integrity and quality of the extracted DNA for WES. The process included tissue sectioning, DNA extraction, quality control, library preparation, and sequencing on an Illumina platform. The bioinformatic analysis involved mapping the sequencing reads to the human reference genome, followed by variant calling, annotation, and filtering to identify mutations with clinical significance. Variants were classified based on their predicted impact on protein function, with pathogenic and likely pathogenic

variants prioritized for further analysis. The study also evaluated the potential therapeutic implications of these mutations, considering existing targeted therapies and ongoing clinical trials.

5.3 Results and discussion

The WES analysis identified a diverse mutational landscape in the 13 endometrial cancer patients, with a total of 352 unique variants, including single nucleotide variants (SNVs), insertions, and deletions (indels). Key genes frequently mutated across the cohort included PIK3CA, PTEN, ARID1A, KRAS, FGFR2, TP53, MLH1, and MSH2. Notably, PIK3CA mutations were the most common, identified in 8 patients, followed by PTEN mutations in 6 patients, and KRAS mutations in 4 patients.

PIK3CA mutations, particularly the hotspot mutation p.His1047Arg, were found in multiple patients, highlighting the PI3K/AKT/mTOR pathway's central role in endometrial cancer pathogenesis. These mutations suggest that patients could benefit from PI3K inhibitors like alpelisib, which is already approved for use in breast cancer with PIK3CA mutations.

PTEN, a tumor suppressor gene that negatively regulates the PI3K/AKT/mTOR pathway, was also frequently mutated. The loss of PTEN function, due to nonsense mutations or frameshift indels, leads to uncontrolled cellular proliferation, suggesting that therapies targeting downstream components of the pathway, such as mTOR inhibitors (e.g., everolimus), could be effective in these patients.

ARID1A, involved in chromatin remodeling, was mutated in 5 patients, with several mutations classified as pathogenic. The loss of ARID1A function is associated with a poor prognosis and aggressive tumor behavior, indicating a need for targeted therapeutic approaches, potentially involving epigenetic modifiers such as EZH2 inhibitors. KRAS mutations, found in 4 patients, are traditionally difficult to target, but the recent development of KRAS G12C inhibitors offers new therapeutic opportunities, even though this specific mutation was not identified in the cohort.

Mutations in MMR genes, identified in 2 patients, are linked to microsatellite instability (MSI) and a favorable response to immune checkpoint inhibitors such as pembrolizumab. These

findings support the use of immunotherapy in MSI-high endometrial cancers, aligning with current clinical practices.

The study emphasizes the clinical relevance of these mutations, particularly in guiding personalized treatment strategies. For example, patients with PIK3CA mutations might benefit from PI3K inhibitors, while those with ARID1A mutations could be candidates for clinical trials involving epigenetic therapies. The identification of MMR gene mutations further supports the integration of immunotherapy into treatment regimens for these patients.

5.4 Conclusions

This study underscores the transformative potential of WES in identifying actionable mutations in endometrial cancer, paving the way for personalized therapeutic strategies. The identification of key mutations in genes such as PIK3CA, PTEN, KRAS, ARID1A, and MMR genes provides specific treatment opportunities, including the use of targeted therapies and immunotherapy. The findings highlight WES as a valuable tool in precision oncology, driving the development of targeted therapies and advancing the standard of care in endometrial cancer. This study also contributes to the growing body of evidence supporting the integration of genomic data into routine clinical decision-making, with the potential to improve patient outcomes significantly.

Chapter 6. Lynch syndrome-associated genomic variants

The third study focuses on understanding the genetic landscape of endometrial cancer within the context of Lynch syndrome, a hereditary condition characterized by germline mutations in DNA mismatch repair (MMR) genes. Lynch syndrome significantly increases the risk of developing various cancers, including endometrial and colorectal cancers. Despite the established role of MMR deficiency in tumorigenesis, the specific genomic changes driving Lynch syndrome-associated endometrial cancer and their overlap with colorectal cancer remain incompletely understood. This study aims to fill this gap by conducting a detailed comparative analysis of germline and somatic mutations in endometrial cancer associated with Lynch syndrome. Whole-exome sequencing (WES) was performed on both germline and somatic DNA from 13 patients diagnosed with Lynch syndrome-associated endometrial cancer.

6.2 Material and methods

This study involved 13 female patients diagnosed with endometrial cancer, aged between 47 and 75 years, with a mean age of 60 at diagnosis. All patients had histopathologically confirmed endometrial cancer, and tumor staging was conducted according to the FIGO system. The tumors were uniformly classified as endometrioid adenocarcinoma, the most common histological subtype associated with Lynch syndrome in endometrial cancer. Blood samples were collected for germline DNA extraction, and formalin-fixed, paraffin-embedded (FFPE) tumor tissue samples were used for somatic DNA extraction. WES was performed on both germline and somatic DNA. Bioinformatics analysis was conducted to identify and annotate variants, focusing on their potential pathogenicity and relevance to both endometrial and colorectal cancer.

6.3 Results

The WES analysis revealed a wide array of genomic variants contributing to the pathogenesis of endometrial cancer in the context of Lynch syndrome. A total of 1,118 germline and 14,051 somatic variants were identified, with 493 variants being common to both. These common variants highlighted the roles of both inherited predisposition and somatic tumorigenesis in cancer development. The study confirmed the presence of pathogenic mutations in MMR genes, such as MLH1, MSH2, and MSH6, which are critical in Lynch syndrome. In particular, frequent somatic mutations were identified in PIK3CA and PTEN, implicating the PI3K/AKT/mTOR pathway as a key oncogenic driver in these cancers. Additionally, novel somatic mutations were discovered in genes related to the extracellular matrix (ECM), such as FBN1 and SPARC, suggesting a unique role in endometrial tumor progression.

6.4 Discussion

This study provides new insights into the molecular basis of Lynch syndrome-associated endometrial cancer, emphasizing the overlap in oncogenic pathways with colorectal cancer. The identification of both common and unique genetic mutations underscores the importance of developing combined treatment strategies that target these specific mutations. The frequent mutations in PIK3CA and PTEN point to the PI3K/AKT/mTOR pathway as a critical therapeutic

target, while novel findings in ECM-related genes like FBN1 and SPARC suggest additional avenues for treatment.

The study also highlights the importance of integrating germline and somatic mutation data to fully understand the tumorigenesis in Lynch syndrome-associated cancers. This integrated approach not only advances our understanding of the disease but also has significant implications for the development of personalized treatment strategies that could improve outcomes for patients with Lynch syndrome.

6.5 Conclusions

This study significantly advances our understanding of the genomic landscape of endometrial cancer in Lynch syndrome, revealing key similarities and differences with colorectal cancer in this context. The findings highlight the critical role of MMR gene mutations in driving tumorigenesis and suggest that targeting the PI3K/AKT/mTOR pathway could be particularly effective in treating these cancers. Additionally, the discovery of novel mutations in ECM-related genes opens new avenues for research and therapy. These insights underscore the potential for personalized treatment strategies that consider both germline and somatic mutations, ultimately aiming to improve outcomes for patients with Lynch syndrome.

CONCLUSIONS

This PhD thesis represents a significant contribution to the field of gynecological oncology, specifically in understanding the complex genetic landscape of endometrial cancer within the context of Lynch syndrome. Through three comprehensive studies, this research has provided critical insights into the molecular drivers of endometrial cancer, identified actionable genetic mutations that can inform personalized treatment strategies, and highlighted the genetic overlaps between Lynch syndrome-associated cancers. These findings not only advance our understanding of the disease but also pave the way for more targeted and effective therapies, ultimately improving patient outcomes.

The first study highlighted the complex connection between somatic and germline mutations in endometrial cancer, revealing the significant role of inherited genetic predispositions alongside tumor-specific alterations. By comparing these mutations, the research underscored the importance of considering both genetic origins when developing personalized treatment plans. This comprehensive approach enhances our understanding of the disease and informs the development of more effective therapeutic strategies.

The second study used whole-exome sequencing (WES) to identify pharmacologically relevant mutations in endometrial cancer, underscoring the utility of genomic profiling in clinical practice. The identification of key mutations in genes such as PIK3CA, PTEN, and KRAS provided actionable targets for existing and investigational therapies, demonstrating the feasibility and value of integrating WES into routine oncology care. This study not only contributes to the growing body of evidence supporting precision oncology but also highlights the potential for WES to revolutionize the treatment of endometrial cancer.

The third study focused on Lynch syndrome-associated endometrial cancer, providing new insights into the unique genetic profile of these tumors and their implications for patient management. By identifying novel mutations and exploring their clinical significance, this research has expanded our knowledge of how Lynch syndrome drives cancer development and progression. The study's findings underscore the importance of personalized treatment strategies that consider both the inherited and acquired genetic factors, offering new avenues for improving the care of patients with Lynch syndrome.

The technical and economic implications of this research are significant. The adoption of WES in routine clinical practice offers substantial advantages, including the ability to identify

actionable mutations that can guide personalized treatment strategies, leading to better patient outcomes and more efficient use of healthcare resources. Moreover, the integration of genomic data into clinical decision-making has the potential to reduce the trial-and-error approach in cancer treatment, thereby lowering costs associated with ineffective therapies. However, there are also challenges to consider. The initial costs of implementing WES, including the infrastructure, training, and ongoing data analysis, can be substantial, particularly in resource-limited settings. Additionally, the interpretation of complex genomic data requires specialized expertise, which may not be readily available in all clinical settings. These economic and logistical barriers must be addressed to fully realize the benefits of genomic medicine in oncology.

Despite the significant advancements made through this research, several unresolved issues remain. The long-term impact of integrating WES into routine clinical practice, particularly in terms of patient outcomes and healthcare costs, needs further exploration. Additionally, the clinical utility of novel mutations identified in Lynch syndrome-associated endometrial cancer requires validation through larger, multi-center studies. Understanding the functional implications of these mutations and their potential as therapeutic targets is a critical next step. Future research should focus on refining the use of WES in clinical settings, exploring its application in diverse populations and different cancer types. There is also a need to develop robust bioinformatics tools and clinical guidelines to support the interpretation of genomic data and its integration into personalized treatment plans. Furthermore, investigating the role of environmental and lifestyle factors in modulating the effects of genetic mutations could provide a more holistic approach to cancer prevention and treatment.

However, this PhD thesis has made substantial contributions to the field of endometrial cancer research, particularly in the context of Lynch syndrome. By integrating advanced genomic technologies with a focus on clinical applicability, this work has not only enhanced our understanding of the genetic underpinnings of endometrial cancer but also provided a solid foundation for the development of personalized treatment strategies. As the field of precision oncology continues to evolve, the findings from this research will undoubtedly play a crucial role in shaping the future of cancer care, offering new hope for patients and advancing the science of oncology.

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