Review

Genetic Basis of Familial Cancer Risk: A Narrative Review

Eman Fares Sabik *

Posted Date: 27 November 2025

doi: 10.20944/preprints202511.2088.v1

Keywords: familial cancer; tumor suppressor genes; oncogenes; mutations; epigenetic

Review

Genetic Basis of Familial Cancer Risk: A Narrative Review

Eman Fares Sabik

Department of Chemistry-Biology, The Arab Academic College of Education, Haifa 33145, Israel; ffares@univ.haifa.ac.il

Abstract

Familial cancers are caused by inherited mutations in specific genes that regulate cell growth, division, and repair. Approximately 5–10% of all cancer cases have a hereditary component, where germline mutations in certain genes increase an individual's susceptibility to developing cancer. Two major categories of genes are involved in cancer development: tumour suppressor genes and oncogenes. Both play critical roles in regulating normal cell behaviour, and when mutated, they can contribute to uncontrolled cell proliferation and tumour formation. In addition to genetic mutations, epigenetic alterations also play a significant role in familial cancer. Epigenetics refers to changes in gene expression due to DNA methylation, histone modifications, and the dysregulation of non-coding RNAs without alter the underlying DNA sequence. Familial cancer syndromes follow various inheritance patterns, including autosomal dominant, autosomal recessive, X-linked, and mitochondrial inheritance, each with distinct characteristics. Identifying genetic mutations associated with familial cancers is a cornerstone of genetic counselling, which helps individuals and families navigate the complex intersection of genetics, cancer risk, and prevention. Early identification of mutations enables personalized strategies for risk reduction, early detection, and, when applicable, targeted treatment options, ultimately improving patient outcomes.

Keywords: familial cancer; tumor suppressor genes; oncogenes; mutations; epigenetic

1. Introduction

Cancer is a multifactorial disease that combined genetic and environmental factors. Approximately 5-10% of all cases has a hereditary character where germinal mutations in specific genes increase the susceptibility to develop cancer [1]. Familial cancers that occur in families more frequently than would be expected by chance, are often caused by inherited mutations in specific genes that regulate cell growth, division, and repair. These mutations may be passed down through generations, increasing the risk of developing certain types of cancer [2,3]. The common familial cancers described in the literature are: breast cancer (BC) ovarian cancers (OC) [4–6] , prostate cancer (PC) [7,8], colorectal cancer (CC) [9,10], endometrial cancer (EC) [11], melanoma [12], Thyroid cancer (TC) [13,14] and pancreatic cancer (PnC) [15,16]. Familial cancers are often inherited according to specific genetic patterns, which influence how cancer risks are passed down through generations. These inheritance patterns can be **autosomal dominant and** [17–19] autosomal **recessive** and **X-linked [20].** Cancers can develop in various organs of the body and each organ is associated with specific genetic mutations include oncogenes and tumor suppressor genes that can predispose individuals to cancer [21].

Cancer is often the result of alterations in genes that regulate cell growth, division, and death. Two major categories of genes involved in cancer development are **tumor suppressor genes** and **oncogenes** [22–25]**.** These genes play critical roles in normal cellular processes, and when they become mutated or altered, they can contribute to the initiation and progression of cancer.

 doi:10.20944/preprints202511.2088.v1

In addition to the genetic mutations that are typically passed from parent to child, epigenetic alterations can also be inherited across generations. This inheritance is referred to as **epigenetic inheritance** and can occur without changes to the DNA sequence itself. Several familial cancer syndromes may have epigenetic components that contribute to the predisposition to cancer [26,27] . Analyses of 4,034 cancer cases representing 12 cancer types indicated that the frequency of rare germline truncations in cancer-susceptibility-associated genes varies from 4% in glioblastoma and acute myeloid leukemia (AML) to 19% in ovarian cancer (Figure 1) [28].

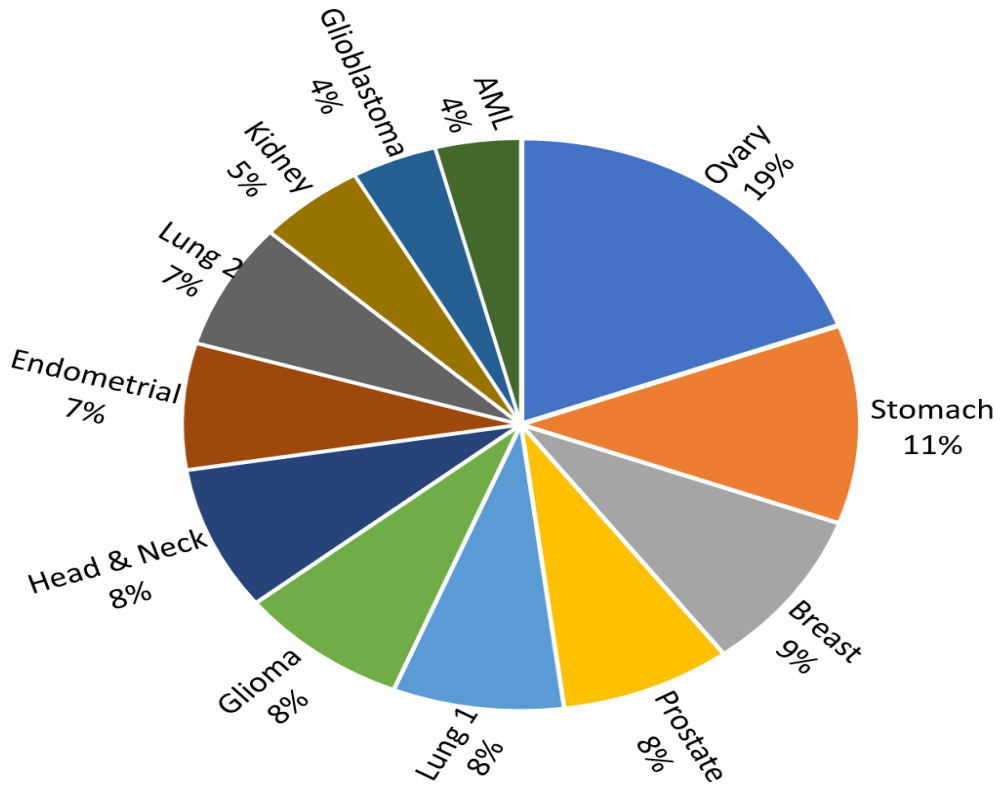

Figure 1. Distribution of candidate germline variants associated with cancer predisposition, based on exome sequencing data from patients representing 12 distinct cancer types.

The goal of the present manuscript is to provide a comprehensive understanding of the hereditary nature, genetic and epigenetic factors, that involve in familial cancer. It can help inform individuals, researchers, and healthcare professionals about the risk factors, inheritance patterns, and potential prevention strategies for familial cancer.

2. Key Genes Involved in Familial Cancer

Cancer is often the result of alterations in genes that regulate cell growth, division, and death. Two major categories of genes involved in cancer development; tumor **suppressor genes** and **oncogenes** [22–24]**.** These genes play critical roles in normal cellular processes, and when they become mutated or altered, they can contribute to the initiation and progression of cancer.

2.1. Tumor Suppressor Genes

Tumor suppressor genes are genes that normally function to regulate cell growth and prevent uncontrolled cell division. When these genes are inactivated by mutations or deletions, cells can begin to proliferate uncontrollably, leading to cancer. Common Tumor Suppressor Genes are:

2.1.1. BRCA1 and BRCA2

 doi:10.20944/preprints202511.2088.v1

The BRCA1 and BRCA2 genes are tumour suppressor genes that play a critical role in maintaining genomic stability by facilitating the repair of DNA double-strand breaks (DSBs) through the homologous recombination (HR) pathway. This high-fidelity repair mechanism is essential for preventing the accumulation of mutations and chromosomal aberrations. When either BRCA1 or BRCA2 is mutated, the homologous recombination process becomes defective, leading to genomic instability—a hallmark feature of many cancers [29,30]. Germline mutations in BRCA1/2 are strongly associated with a significantly increased risk of developing several cancer types, most notably breast cancer (BC), ovarian cancer (OC), prostate cancer (PC), male breast cancer, and others. These mutations are typically inherited in an autosomal dominant pattern, meaning a single mutated copy of the gene from either parent can confer elevated cancer risk. This inheritance pattern underlies hereditary cancer syndromes, such as Hereditary Breast and Ovarian Cancer (HBOC) syndrome, which substantially increase the lifetime risk of specific cancers—particularly in individuals with a family history of cancer [29,30].

Women with a BRCA1 mutation have an estimated 55-65% lifetime risk of developing BC and 39% of OC by age 70, compared to about 12% in the general population. Women with a BRCA2 mutation have a 45% and 11-17% lifetime risk of developing BC and OC by age 70, respectively. Men with BRCA2 mutations are also at increased risk for BC, although this is much rarer than in women. In addition, both BRCA1 and BRCA2 mutations are linked to an increased risk of pancreatic cancer [31–37].

2.1.2. RB1

The RB1 gene produces the retinoblastoma protein, which regulates the cell cycle by inhibiting cell division. It is a critical regulator of the G1/S checkpoint of the cell cycle. RB1 inhibits E2F transcription factors to prevent uncontrolled cell proliferation. Loss of function of RB1 is associated with retinoblastoma (a childhood eye cancer), osteosarcoma, and other cancers. The general frequency of *RB1* gene mutation in the germline of retinoblastoma patients with retinoblastoma was estimated to be 40-60% [38].

2.1.3. APC (Adenomatous *Polyposis Coli)*

The **APC gene** (Adenomatous Polyposis Coli) is a tumor suppressor gene that helps regulate cell growth and prevent the formation of tumors by controlling cell division. **APC** is a negative regulator of the **Wnt/β-catenin signaling pathway** which controls cell growth and differentiation. It also regulates the actin cytoskeleton and interacts with other proteins to control cell adhesion. When this gene is mutated, it can lead to the development of numerous polyps in the colon and rectum, which can eventually turn into cancer if left untreated. **APC hereditary mutations** are associated with a genetic condition called **familial adenomatous polyposis (FAP),** which significantly increases the risk of **colon cancer** and other cancers. FAP is a genetic disorder that causes cancer, primarily in the colon and rectum, due to the growth of numerous polyps (abnormal growths) in the gastrointestinal tract. Mutations in the APC gene are commonly found in familial adenomatous polyposis (FAP) and in sporadic colorectal cancers. The risk of carriers to develop cancer is significantly higher. Without intervention almost, all APC carriers (~100%) **will develop colon cancer** by the age of 40 to 50. It is estimated that by 2030, the number of colorectal cancer cases under 50 years of age will be 11% and the total number of rectal cancer cases will be 23% [39–41].

2.1.4. DNA Mismatch Repair Genes

The DNA mismatch repair (MMR) system is a highly conserved cellular mechanism that corrects errors introduced during DNA replication, such as: Base-base mismatches (e.g., A-G instead of A-T) and small insertions or deletions, particularly in microsatellite regions. Key MMR genes such as MLH1, MSH2, MSH6, and PMS2 remain central to understanding microsatellite instability (MSI) and deficiency in mismatch repair (dMMR), which is a biomarker for response to immune checkpoint inhibitors. New findings also highlighted non-repair functions of MMR proteins in cell cycle,

 doi:10.20944/preprints202511.2088.v1

apoptosis, and the cellular secretome, suggesting a broader impact on cancer development and progression. dMMR is a classic hallmark of Lynch Syndrome, a hereditary cancer predisposition syndrome [42–45]. Lynch syndrome is inherited in an autosomal dominant fashion. The hallmark of Lynch syndrome is defective DNA mismatch repair, which causes an elevated rate of single nucleotide changes and microsatellite instability, also known as MSI-H (the H is "high"). MSI is identifiable in cancer specimens in the pathology laboratory. Most cases result in changes in the lengths of dinucleotide repeats of the nucleobases cytosine and adenine (sequence: CACACACACA...) [43,46].

2.1.5. PTEN

PTEN is a lipid phosphatase that antagonizes the **PI3K/AKT/mTOR pathway**, thereby promoting apoptosis and inhibiting cell survival signals. Normally, PTEN is involved in regulating the PI3K/AKT signaling pathway and acts as a tumor suppressor, helping to regulate cell growth and division. Germline PTEN mutations underlie **PTEN hamartoma tumor syndrome (PHTS)**, which includes Cowden syndrome, and predispose to **breast, thyroid, endometrial, and renal cancers** [47]. When the PTEN gene is mutated, it can lead to uncontrolled cell growth and the formation of tumors in various parts of the body such as: breast (25-85% by the age of 70), endometrial (20-30% by the age of 70), thyroid (10-35% of life time), kidney (10% of life time), and rarely in skin, colon and liver [47,48].

2.1.6. TP53 (p53)

TP53 is one of the most important tumor suppressors, involved in regulating cell cycle, DNA repair, and apoptosis (programmed cell death). It acts as a checkpoint in response to DNA damage, ensuring that damaged cells do not divide and propagate mutations. Mutations in TP53 are found in over 50% of human cancers, including those of the lung, breast, colon, and liver. Germline mutations in the **p53 gene** are most commonly associated with a rare inherited cancer syndrome known as **Li-Fraumeni syndrome (LFS)**. LFS syndrome is characterized by a high lifetime risk of developing multiple types of cancer, often at a young age. The risk is extremely elevated compared to the general population, and individuals with LFS can develop different cancers throughout their lifetime such as: Breast (50-70%, often at a younger age), soft tissue sarcoma (the life time risk is around 20-30%), Osteosarcoma (tends to develop in childhood), Brain, leukemia, adrenocortical, and other cancers including liver, colon and pancreatic. The risk of developing cancer in carriers of a germline p53 mutation is elevated throughout life, but cancer tends to appear earlier than in the general population. It was estimated that by age of 30, there is a 50% chance of having developed cancer and by age **60**, the lifetime cancer risk can be as high as 90% or more [49–52].

2.2. Oncogenes

Oncogenes are genes that, when mutated or abnormally expressed, have the potential to cause normal cells to transform into cancerous cells. These genes typically promote cell growth and division. In a healthy cell, oncogenes are usually involved in regulating processes like cell proliferation, survival, and differentiation, but when mutated or overexpressed, they can lead to uncontrolled cell growth, resistance to apoptosis and increase angiogenesis, a hallmark of cancer. Common Oncogenes in Cancer are:

2.2.1. HER2/neu (ERBB2)

HER2/neu encodes a receptor tyrosine kinase that is involved in cell growth signaling. Overexpression of HER2 is a hallmark of BC and is associated with aggressive disease. Germline (inherited) mutations in **HER2** (also known as **ERBB2**) are extremely rare in breast cancer **Somatic mutations or overexpression** of HER2 are common in **HER2-positive breast cancer** which occurs in approximately 15–30% of breast cancer tumors . HER2-targeted therapies, such as trastuzumab (Herceptin), have improved outcomes for patients with HER2-positive breast cancer [53–55].

 doi:10.20944/preprints202511.2088.v1

2.2.2. Ras

Ras's proteins are small GTPases that play a key role in cell signaling pathways regulating growth, differentiation, and survival. Mutations in Ras genes lead to constitutive activation of downstream signaling pathways, contributing to the development of various cancers, including lung, colorectal, and pancreatic cancers. Some hereditary cancer syndromes are linked to *RAS* mutations, particularly the *HRAS* gene in Costello syndrome, and occasionally *KRAS* and *NRAS* mutations in certain familial cancer syndromes. These mutations are passed down from one generation to the next and can increase the likelihood of cancer developing in affected individuals [56–58]. Germline mutations in RAS genes (KRAS, NRAS, HRAS) are extremely rare in human cancers, with most RAS alterations arising somatically—meaning they occur in tumour cells, not inherited or present in all cells of the body. KRAS mutations account for 11–14% of all human cancers.

Mutations in the *RAS* genes lead to an activation of the RAS signaling pathway, which is crucial for regulating cell growth, differentiation, and survival. Mutations in *KRAS*, *NRAS*, or *HRAS* cause constitutive activation of RAS proteins, leading to Uncontrolled cell proliferation, Resistance to apoptosis (cell death), Enhanced survival and growth of tumors. These mutations often affect critical regions of the RAS protein, such as the GTPase domain, which normally helps turn off RAS signaling. When mutated, the proteins remain active in an unregulated manner, pushing cells to grow and divide inappropriately [59,60].

2.2.3. MYC

MYC encodes a transcription factor that regulates the expression of genes involved in cell growth and metabolism. Overexpression of MYC is seen in many types of cancer, including lymphoma, leukemia, and breast cancer, and leads to uncontrolled cell proliferation. Point mutations in MYC disrupt phosphorylation that frequently observed in translocated *MYC* alleles in cancer. Therefore, mutations that disrupt T58 phosphorylation are selected genetic events acquired during initiation or progression of MYC-associated cancers [61,62]. Germline mutations in the *MYC* gene are indeed rare, and while most of the literature focuses on **somatic mutations** (acquired mutations in specific tissues during a person's life), there is emerging interest in understanding whether germline alterations in *MYC* or related pathways contribute to inherited cancer risk [63].

2.2.4. BCR-ABL

BCR-ABL is a fusion gene that results from a chromosomal translocation between chromosomes 9 and 22, known as the Philadelphia chromosome. This fusion gene encodes a constitutively active tyrosine kinase that leads to the development of chronic myelogenous leukemia (CML) and other hematologic cancers by promoting unchecked cell division [64].

Germline BCR-ABL mutations are **extremely rare** or essentially nonexistent in the medical literature. Most familial cases of **CML** likely involve inherited predispositions to develop the disease due to genetic or environmental factors, rather than the direct inheritance of the BCR-ABL fusion gene. The somatic nature of the BCR-ABL translocation in CML means it typically arises **de novo** during the lifetime of an individual rather than being passed down from parent to offspring. Mutations in the Bcr-Abl kinase domain may contribute to, resistance to tyrosine kinase inhibitors in CML patients [65].

3. Epigenetic Inheritance in Familial Cancer

Epigenetic inheritance refers to heritable changes in gene expression or phenotype that do not involve changes to the underlying DNA sequence. In familial cancer, epigenetic mechanisms can play a significant role in the transmission of cancer susceptibility across generations. Epigenetic changes, such as DNA methylation, histone modifications, and non-coding RNA regulation, can influence tumorigenesis and may be passed down from parent to offspring, contributing to familial cancer syndromes [66]. Recently it was reported that ~33.9% of women with early-onset triple-negative breast cancer (TNBC) (who tested negative for BRCA1/2 germline mutations) had constitutional

 doi:10.20944/preprints202511.2088.v1

BRCA1 promoter methylation detectable in blood. This suggests a significant epigenetic predisposition in a subset of breast cancer patients. [67], Other study reported that MLH1 promoter is methylated in <2% of patients with MMR-deficient colorectal cancer who do not carry detectable germline mutations. This form of epimutation can mimic Lynch syndrome but is often sporadic or mosaic [68]. Changes in DNA methylation in cancer have been heralded as promising targets for the development of powerful diagnostic, prognostic, and predictive biomarkers. Some epigenetic tests are already routine in specific clinical settings, but most epigenetic profiling remains primarily a research tool or used in specialized cases [69].

3.1. Mechanisms of Epigenetic Inheritance

Epigenetic changes regulate gene expression and can be influenced by environmental factors, lifestyle choices, and genetic predispositions. In familial cancer, these changes may affect the expression of key tumor suppressor genes, oncogenes, or other regulatory genes involved in cell growth and apoptosis [70,71]. Three primary epigenetic mechanisms are implicated in familial cancer:

3.2. DNA Methylation

DNA methylation typically occurs at cytosine residues in CpG dinucleotides and is associated with gene silencing when it occurs in the promoter regions of genes.

Aberrant DNA methylation, such as hypermethylation of tumor suppressor genes or hypomethylation of oncogenes, is a well-established mechanism in cancer. In familial cancer, inherited methylation patterns may predispose individuals to certain cancers. For example, the MLH1 gene in Lynch syndrome (hereditary non-polyposis colorectal cancer) can be silenced through promoter hypermethylation, leading to loss of DNA mismatch repair and increased cancer risk [72–74].

3.3. Histone Modifications

Histones are proteins around which DNA is wrapped. Post-translational modifications of histones, such as acetylation, methylation, and phosphorylation, can alter chromatin structure and, consequently, gene expression. In familial cancers, mutations in histone-modifying enzymes or altered histone marks may lead to abnormal gene expression, influencing tumorigenesis. For instance, mutations in EZH2, a histone methyltransferase, are found in various cancers, including familial cancers like prostate cancer [75].

3.4. Non-Coding RNAs

Non-coding RNAs, including microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), Circular RNAs **(**CircRNAs), and **mall Nucleolar RNAs (snoRNAs)** that regulate gene expression post-transcriptionally.

miRNAs are short, single-stranded RNA molecules (about 20-22 nucleotides) that typically regulate gene expression post-transcriptionally by binding to the 3' untranslated region (UTR) of target messenger RNAs (mRNAs), leading to their degradation or translational repression. miRNAs can function as oncogenes (oncomiRs) or tumor suppressors depending on the genes they target. miRNAs that are upregulated in cancers and promote oncogenesis by inhibiting tumor suppressor genes. miRNAs that are downregulated in cancers and prevent tumor formation by targeting oncogenes [76–78].

LncRNAs are RNA molecules longer than 200 nucleotides that regulate gene expression at various levels, including transcriptional and post-transcriptional regulation. Many lncRNAs are involved in cancer initiation, progression, and metastasis by influencing chromatin remodeling, transcriptional activation, and repression, as well as alternative splicing [79,80].

 doi:10.20944/preprints202511.2088.v1

CircRNAs are a subclass of non-coding RNAs that form covalently closed loops and are involved in regulating gene expression. They can act as sponges for miRNAs or interact with RNA-binding proteins to regulate gene transcription [81,82].

SnoRNAs are involved in the chemical modification of ribosomal RNA (rRNA) and small nuclear RNA (snRNA). Some snoRNAs have been implicated in cancer progression by regulating the modification of rRNAs that impact protein synthesis and cell proliferation [83].

Dysregulated expression of non-coding RNAs can lead to cancer development by altering the expression of genes involved in cell cycle regulation, apoptosis, and metastasis.

In familial cancers, the inheritance of mutations or altered expression of non-coding RNAs can contribute to cancer susceptibility and progression. For example, miR-21 is often overexpressed in various cancers and can inhibit tumor suppressor genes [84]. Other examples are listed in Table 1.

Table 1. Examples of Familial Cancer Syndromes with miRNA Involvement.

Syndrome	miRNA Role
DICER1 syndrome	Germline mutations in *DICER1* → impaired miRNA processing tumours in lung, ovary, thyroid, etc.
Li-Fraumeni syndrome	miR-34 family is regulated by *TP53*; dysfunction may amplify cancer risk in *TP53* mutation carriers.
HBOC (Hereditary Breast and Ovarian Cancer)	miR-182 and others regulate *BRCA1* expression; dysregulation may affect DNA repair.
Familial colorectal cancer	miR-155 and others can target MMR genes (*MLH1*, *MSH2*), influencing Lynch syndrome pathogenesis.

4. Inheritance Patterns

Inheritance patterns refer to the ways in which genetic traits are passed from parents to offspring. These patterns help explain how traits are inherited and why they can vary among individuals within a family or population. Each of these inheritance patterns helps to explain the genetic variability observed in families and populations, and understanding them is crucial for genetic counseling, diagnosing inherited diseases, and studying evolution.

There are several main inheritance patterns, each with its own characteristics. Some of the most common inheritance patterns include:

4.1. Autosomal Dominant

The most common pattern in hereditary cancers. A mutation in one copy of a gene (e.g., *BRCA1*, *BRCA2*, *TP53*) is sufficient to increase cancer risk. Affected individuals have a 50% chance of passing the mutation to offspring [85,86]. The risk of developing cancer among carriers of hereditary mutations in cancer-related genes often ranges from 20% to nearly 90%, depending on the specific gene and type of cancer [87]. Examples of autosomal dominant are summarized in Table 2.

Table 2. Autosomal Dominant Cancer Syndromes, the genes involve and associated cancers.

Syndrome / Condition	Gene(s) Involved	Associated Cancers
Hereditary Breast and Ovarian Cancer	*BRCA1*, *BRCA2*	Breast, ovarian, prostate, pancreatic
Lynch Syndrome (HNPCC)	*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*	Colorectal, endometrial, ovarian, gastric, urinary tract
Li-Fraumeni Syndrome	*TP53*	Breast, brain, sarcomas, adrenal, leukemia

 doi:10.20944/preprints202511.2088.v1

Familial Adenomatous Polyposis (FAP)	*APC*	Colorectal (almost 100% risk), small intestine, stomach
Cowden Syndrome	*PTEN*	Breast, thyroid (follicular), endometrial
Peutz-Jeghers Syndrome	*STK11 (LKB1)*	GI tract (colon, stomach, pancreas), breast, cervix, testes
Hereditary Retinoblastoma	*RB1*	Retinoblastoma (eye), osteosarcoma
Von Hippel–Lindau Disease (VHL)	*VHL*	Kidney (RCC), pheochromocytoma, CNS hemangioblastomas
Multiple Endocrine Neoplasia type 1 (MEN1)	*MEN1*	Parathyroid, pancreatic, pituitary tumours
Multiple Endocrine Neoplasia type 2 (MEN2)	*RET*	Medullary thyroid carcinoma, pheochromocytoma

4.2. Autosomal Recessive

The less common pattern in hereditary cancers. Cancer risk increases when both copies of a gene are mutated (e.g., *MUTYH-associated polyposis*). Carriers typically do not show symptoms but can pass the mutation to children. Examples of autosomal recessive cancer disease are: Fanconi anemia [88], Bloom syndrome [89], Werner Syndrome [90] and ataxia telangiectasia [91].

4.3. X-Linked Hereditary Cancer

X-linked inheritance is rare in hereditary cancer syndromes. Mutations in X-linked genes are transmitted through the maternal line and typically affect males more severely due to the presence of a single X chromosome. One example is Wiskott–Aldrich syndrome (WAS), a rare immunodeficiency disorder associated with an increased risk of malignancies. WAS is caused by mutations in the WAS gene located on the short arm of the X chromosome (Xp11.23) [92]. Another example of X-linked hereditary cancer is Lymphoproliferative Syndrome Type 1 associated with Burkitt lymphoma [93] **.**

4.4. Mitochondrial Inheritance (Maternal Inheritance)

Mitochondrial inheritance refers to the maternal transmission of mitochondrial DNA (mtDNA), which can affect both sexes but is passed on only by females. Mutations in mtDNA have been linked to several cancers—including breast, colorectal, ovarian, and lung cancer—by disrupting energy metabolism and promoting tumor growth. While some evidence suggests that maternally inherited mtDNA mutations may increase cancer risk, the relationship remains complex and involves interactions with nuclear genes [94–97] .

5. General Recommendations for Cancer Genetic Testing in the Community

Recommendations for **genetic testing for cancer predisposition** in the general population vary based on **risk factors**, **population background**, and **family history**. While **universal genetic testing**

 doi:10.20944/preprints202511.2088.v1

is not yet standard for everyone, guidelines **strongly recommend testing** for people with **personal or familial risk factors** — and in some cases, for specific populations even without a family history. The most common hereditary syndromes and the suggested genetic tests are summarized in Table 3.

Table 3. Key Conditions for Hereditary Cancer Testing.

Syndrome	Common Genes	Associated Cancers
Hereditary Breast & Ovarian Cancer (HBOC)	BRCA1, BRCA2	Breast, ovarian, prostate, pancreas
ndrome	MLH1, MSH2, MSH6, PMS2, EPCAM	Colorectal, endometrial, ovarian, gastric
Li-Fraumeni Syndrome	TP53	Sarcomas, brain, breast, adrenal
Cowden Syndrome	PTEN	Breast, thyroid, endometrial
Familial Adenomatous Polyposis (FAP)	APC	Colorectal (hundreds of polyps)
MUTYH-Associated Polyposis	MUTYH	Colorectal polyps/cancer

6. Concluding Remarks

Hereditary cancers represent a significant portion of cancer cases, driven by inherited mutations in specific genes that regulate essential cellular processes such as growth, division, repair, and apoptosis. Understanding the genetic basis of these cancers is crucial, as it not only enhances our knowledge of cancer biology but also enables earlier detection, more effective prevention, and personalized treatment strategies. Mutations in tumor suppressor genes or oncogenes, along with epigenetic alterations, contribute to the initiation and progression of cancer in genetically predisposed individuals. Familial cancers follow various inheritance patterns, each with unique characteristics, which underscores the complexity of hereditary cancer risk. Identifying Genetic Changes in families enables genetic counseling that plays an essential role in managing hereditary cancer risk. It provides individuals and families with vital information about their genetic predisposition, guiding them through informed decision-making regarding testing, surveillance, and preventive measures. By identifying genetic mutations early, individuals can take proactive steps to reduce their cancer risk, undergo regular screenings, and consider preventive treatments, ultimately improving outcomes and quality of life.

Despite the progress in understanding the genetic and epigenetic factors involved in hereditary cancers, much remains to be learned. Ongoing research into genetic mutations, epigenetic modifications, and the molecular mechanisms underlying these cancers will continue to shape future diagnostic, therapeutic, and preventive approaches.

In conclusion, hereditary cancer risk is driven by a complex interplay of high-penetrance mutations, moderate-risk genes, and polygenic factors. While significant progress has been made in identifying key genetic contributors to familial cancer syndromes, many challenges remain. Future research should focus on integrating next-generation sequencing technologies into routine clinical practice to enable earlier and more accurate identification of at-risk individuals. Moreover, the use of polygenic risk scores may offer a more nuanced understanding of cancer susceptibility, especially in individuals without strong family histories. Advances in gene editing, epigenetics, and AI-driven risk modelling, also hold promise for improving prevention and personalized treatment strategies. Continued efforts in patient education, genetic counselling, and ethical frameworks will be critical as the field evolves.

Funding: No funding has been provided.

 doi:10.20944/preprints202511.2088.v1

Acknowledgments: The author would like to thank Fuad Fares from the Department of Human Biology, University of Haifa for reviewing the article.

Conflicts of Interest: The author confirms that there are no actual or potential conflicts of interest related to this work. All authors are disclosing any actual or potential conflict of interest including any financial, personal, or other relationships with other people or organizations.

References

1. Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, et al. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021. *J Natl Compr Canc Netw* **2021**;19:77–102. doi: 10.6004/jnccn.2021.0001
2. RC, Selander I, Connor AA, Selvarajah S, Borgida A, Briollais L. et al. Prevalence of Germline Mutations in Cancer Predisposition Genes in Patients With Pancreatic Cancer. *Gastroenterology* **2015**; 148: 556-564. doi: 10.1053/j.gastro.2014.11.042
3. Tung N , Lin NU, Kidd J, Allen BA, Singh N, Wenstrup RJ, *et al*. Frequency of Germline Mutations in 25 Cancer Susceptibility Genes in a Sequential Series of Patients With Breast Cancer. *J Clin Oncol* **2016**;34:1460-8. doi: 10.1200/JCO.2015.65.0747.
4. Pourmasoumi P, Ali Moradi A, Bayat M. BRCA1/2 mutations and breast/ovarian cancer risk: A new insights review. Gynecol Onvol 2024; 31:3624-3634. https://doi.org/10.1007/s43032-024-01666-w
5. Lakeman IMM, Broek AJ, Vos JAM, Barnes DRB, Adlard J, Andrulis IL,*et al*. The predictive ability of the 313 variant–based polygenic risk score for contralateral breast cancer risk prediction in women of European ancestry with a heterozygous *BRCA1* or *BRCA2* pathogenic variant. *Genet Med* **2021**;23: 1726–1737. https://doi.org/10.1038/s41436-021-01198-7
6. Li H, Engel C, Hoya M, Peterlongo P, Yannoukakos D, Livragh L, *et al*. Risks of breast and ovarian **cancer** for women harboring pathogenic missense variants in *BRCA1* and *BRCA2* compared with those harboring protein truncating variants. *Genet Med* **2022**;24:119–129. https://doi.org/10.1016/j.gim.2021.08.016
7. Raghallaigh ON, Eeles R. Genetic predisposition to prastate cancer: an update. *Familial Cancer* **2022**; 21:101–114. https://doi.org/10.1007/s10689-021-00227-3
8. Rajwa P, Quhal F, Pradere B, Gandaglia G, Ploussard G, Leapman MS, et al. Prostate cancer risk, screening and management in patients with germline *BRCA1/2* mutations. *Nature Reviews Urology* **2023**;20:205–216. https://doi.org/10.1038/s41585-022-00680-4
9. Yang W, Ding P-R. Update on Familial Adenomatous Polyposis-Associated Desmoid Tumors. *Clin Colon Rectal Surg* **2023**;36:400-405. DOI: 10.1055/s-0043-1767709
10. Win AK, Dowty JG, Reece JC, Lee G, Templeton AS, Plazzer J-P, *et al*. Variation in the Risk of Colorectal Cancer for Lynch Syndrome: A retrospective family cohort study. *Lancet Oncol* **2021**; 22:1014–1022. doi: 10.1016/S1470-2045(21)00189-3
11. Stephanie A Cohen SA, Leininger A. The genetic basis of Lynch syndrome and its implications for clinical practice and risk management. *The Application of Clinical Genetics* **2014;** 7: 147–158. https://doi.org/10.2147/TACG.S51483
12. Yang X, Karapetyan L, Huang Z, Knight AD, Rajendran S, Sander C, *et al*. Multiple primary melanoma in association with other personal and familial cancers. *Cancer Med* 2023;12: 2474–2483. doi: 10.1002/cam4.5088
13. Angelina T. Regua AT, Najjar M, Lo H-W. RET signaling pathway and RET inhibitors in human cancer. *Front. Oncol* **2022**;12 – 2022. https://doi.org/10.3389/fonc.2022.932353
14. Azzam N, Bar-Shalom RB, Saab A, Fares F. Germline Polymorphisms on RET Proto-oncogene involved in Medullary Thyroid Carcinoma in a Druze Family –A case study. *European Journal of Cancer* **2017**;82:149-152. doi: 10.1016/j.ejca.2017.06.007
15. Mocci E, Milne RL, Méndez-Villamil EY, Hopper JL, John EM, Andrulis IL, *et al*. Risk of Pancreatic Cancer in Breast Cancer Families from the Breast Cancer Family Registry. *Cancer Epidemiol Biomarkers Prev* **2013**;22: 803–811. https://doi.org/10.1158/1055-9965.EPI-12-0195
16. Vasen HFA, Canto MI, Goggins M. Twenty-five years of surveillance for familial and hereditary pancreatic ductal adenocarcinoma: Historical perspectives and introduction to the special issue. 21. *Fam Cancer*. 2024;23:209–215. doi: 10.1007/s10689-024-00404-0

 doi:10.20944/preprints202511.2088.v1

17. Schubert SA, Ruano D, Joruiz SM, Stroosma J, Glavak N, Montali A, *et al*. Germline variant affecting p53β isoforms predisposes to familial cancer. *Nat Commun* **2024**;18:15:8208. doi: 10.1038/s41467-024-52551-8
18. Palles C, Cazier JB, Howarth KM, Domingo E, AJones AM, Broderick P, *et al*. Germline mutations afecting the proofreading domains of POLE and POLD1 predispose to colorectal adenomas and carcinomas. *Nat Genet* **2013**;45:136–144. doi:10.1038/ng.2503
19. Zhu L-H, Dong J, Li W-L, Kou Z-Y, Yang J. Genotype–Phenotype Correlations in Autosomal Dominant and Recessive *APC* Mutation-Negative Colorectal Adenomatous Polyposis. *Dig Dis Sci* **2023**;68:2799–2810. doi: 10.1007/s10620-023-07890-9
20. Renella R, Gagne K, Beauchamp E, Fogel J, Perlov A, Sola M, *et al*. Congenital X-linked Neutropenia with Myelodysplasia and Somatic Tetraploidy due to a Germline Mutation in SEPT6. *Am J Hematol* **2023**;97:18-29. doi: 10.1002/ajh.26382
21. Imyanitov EN, Kuligina ES, Sokolenko AP, Suspitsin EN, Yanus GA, Iyevleva AG, *et al*. *World J Clin Oncol* **2023**;14: 40-68. doi: 10.5306/wjco.v14.i2.40
22. Aryanti C, Uwuratuw JA, Labeda I, Raharjo W, Lusikooy RE, Rauf MA, *et al*. The Mutation Portraits of Oncogenes and Tumor Supressor Genes in Predicting the Overall Survival in Pancreatic Cancer: A Bayesian Network Meta-Analysis. *Asian Pac J Cancer Prev* **2023**;24: 2895–2902. doi: 10.31557/APJCP.2023.24.8.2895
23. D'Orazi G. p53 Function and Dysfunction in Human Health and Diseases. *Biomolecules* **2023**; *13*:506. https://doi.org/10.3390/biom13030506
24. Ngeow J, Eng C. PTEN in Hereditary and Sporadic Cancer. *Cold Spring Harb Perspect Med* **2020**;10: a036087. doi: 10.1101/cshperspect.a036087
25. Hodgson SV, Foulkes WD, Maher ER, ClareTurnbull C. Inherited Susceptibility to Cancer: Past, Present and Future. *Annals of HumanGenetics*, **2025**; 89:354–36. https://doi.org/10.1111/ahg.70013
26. Kanai Y. Molecular pathological approach to **cancer epigenomics** and its clinical application. *Pathol Int* **2024**;74:167–186. doi: 10.1111/pin.13418
27. Gu M, Ren B, Fang Y, Ren J, Liu X, Wang X, *et al*. Epigenetic regulation in cancer. *Med Comm* **2024**; e495. doi: 10.1002/mco2.495
28. Lu C, Xie M, Wendl MC, Wang J, McLellan MD, Leiserson MDM, *et al*. Patterns and functional implications of rare germline variants across 12 cancer types. *Nature Communications* **2015**;6:10086 DOI: 10.1038/ncomms10086
29. Li S, Silvestri V, Leslie G, Rebbeck TR, Neuhausen SL, Hopper JL, *et al*. Cancer Risks Associated With *BRCA1* and *BRCA2* Pathogenic Variants. *J Cilin Oncol* **2022**;40:1529-1541 https://doi.org/10.1200/JCO.21.021
30. Narod, SA, Foulkes WD (2004). "BRCA1 and BRCA2: 1994 and beyond." *Nature Reviews Cancer* **2004**; 4: 814-819. DOI.10.1038/nrc1431
31. Al-Shamsi HO, Alwbari A, Azribi F, Calaud F, Thuruthel S, Tirmazy SHH, *et al*. RCA testing and management of BRCA-mutated early-stage breast cancer: a comprehensive statement by expert group from GCC region. *Front Oncol* **2024**;14:1358982. doi: 10.3389/fonc.2024.1358982
32. Miki Y, Swensen J, Shattuck-Eidens D, Futreal PA, Harshman K, Tavtigian S, Liu Q. A Strong Candidate for the Breast and Ovarian Cancer Susceptibility Gene *BRCA1*. *Science* **1994;**266**:**66-7. doi: 10.1126/science.7545954
33. Antoniou A, Pharoah PDP, Narod S, Risch HA, Eyfjord JE, Hopper JL, *et al*. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: a combined analysis of 22 studies. *The American Journal of Human Genetics*, **2003**;72:1117–1130. DOI: 10.1086/375033
34. Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for *BRCA1* and *BRCA2* Mutation Carriers. *JAMA*. **2017**;317:2402-2416. doi:10.1001/jama.2017.7112
35. Mavaddat N, Peock S, Frost D, Ellis S, Platte R, Fineberg E, et al. Cancer Risks for *BRCA1* and *BRCA2* Mutation Carriers: Results From Prospective Analysis of EMBRACE. *J Nat Can Inst* **2013**;105. https://doi.org/10.1093/jnci/djt095
36. Tai YC, Domchek S, Parmigiani G, Chen S. Breast Cancer Risk Among Male BRCA1 and BRCA2 Mutation Carriers. *J Nat Can Inst* **2007**; 99. https://doi.org/10.1093/jnci/djm203

37. Mastrodomenico L, Piombino C, Riccò B, Barbieri E, Venturelli M, Federico Piacentini F, Dominici M, Cortesi L, Toss A. Personalized Systemic Therapies in Hereditary Cancer Syndromes. *Genes (Basel)*;**2023**:14:684. doi: 10.3390/genes14030684
38. Odemis DA, Kebudi R, Bayramova J, Erciyas SK, Turkcan GK, Tuncer SB, *et al*. *RB1* gene mutations and genetic spectrum in retinoblastoma cases. *Medicine (Baltimore)* **2023**;102: e35068. doi: 10.1097/MD.0000000000035068
39. Wang T, Fu J, Huang Y, Fu C. Mechanism of **APC** truncation involved in colorectal cancer tumorigenesis (Review) *Oncol Lett*. **2025**;29:2. doi: 10.3892/ol.2024.14748
40. Groden J, Thliveris A, Samowitz W, Carlson M, Gelbert L, Albertsen H, Joslyn G, J Stevens J. et al. *Cell* **1991**; 66: 3589-600. DOI: 10.1016/0092-8674(81)90021-0
41. Aelvoet S, Buttitta F, Ricciardiello L, Dekker E. Management of familial adenomatous polyposis and MUTYH-associated polyposis; new insights. *Best Practice & Research Clinical Gastroenterology* **2022**;58–59:101793. https://doi.org/10.1016/j.bpg.2022.101793
42. Kayhanian H, Cross W, van der Horst SEM, Barmpoutis P, Lakatos E, Caravagna G, Zapata L, et al. Homopolymer switches mediate adaptive mutability in mismatch repair-deficient colorectal cancer. *Nat Genet*, **2024** ;56:1420-1433. doi: 10.1038/s41588-024-01777-9
43. Lindner AK, Schachtner G, Tulchiner G, Thurnher M, Untergasser G, Obrist, et al. Lynch Syndrome: Its Impact on Urothelial Carcinoma. *Int J Mol Sci.* **2021**;22:531. doi: 10.3390/ijms22020531
44. Li GM. Mechanisms and functions of DNA mismatch repair. *Cell Res.* **2008**;18:85–98. https://doi.org/10.1038/cr.2008.1
45. Jiricny J. The multifaceted mismatch-repair system. *Nat Rev Mol Cell Biol.* **2006**;7:335–346. https://doi.org/10.1038/nrm1907
46. Campos FG, Bustamante-Lopez LA, D'Albuquerque LAC, Ribeiro Junior U, Herman P, Martinez CAR. A review to honor the historical contribution of pauline gross, Aldred Warthin and Henry Lynch in the description and recognition of inheritance in colorectal cancer. *Arq Bras Cir Dig*. **2024** Jul 1;37:e1812. doi: 10.1590/0102-6720202400019e1812.
47. Hollander MC, Blumenthal GM, Dennis PA. PTEN loss in the continuum of common cancers, rare syndromes and mouse models. *Nat Rev Cancer* **2011**;11:289-301. doi:10.1038/nrc3037
48. Liu A, Zhu Y, Chen W, Merlino G, Yu Y. PTEN Dual Lipid- and Protein-Phosphatase Function in Tumor Progression. *Cancers (Basel)* **2022**;14: 3666. doi: 10.3390/cancers14153666
49. Zhang P, Kitchen-Smith I, Xiong L, Stracquadanio G, Brown K, Richter PH, et al. Germline and Somatic Genetic Variants in the p53 Pathway Interact to Affect Cancer Risk, Progression, and Drug Response. *Cancer Res* 2021;81:1667–1680. https://doi.org/10.1158/0008-5472.CAN-20-0177
50. Liu Y, Su Z, Tavana O, Gu W. Understanding the complexity of **p53** in a new era of tumor suppression. *Cancer Cell* **2024**;42: 946–967. DOI: 10.1016/j.ccell.2024.04.009
51. Ghatak D, Ghosh DD, Roychoudhury S. Cancer Stemness: p53 at the Wheel *Front Oncol* **2021**;10:604124. https://doi.org/10.3389/fonc.2020.604124
52. Gabriella D'Orazi G. p53 Function and Dysfunction in Human Health and Diseases. *Biomolecules* **2023**;*13*:506. https://doi.org/10.3390/biom13030506
53. Baumont AC, Cadore NA, Pedrotti LG, Curzel GD, Schuch JB, Marina Bessel M, et al. Germline rare variants in HER2-positive breast cancer predisposition: a systematic review and meta-analysis. *Front Oncol* 2024;14:1395970. doi: 10.3389/fonc.2024.1395970
54. Kang S, Kim SB. HER2-Low Breast Cancer: Now and in the Future. *Cancer Res Treat* **2024**;56: 700–720. doi: 10.4143/crt.2023.1138
55. Mahar F, Haider G, Priyanka, Zahoor S. Correlation between grade of the tumour and HER2NEU status in breast cancer. *The professional Medical Journal* **2025**;32. https://doi.org/10.29309/TPMJ/2025.32.01.8399
56. Dunnett-Kane V, Burkitt-Wright E, Blackhall FH, Malliri A, Evans DG, Lindsay CR. Germline and sporadic cancers driven by the RAS pathway: parallels and contrasts. *Ann Oncol* **2020**;3:873–883. doi: 10.1016/j.annonc.2020.03.291
57. Fernández-Medarde AF, Rivas JDL, Santos E. 40 Years of RAS—A Historic Overview. *Genes (Basel)* **2021**; 12:681. doi: 10.3390/genes12050681

 doi:10.20944/preprints202511.2088.v1

58. Chen K, Zhang Y, Qian L, Wang P. Emerging strategies to target RAS signaling in human cancer therapy. *Journal of Hematology & Oncology* **2021**;14:116. https://doi.org/10.1186/s13045-021-01127-w
59. Jafry M, Sidbury R. **RASopathies**. *Clin Dermatol* 2020;38:455-461. doi: 10.1016/j.clindermatol.2020.03.010.
60. Dunnett-Kane V, Burkitt-Wright E, Blackhall FH, Malliri A, Evans DG, Lindsay CR. Germline and sporadic cancers driven by the RAS pathway: parallels and contrasts. Ann Oncol 2020;31:873-883. doi: 10.1016/j.annonc.2020.03.291.
61. Freie B, Carroll PA, Varnum-Finney BJ, Ramsey EL, Ramani V, Bernstein I, Eisenman RN. A germline point mutation in the MYC-FBW7 phosphodegron initiates hematopoietic malignancies. *Genes Dev* **2024**; 38:253–272. doi:10.1101/gad.351292.123
62. Dang CV. MYC on the path to cancer." *Cell* 2012;149:22-35. doi:10.1016/j.cell.2012.03.003.
63. Nadeu F, Garcia N, Wang L, Verdú-Amorós J, Andrés M, Conde N, *et al*. *MYC*-rearranged mature B-cell lymphomas in children and young adults are molecularly Burkitt Lymphoma. *Blood Cancer Journal* **2024**;14: 171. https://doi.org/10.1038/s41408-024-01153-0
64. Hidaka M, Inokuchi K, Uoshima N, Takahashi N, Yoshida N, Ota S, et al. Development and evaluation of a rapid one-step high sensitivity real-time quantitative PCR system for minor *BCR-ABL* (e1a2) test in Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). *Jpn J Clin Oncol* **2024**;54:153–159. doi: 10.1093/jjco/hyad156
65. Soverini S, Hochhaus A, Nicolini FE, Gruber F, Lange T, Saglio G, et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. *Blood* 2011;118: 1208–1215. https://doi.org/10.1182/blood-2010-12-326405
66. Nicolella HD, de Assis S. Epigenetic Inheritance: Intergenerational Effects of Pesticides and Other Endocrine Disruptors on Cancer Development. *Int J Mol Sci* **2022**;23:4671. doi: 10.3390/ijms23094671
67. Lonning PE, Nikolaienko O, Pan K, Kurian AW, Eikesdal HPP, Pettinger M, et al. Constitutional *BRCA1* methylation and risk of incident triple-negative breast cancer and high-grade serous ovarian cancer. *Journal of Clinical Oncology*, **2025;** 40;16 suppl. https://doi.org/10.1200/JCO.2022.40.16_suppl.10509
68. Hitchins MP. Constitutional epimutation as a mechanism for cancer causality and heritability? *Nature Reviews Cancer* **2015**;15:625–634. https://www.nature.com/articles/nrc4001
69. Koch A, Joosten SC, Feng Z, de Ruijter TC, Draht MX, Melotte V, etal. Analysis of DNA methylation in cancer: location revisited. Nat Rev Clin Oncol **2018**;15:459-466. doi: 10.1038/s41571-018-0004-4
70. Costa FF. Epigenomics in cancer management. *Cancer Manag Res* **2010**; 2:255–265. doi: 10.2147/CMR.S7280
71. Sherif ZA, Ogunwobi OO, Ressom HW. Mechanisms and technologies in cancer epigenetics. *Front Oncol.* **2024**;14:1513654. doi: 10.3389/fonc.2024.1513654
72. Helderman NC, Andini KD, van Leerdam ME, van Wezel T, Morreau H, Nielsen M, et al. *MLH1* Promotor Hypermethylation in Colorectal and Endometrial Carcinomas from Patients with Lynch Syndrome. *J Mol Diagnosis* **2024**;26:P106-114. https://doi.org/10.1016/j.jmoldx.2023.10.005
73. Younesian S, Mohammadi MH, Younesian O, Momeny M, Ghaffari SH, Bashash D. DNA methylation in human diseases. *Heliyon* **2024**;15:e32366. doi: 10.1016/j.heliyon.2024.e3236
74. Martisova A, Holcakova J, Izadi N, Sebuyoya R, Hrstka R, Martin Bartosik M. DNA Methylation in Solid Tumors: Functions and Methods of Detection *Int J Mol Sci* **2021**; 228: 4247. doi: 10.3390/ijms22084247
75. Voss TC, Hager GL. Dynamic regulation of transcriptional states by chromatin and transcription factors. *Nat Rev Genet* **2014**;152: 69–81.doi: 10.1038/nrg3623
76. Chris P. Ponting, Peter L. Oliver, Wolf Reik. Evolution and Functions of Long Noncoding RNAs. *Cell* **2009**;136: 629–641, February 20, 2009. DOI 10.1016/j.cell.2009.02.006
77. Lauria F, Iacomino G. The landscape of circulating miRNAs in the post-genomic era. *Genes* **2021**;13: 94. https://doi.org/10.3390/genes13010094
78. Lin S, Gregory RI. MicroRNA biogenesis pathways in cancer. *Nature Reviews Cancer* **2015**;15:321–333. https://doi.org/10.1038/nrc3932
79. Ponting CP, Oliver PL, Reik W. Evolution and functions of long noncoding RNAs. *Cell* **2009**;1364:629-641.DOI 10.1016/j.cell.2009.02.006

 doi:10.20944/preprints202511.2088.v1

80. Gupta RA, Shah N, Wang KC, Kim J, Horlings HM, Wong DJ, Tsai MC, T Hung T, Argani P *et al*…Long non-coding RNA *HOTAIR* reprograms chromatin state to promote cancer metastasis. *Nature* **464**:1071–1076. doi:10.1038/nature08975
81. Wang X, Li H, Lu Y, Cheng L. -Circular RNAs in human cancer. *Frontiers in oncology* **2021**;10. https://doi.org/10.3389/fonc.2020.577118
82. Hansen TB, Jensen TI, Clausen BH, Bramsen JB, Finsen B, Damgaard CK, Kjems J. Natural RNA circles function as efficient microRNA sponges. *Nature* **2013;**495:384–388. doi:10.1038/nature11993
83. Liang J, Wen J, Huang Z, Chen X, Zhang B and Chu L. Small Nucleolar RNAs: Insight Into Their Function in Cancer. *Front. Oncol*. **2019**;9:587. https://doi.org/10.3389/fonc.2019.00587
84. Hussen BM, Hidayat HJ, Salihi A, Sabir D, Taheri M, Ghafouri-Fard S. MicroRNA: A signature for cancer progression. *Biomedicine & Pharmacotherapy* **2021**;138:111528. https://doi.org/10.1016/j.biopha.2021.111528
85. Kabbage M, Ben Aissa-Haj J, Othman H, Jaballah-Gabteni A, Laarayedh S, Elouej S, Medhioub M. et al. A Rare MSH2 Variant as a Candidate Marker for Lynch Syndrome II Screening in Tunisia: A Case of Diffuse Gastric Carcinoma. *Genes (Basel)* **2022**;13:1355. doi: 10.3390/genes13081355.
86. Garutti M, Foffano L, Mazzeo R, Michelotti A, Da Ros L, Viel A, et al. Hereditary Cancer Syndromes: A Comprehensive Review with a Visual Tool. *Genes (Basel)* **2023**;14:1025. doi: 10.3390/genes14051025.
87. Jackson L, Weedon MN, Harrison JW, Wood AR, Ruth KS, Tyrrell J, et al. Influence of family history on penetrance of hereditary cancers in a population setting. EClinicalMedicine **2023**; 64:102159. doi:10.1016/j.eclinm.2023.102159.
88. Alter BP, Cancer in Fanconi anemia, 1927-2001. Cancer 2003; 97:425-440 https://doi.org/10.1002/cncr.11046
89. Muralidharan M, Muthupandian S, Dejene TA. Bloom syndrome: an oral potentially malignant disorders aiding in malignancy vigour. *Int J Surg*. **2023**;109:529-530. doi: 10.1097/JS9.0000000000000009.
90. Tsuge K, Shimamoto A. Research on Werner Syndrome: Trends from Past to Present and Future Prospects. *Genes (Basel)*. **2022**;13:1802. doi: 10.3390/genes13101802.
91. Lee J.-H., Paull T.T. Cellular Functions of the Protein Kinase ATM and Their Relevance to Human Disease. *Nat. Rev. Mol. Cell Biol.* **2021**;22:796–814. doi: 10.1038/s41580-021-00394-2.
92. Sun Y, Song X, Pan H, Li X, Sun L, Song L, et al. Wiskott-Aldrich syndrome: A new synonym mutation in the WAS gene. *Intractable Rare Dis Res* **2024**; 13:69-72. doi: 10.5582/irdr.2023.01102
93. Xue K, Zhang A, Yan X, Liu S, Chen D. Primary central nervous system Burkitt lymphoma in a 38-year-old immunocompetent woman: A case report. Medicine (Baltimore) **2025**; 104:e42321. doi: 10.1097/MD.0000000000042321
94. Alston CL, Stenton SL, Hudson G, Prokisch H, Taylor RW. The genetics of mitochondrial disease: dissecting mitochondrial pathology using multi-omic pipelines. *Journal of Pathology* **2021**;254: 430–442. https://doi.org/10.1002/path.5641
95. Wallace DC. Mitochondria and cancer. *Nature Reviews Cancer* **2012**;12:685–698. doi:10.1038/nrc3365
96. Martínez-Reyes I & Chandel NS. Cancer metabolism: looking forward. *Nature Reviews Cancer* **2021;21**:669–680. https://doi.org/10.1038/s41568-021-00378-6
97. Kim M, Mahmood M, Reznik E, Gammage PA. Mitochondrial DNA is a major source of driver mutations in cancer. *Trends in Cancer* **2022**;8:1046-1059. https://doi.org/10.1016/j.trecan.2022.08.001