Lynch Syndrome, Hereditary Non-Polyposis Colorectal Cancer, is an Autosomal Dominant Disorder that is Caused by a Germline Mutation

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Abstract— **Lynch syndrome, which is now recognized as the most common hereditary colorectal cancer condition, is characterized by the predisposition to a spectrum of cancers, primarily colorectal cancer, and endometrial cancer, also known as hereditary nonpolyposis colorectal cancer (HNPCC). Lynch syndrome caused by a heterozygous germline pathogenic variant in MLH1, MSH2, MSH6, or PMS2 or by an EPCAM deletion is inherited in an autosomal dominant manner. Each case belongs to a family with clinical needs that require genetic counseling, DNA testing for mismatch repair genes (most frequently MLH1 or MSH2), and screening for colorectal cancer (CRC). this kind of mutation leads to a higher risk of developing cancer tissue at an early age. The management options differ according to the type of cancer, but it's narrowed in immunotherapy, surgery, and chemotherapy. Few studies recommended using aspirin as it significantly can reduce the risk of overall cancer, especially gastrointestinal tract tumors. Regular aspirin use may prevent a substantial proportion of colorectal cancers and complement the benefits of screening. Regular screening for CRC should be advised for Lynch Syndrome mutation carriers as early diagnoses can be useful in the treatment stage.**

Keywords— Bioinformatics, Lynch Syndrome, Cancer, Germline Mutation, Inheritance Disease, HNPCC.

I. Introduction

Lynch syndrome is a genetic condition transmitted from the parents' generation to children. Cells grow and form new cells, producing copies of their DNA, and copies may contain errors. People with this syndrome do not have their match repair genes working, so if an error occurs in the DNA that cannot be repaired and gets out of control, causing cancer cells. Common symptoms of lynch syndrome are benign colon polyps and polyps that may develop into malignant tumors, fatigue, abnormal weight loss, abdominal and stomach pain, constipation, diarrhea, blood in the stool, bleeding within the gut, and anemia. Typically, patients with Lynch syndrome develop rectal and colon cancer so surgery is the first step by removing the polyps and any presence of cancer and Colectomy with Ileorectostomy. The world is filled with everything that is polluted and dangerous and threatens human health. The risk of developing cancers and genetic mutations resulting from a genetic factor. This harm is not limited to the parents but extends to the children and transcends the generations. This may result in a weak, sick, and threatened generation with the most dangerous diseases, but the world is now seeking to do more research and examinations to prevent or predict the incidence of cancer and to identify mutations, the extent of their damage, their causes, and the attempt to treat them.

One of the most dangerous types of genetic mutations (Germline mutation) occurs in a sperm cell or an egg and is transmitted from the father to the son directly during pregnancy when the fetus grows into a child, and because the mutation affects the reproductive cells, so it is transmitted from generation to generation(fig. 1), This mutation causes a dangerous type of syndrome called Lynch syndrome, which is a genetic disorder that increases the risk of many types of cancer, especially colon cancer and endometrial cancer, Lynch Syndrome is also known as hereditary non-polyposis colorectal cancer (HNPCC). People who have Lynch syndrome have a significantly increased risk of developing colorectal cancer. There is also an increased risk of developing other types of cancers, such as endometrial (uterine), gastric (stomach), ovarian, small bowel (small intestines), pancreatic, prostate, urinary tract, kidney, bile duct, and brain cancers.

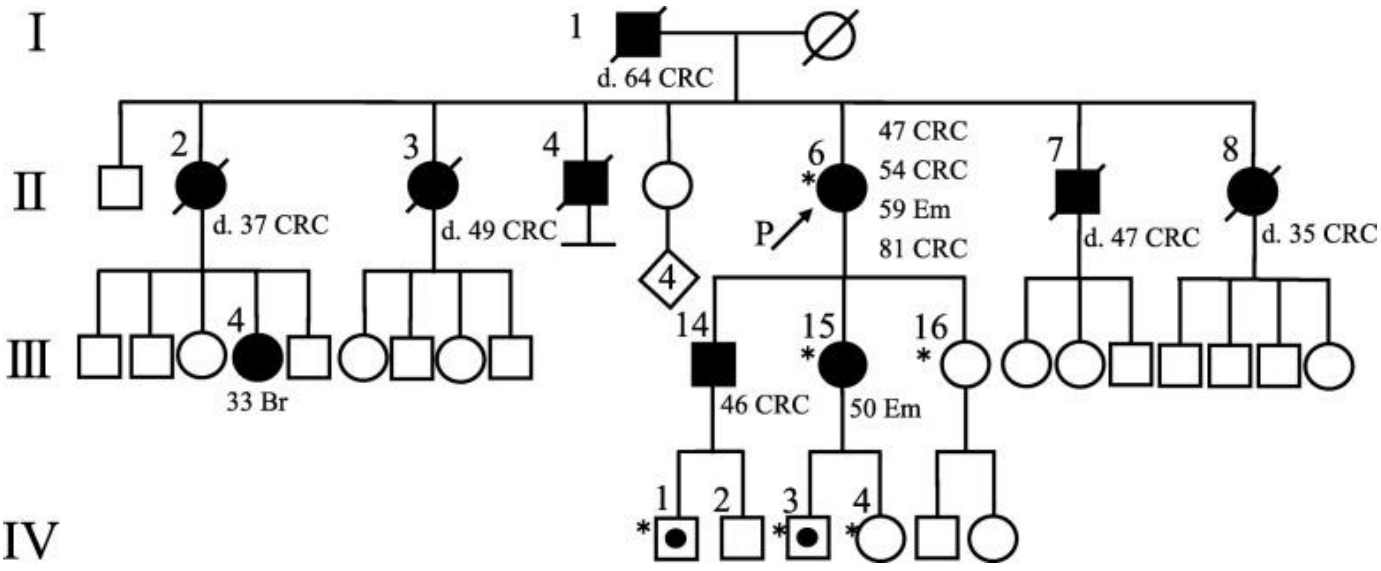

Fig 1. Family pedigree. The reconstructed pedigree shows that the proband (II-6), her son's son (VI-1), her daughter (III-15), and her daughter's son (IV-3) share the mutation. I-1 T-colon cancer. II-2 A-colon cancer. II-3 T-colon cancer. II-4 primary cancer unknown, age unknown. II-6 rectal cancer, sigmoid cancer, endometrial cancer, and rectal cancer. II-7 A-colon cancer. II-8 caecal cancer. III-4 breast cancer. III-14 A-colon cancer and sigmoid cancer. III-15 Endometrial cancer. II-6, III-15, III-16, IV-1, IV-3 and IV-4 underwent genetic testing. IV-1 and IV-3 were found to be mutation carriers. Squares denote male family members, circles denote female family members, solid symbols show individuals affected by cancer, the arrow denotes the proband, a symbol with a slash shows a deceased person with the age at death, and types of primary tumors are listed below the symbols. The solid circle in the square shows a mutation carrier. P: proband, CRC: colorectal cancer, Em: endometrial cancer, Br: breast cancer, *: genetic testing was performed

Why lynch syndrome? Mismatch repair genes are necessary for repairing incorrect pairing of nucleotide bases during DNA replication. If mutations occur in these genes, it causes Lynch syndrome because it results from a germline mutation in one of four mismatch repair (MMR) genes called MLH1, MSH2, MSH6, and PMS2 or loss of expression of MSH2 due to deletion in the EPCAM gene (previously called TACSTD1) have also been found to cause Lynch syndrome.

Lynch syndrome has some features that make doctor suspect and ask for a test Like Developing colorectal cancer at an earlier age compared to normal cases (45 years in Lynch syndrome v. 63 years in normal cases), Having a family history of cancer, especially these cases (Three or more family members, one of whom is a first-degree relative of the other two, are diagnosed with HNPCC-related cancer, two successive affected generations, one or more of the HNPCC-related cancers are diagnosed before age 50 years, exclusion of familial adenomatous polyposis), Higher risk of developing the malignant disease at other places outside the colon: endometrium (40%–60% lifetime risk for female mutation carriers), ovary (12%–15% lifetime risk for female mutation carriers), stomach small bowel hepatobiliary tract, pancreas upper uroepithelial tract, brain, and the increased survival rate from colorectal cancer.

There is no cure for Lynch syndrome yet, after testing If the cancer is initially found to be small, the chance of successful treatment increases but sometimes cancer can be prevented by removing certain organs before they develop into cancer. Fortunately, there are risk management guidelines for carriers of Lynch syndrome that are associated with lower cancer-related deaths. The recommended monitoring for carriers of Lynch syndrome is described as Cancer screening for people with Lynch syndrome. The cancer tests you need depend on your condition. you may have tests to look for Colon Cancer, Endometrial cancer, ovarian cancer (for females), Stomach cancer, Urinary tract cancer, Pancreas cancer, brain cancer, and skin cancer. Reduced risk of other malignancies associated with Lynch syndrome has been reported in carriers of MSH6 and PMS2; Due to limited data, the NCCN does not make recommendations for the management of these other MSH6- and PMS2-related malignancies at this time. Recommendations can be made by the attending physician(s). Despite data indicating an increased risk of pancreatic cancer, effective screening techniques have not been identified; Hence, there are no guidelines this time around.

It should be noted that it is still not clear whether there is an increased risk of breast cancer in individuals with Lynch syndrome; Therefore, breast cancer screening is currently based on personal and family history. The efficacy of non-steroidal anti-inflammatory drugs in individuals with Lynch syndrome is still under investigation. There is data to suggest that aspirin use may reduce the risk of colon cancer in Lynch syndrome, but the optimal dose and duration are still uncertain. A diagnosis of Lynch syndrome in a patient can also be of interest to family members at risk. Patients should be advised to discuss with family members about potential cancer risks and their opportunities for testing, screening, and monitoring. Genetic counseling should be given to family members at risk, and tests carried out if they wish.

II. Background and Problem Definition

According to the Ohio State University Comprehensive Cancer Center in the United States, 145,000 people are diagnosed with colorectal cancer every year. Approximately 3% of colorectal cancers are associated with Lynch Syndrome. This percentage can’t be lightened. Many families suffer from the death of their beloved ones because of cancer and undiagnosed lynch syndrome. This syndrome happens due to a specific deletion of the mismatch repair (MMR) genes. These genes are responsible for repairing the damaged DNA nucleotide bases during the DNA replication process. And because of that, cell growth goes out of control.

Cancer is a disease in which some of the body’s cells grow uncontrollably and spread to other parts of the body. Cancer can start almost anywhere in the human body, which is made up of trillions of cells. Normally, human cells grow and multiply (through a process called cell division) to form new cells as the body needs them. When cells grow old or become damaged, they die, and new cells take their place.

Because of the lack of MMR genes in lynch syndrome mutation carriers, they develop cancer tissue at in early age with a 20% to 80% chance of developing Colorectal cancer, a 1% to 13% chance of developing Stomach cancer, a 1% to 18% chance of developing Urinary tract (renal pelvis, ureter, bladder) cancer, a 1% to 6% chance of developing Small bowel cancer, a 1% to 6% chance of developing Pancreatic cancer, a 1% to 4% chance of developing Hepatobiliary tract cancer (liver/bile duct), a 1% to 3% chance of developing Brain or central nervous system tumor and for women, a 15% to 60% chance of developing Endometrial cancer and a 1% to 38% chance of developing Ovarian cancer. Lynch syndrome patients tend to develop Colorectal cancer and another type of cancer linked with lynch syndrome separately or at the same time.

Lynch syndrome is a genetic disorder resulting from a deletion in one or more of the MMR genes (MLH1, MSH2, MSH6, PMS2, and EPCAM). This means that this condition can be transmitted to the offspring through genetic material. Lynch syndrome follows an autosomal dominant inheritance pattern, in which a mutation needs to happen in only 1 copy of the gene for the person to have an increased risk of getting that disease. Therefore, a child who has a parent with a mutation has a 50% chance of inheriting that mutation. A sibling or parent of a person who has a mutation also has a 50% chance of having the same mutation. To overcome this, people with lynch syndrome mutation have one option. Preimplantation genetic diagnosis (PGD) is a medical procedure done in conjunction with in-vitro fertilization (IVF). It allows people who carry a specific known genetic mutation to reduce the likelihood that their children will inherit the mutation. A person's eggs are removed and fertilized in a laboratory.

Lynch syndrome can be confirmed through a blood or saliva test of someone's inherited DNA. The test can determine if someone carries a mutation that can be passed down (called heritable) in 1 or more of the genes associated with Lynch syndrome. Currently, testing is available for the MLH1, MSH2, MSH6, PMS2, and EPCAM genes. However, not all families with Lynch syndrome will have an identifiable mutation in 1 of these genes. Cancer tissue can also be subjected to screening tests to ascertain the likelihood of Lynch syndrome. The 2 screening tests suggested are microsatellite instability testing (MSI) and immunohistochemistry testing (IHC). The results of these tests can indicate whether more specific genetic testing should be considered.

There is no cure for lynch syndrome, but a few studies refer to immunotherapy as the promising hope for lynch syndrome mutation carriers, and recent trials showed that lynch syndrome patients have a slightly high resistance to the most used chemotherapeutic agents such as 5-FU and cisplatin. In the recent updates of immunotherapy trials, they found out that neoepitopes offer new possibilities to enhance the immune system’s ability to recognize and destroy tumor cells. A clinical trial conducted in Cancer Research UK refers showed that the long-term use of aspirin (600 mg/day, at least 2 years) has been shown to significantly lower CRC risk and extracolonic lynch syndrome-associated tumors. The following figure shows that 60% of those on aspirin and 58% of those on aspirin placebo were treated for 2 years or longer. The HR for those taking aspirin for 2 years or longer was 0·41.[26]

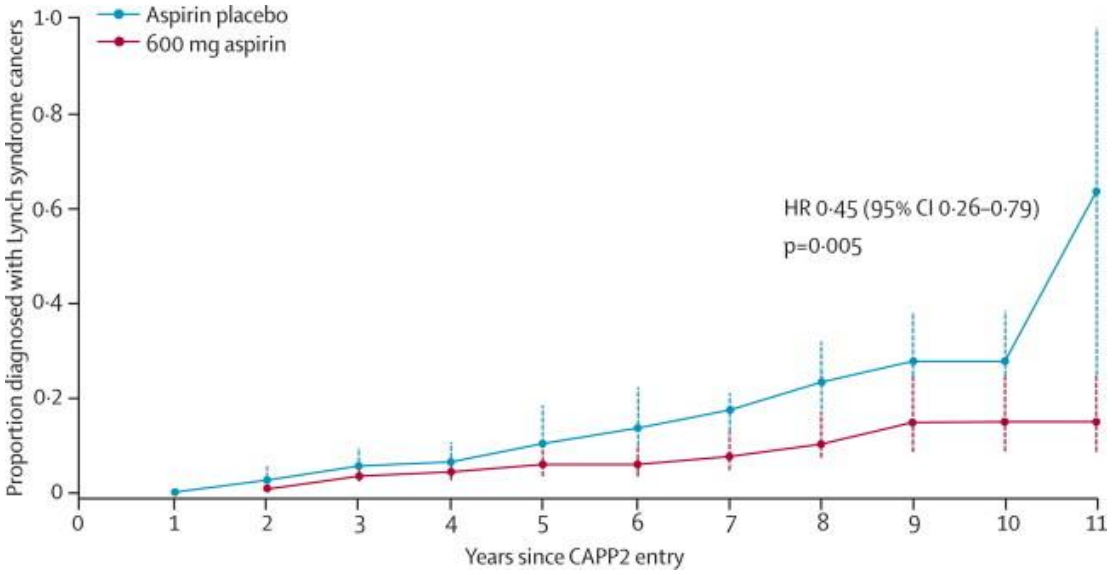

Fig 2. Time to first Lynch syndrome cancer in participants randomly assigned to aspirin compared with those assigned to aspirin placebo

Lynch syndrome is due to inherited changes (mutations) in genes that affect DNA mismatch repair, a process that fixes mistakes made when DNA is copied. These genes (MLHL, MSH2, MSH6, PMS2, and EPCAM) normally protect you from getting certain cancers, but some mutations in these genes prevent them from working properly. Those who have a family history or are at high risk of developing cancer are advised that early identification will significantly speed up treatment and reduce risk.

Research has also shown that treating cancer in its early stages increases success rates by up to 90%. Early medical examinations should be done to ensure prompt treatment if the patient shows signs of Lynch syndrome. Treatment options for that person depend on the patient's overall health, the patient's family, the site where the malignancy has particularly expanded, and his or her particular priorities. The patient's expert doctors will suggest urgent surgery to remove most of the damaged organ if medical tests and examination of his family's medical history find that he has cancer and Lynch syndrome. They also recommend removing the uterus in patients with Lynch syndrome who have been diagnosed with ovarian or uterine cancer to reduce the chance of more serious tumors. Sometimes women protest a hysterectomy or removal of their ovaries. To prevent the development of the disease and satisfy her desire to become a mother, doctors consider chemotherapy or radiation as alternatives. People with Lynch syndrome may benefit from chemotherapy or radiation as well, depending on the stage of the tumor.

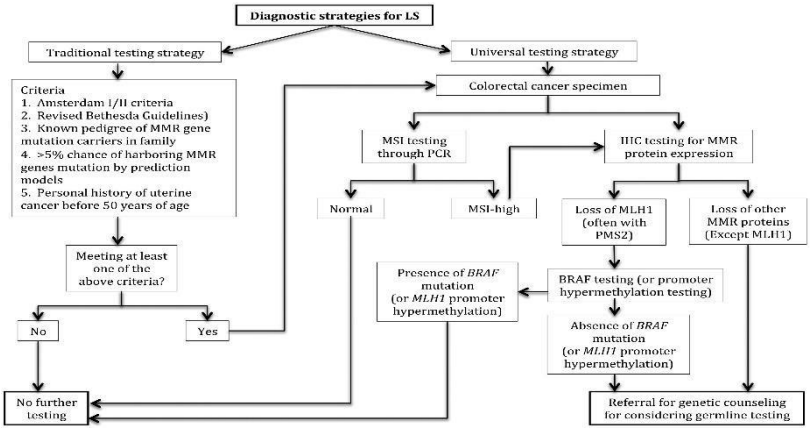

Fig. 3 Diagnostic strategies for LS showing algorithms for traditional and universal testing

The traditional testing strategy is based on pathological clinical criteria, the CRC risk assessment tool, and computational models. These models have been consistently successful in identifying cases of LS. However, up to a quarter of LS cases will be missed even with the most liberal clinical criteria. Similarly, computational models also fall short of expectations and cannot be used clinically reliably. Another less common strategy is molecular testing (polymerase chain reaction, PCR) of CRCs to check for MSI. This is based on the knowledge that over 90% of CRCs in LS are high MSI. Thus, the absence of an MSI has an excellent negative predictive value for LS. So, Colon cancers are most commonly caused by lynch syndrome, and the goal of treating Lynch syndrome is to remove the polyps and any presence of cancer. During the examination, if the doctor found polyps, he or she can remove them during the colonoscopy. Surgery is the best option if there's any indication that these polyps are cancerous. There are multiple surgical options available to deal with colon cancer:

- Total Proctocolectomy with Brooke Ileostomy
- Colectomy with Ileorectostomy
- Restorative Proctocolectomy

There's Chemotherapy as a treatment for colon cancer. Many studies showed resistance to common Chemotherapy agents such as cisplatin and 5-FU and only a few responded to 5-FU. One study reported that oxaliplatin could improve prognosis in stage III colon cancer with MSI-H. Another case reported that dabrafenib alone or combined with trametinib would benefit the therapy of MSI-H BRAF V600E-mutated endometrial adenocarcinoma. More studies are still needed to recommend chemotherapy to treat colon cancer patients with Lynch syndrome. Endometrial cancer prevention, Surgery to remove the uterus is called a hysterectomy. Prevents endometrial cancer. Another option may be the placement of the contraceptive in the uterus. The device, called an intrauterine device (IUD), releases a hormone that reduces the risk of endometrial cancer. Ovarian cancer prevention, Surgery to remove the ovaries is called an oophorectomy. Significantly reduces the risk of ovarian cancer. Another option may be the birth control pill. Research suggests that taking birth control pills for at least 5 years reduces the risk of ovarian cancer.

III. Related Work

Lynch syndrome is a condition that increases the risk of many kinds of cancer. This condition is passed from parents to children. Families that have Lynch syndrome have more instances of cancer than expected. This might include colon cancer, endometrial cancer, and other types of cancer. Lynch syndrome also causes cancers to happen at an earlier age. People with Lynch syndrome may need careful testing to look for cancer when it's small. Treatment is more likely to be successful when the cancer is caught early. Some people with Lynch syndrome might consider treatments to prevent cancer. It used to be called hereditary nonpolyposis colorectal cancer (HNPCC). HNPCC is a term used to describe families with a strong history of colon cancer. Lynch syndrome is the term used when doctors find a gene that runs in the family and causes cancer.[1]
Lynch syndrome is a type of inherited cancer syndrome associated with a genetic predisposition to different cancer types. This means people with Lynch syndrome have a higher risk of certain types of cancer. Lynch Syndrome is also known as hereditary non-polyposis colorectal cancer (HNPCC). Cancer begins when normal cells begin to change and grow out of control, forming a mass called a tumor. A tumor can be benign (non-cancerous) or malignant (cancerous), which means it can spread to other parts of the body. A benign tumor means the tumor can grow but will not spread.[2]
Lynch syndrome, often called hereditary nonpolyposis colorectal cancer (HNPCC), is an inherited disorder that increases the risk of many types of cancer, particularly cancers of the colon (large intestine) and rectum, which are collectively referred to as colorectal cancer. People with Lynch syndrome also have an increased risk of cancers of the stomach, small intestine, liver, gallbladder ducts, urinary tract, brain, and skin. Additionally, women with this disorder have a high risk of cancer of the ovaries and lining of the uterus (endometrial cancer). Women with Lynch syndrome have a higher overall risk of developing cancer than men with the condition because of these cancers of the female reproductive system. In individuals with Lynch syndrome who develop cancer, cancer typically occurs in their forties or fifties. lynch syndrome is among the most common hereditary cancer syndromes. Estimates suggest as many as 1 in every 300 people may be carriers of an alteration in a gene associated with Lynch syndrome. Clues to whether there is Lynch syndrome in a family include diagnoses of colorectal, endometrial, ovarian, and/or other cancers in multiple relatives on the same side of a family. In addition, cancers associated with Lynch syndrome are more likely to be diagnosed at a young age. People with Lynch syndrome are also at an increased risk of developing multiple types of cancers during their lifetime. Lynch syndrome cancer risk is inherited in an autosomal dominant pattern which means one inherited copy of the altered gene in each cell is sufficient to increase cancer risk. It is important to note that people with a variant have an increased risk of cancer; not all people who inherit variants in these genes will develop cancer.[3]

Two standard laboratory tests are available for Lynch syndrome screening of tumor tissue: DNA MSI and MMR protein IHC. These tests can be used independently or together; however, the combination of MSI and IHC maximizes the specificity and sensitivity for Lynch syndrome screening, albeit at a higher individual cost. If either test is positive, germline DNA testing is recommended to make the diagnosis of Lynch syndrome. Immunohistochemistry, IHC for the loss of expression of the MMR proteins can also be performed on CRC tumor tissue to screen for Lynch syndrome. The specific MMR IHC assays that are run vary among institutions. At a minimum, MLH1 and MSH2 expression is evaluated, as pathogenic variants in the MLH1 and MSH2 genes account for approximately 70% of identified Lynch syndrome cases. Recognizing that MLH1/PMS2 and MSH2/MSH6 make heterodimers, some centers additionally test for MSH6 and PMS2 expression, either initially as a set of four stains or secondarily if MLH1 and MSH2 are intact. To reduce costs, some centers take advantage of predictable cellular interactions with a two-stain IHC approach of testing initially for MSH6 and PMS2 expression and then testing for either MLH1 or MSH2 expression only if one of the initial proteins is absent. For completeness of screening, if IHC is used, we recommend testing for all four MMR proteins. IHC has a sensitivity of 83% and specificity of 89% for detecting MSI CRC. Due to cellular interactions, a single germline gene alteration may lead to the loss of one more of the proteins. For example, inactivation of MSH6 leads to loss of MSH6 with or without loss of MSH2. PMS2 loss can secondarily result from either a germline MLH1 pathogenic variant or sporadic MLH1 hypermethylation. As with MSI, if MLH1 alone is absent, BRAF V600E and/or MLH1 promoter hypermethylation testing may be recommended to rule out sporadic CRC before germline testing. Algorithms are available for interpreting different MMR deficiency patterns with or without MSI testing. One purported advantage of MMR IHC was that it may provide a clue for how to narrow confirmatory germline testing. However, in the era of falling costs for high-quality next-generation sequencing (NGS), this is less relevant. In contrast to the poor performance of the clinical Amsterdam criteria, MSI and/or MMR IHC detect more than 90% of Lynch syndrome patients. While MSI and MMR IHC are an improvement over the clinical criteria for Lynch syndrome, true Lynch syndrome cases can still be missed, and the multistep nature of testing can make this process quite cumbersome and sometimes incomplete. This is especially true if follow-up BRAF or MLH1 testing is required. MSI by NGS [e.g., mSINGS and MS sensor] is a further improvement on prior tumor screening

methods with high validity and a comprehensive methodology and may become a clinical standard in the coming years. Furthermore, NGS results highlight not an only deficiency in MMR but also specific pathogenic variants, which is helpful for targeted germline confirmatory sequencing.[4]

Disruptions with EC at an increased risk of LS were identified using clinical criteria such as Amsterdam II (AMSII) or revised Bethesda guidelines, which are dependent on detailed family history.17, 18 These criteria prompt further molecular screening of tumor phenotype using immunohistochemistry (IHC) and microsatellite instability (MSI) testing, in which evidence of a disruption in the MMR pathway indicates possible LS and warrants germline mutation testing. Using these clinical criteria, up to two-thirds of women with LS presenting with EC would not be identified.8, 11 To improve the identification of LS in women with newly diagnosed EC, other strategies have been used, such as IHC or MSI testing in women diagnosed at a young age (<50 years). However, a significant percentage of women with LS develop EC after the age of 50 years,3, 8, 9, and 11 and therefore LS would be missed in these women using this strategy alone. Other strategies, such as the use of EC tumor morphology, have not been evaluated prospectively with germline mutation status.[5]

Lynch syndrome or hereditary nonpolyposis colorectal cancer is an autosomal dominant inherited cancer predisposition underlying approximately 3% of all new cases of colorectal carcinoma (CRC).1 The trait also involves several other cancer types, such as endometrial cancer (EC) and ovarian, gastric, uroepithelial, small bowel, and bile tract carcinomas The predisposition is caused by a mutation in one of several DNA mismatch repair genes, most commonly in MLH1, MSH2, or MSH6.[6]

Lynch syndrome (LS) is caused by an inherited defect in one of the DNA mismatch repairs (MMR) genes (MLH1, MSH2, MSH6, and PMS2) or by an EPCAM deletion. It is characterized by the development of CRC, endometrial cancer, and other malignancies. [7,8]

The function of DNA MMR is to preserve genomic stability, and its dysfunction may result in changes to the number of repetitive sequences in microsatellites, a condition known as microsatellite instability (MSI). Frequently, tumors produced by LS individuals with variants in the MMR genes exhibit a high frequency of MSI (MSI-H). Typically, people with pathogenic variants of each gene frequently run the risk of contracting various cancers. Up to age 75, the cumulative cancer incidences for carriers of the MLH1, MSH2, MSH6, or PMS2 variants were as follows: MLH1: 81% (females), 71.4% (males); MSH2: 84.3% (females), 75.2%(males); MSH6: 61.8% (females), 41.7%(males); and PMS2: 34.1% (both sexes), From age 50, the cumulative cancer incidences of MLH1 or MSH2 variant carriers increase rapidly, and for MSH6 or PMS2 variant carriers often increase rapidly from age 60. Related-LS tumors with microsatellite instability are caused by a lack of MMR complex, which results in a high rate of mutations in the microsatellites, which are repetitive DNA sequences. Microsatellite instability (MSI), which is prevalent in about 95% of all LS-associated cancers, is this problem. Mutations in the TGF-RII and TCF4 genes, which normally inhibit cell growth, as well as the IGF-RII and BAX genes involved in the apoptotic process, predispose people to colon cancer more than mutations in other repetitive sequence-containing genes. Additionally, the minor MMR genes MSH6, MLH3, and MSH3 are targets of the MSI phenotype because their coding sequences contain polyadenine traits. In about 15% of cases, the sporadic CRC also exhibits an MSI phenotype. In this instance, somatic hypermethylation of the MLH1 gene promoter may have caused the MSI. The MLH1 allele's expression was silenced in all major somatic tissues because of hypermethylation at its promoter. A particular BRAF oncogene mutation, typically the V600E missense mutation, is present in 40–87 percent of all sporadic microsatellite unstable tumors with hypermethylation of the MLH1 gene. The MSI phenotype in LS MSI tumors is caused by genetic changes in the MMR genes and is not dependent on epimutation, so this mutation is not present in those tumors. Finally, another type of instability, 'elevated microsatellite alterations at selected tetranucleotide repeats' (EMAST), has also been identified in colon cancers. EMAST has been associated with both MSI. One known cause of EMAST is a deficiency or dysfunction of MSH3, which is required in the repair of tetranucleotide repeat mismatches in complex with MSH2. The MSH3 defect may also cause impairment of homologous repair and increase sensitivity to some targeted therapies, such as poly (ADP-ribose) polymerase 1 (PARP1) inhibitors [9].

MLH1 variant is correlated with the highest risk of developing CRC whereas the MSH2 variant is correlated with the highest risk of developing many cancers, except CRC. The cumulative incidences of overall cancers for PMS2 pathogenic variant carriers are the lowest among the four pathogenic germline variants, with cumulative cancer incidences of 34.1% at the age of 75.[10]

finally, EPCAM is highly expressed in epithelial tissues and tumors. Studies have shown that 3'end EPCAM deletion is a recurrent cause of LS, and these truncating EPCAM deletions cause allele-specific epigenetic silencing of the neighboring DNA

mismatch repair gene MSH2 and subsequent hypermethylation of its CpG island promoter in tissues expressing EPCAM Therefore, deletion analysis of EPCAM is appropriate for the diagnosis of Lynch syndrome [8,10,11]

Lynch syndrome is the most frequent hereditary colorectal cancer (CRC) syndrome, Lynch syndrome-related CRC accounts for 3% of all CRC., affecting approximately 1 in 300 in the Western population. It is caused by pathogenic variants in the mismatch repair (MMR) genes including MLH1, MSH2 (EPCAM), MSH6, and PMS2, and is associated with high risks of CRC, Given these risks, carriers of such variants are encouraged to participate in colonoscopy surveillance programs that are known to substantially improve their prognosis.[12]

While the mechanism of mismatch repair deficiency and microsatellite instability and its role in Lynch-associated carcinogenesis has been known for some time, there have been significant advances recently in diagnostic testing and the understanding of the molecular pathogenesis of Lynch tumors. cancer risk varies by specific mismatch repair mutation, which in turn has implications on surveillance strategies for patients, In the case of Lynch syndrome, there is usually a familial history of cancer. [13,14]

A genetic phenotype that characterizes these tumors. MSI can also be detected in sporadic tumors, through epigenetic events inactivating the MMR system. Progress in diagnosis and molecular biology has allowed for better identification of Lynch patients but also other rare genetic syndromes. While LS has been found in about 1 out of every 35 patients with CRC (3%)20,21 and 1 out of every 56 patients with EC (1.8%),6 estimates of the overall general population frequency of LS have previously been limited to analyses of datasets of patients with this cancer history. Of note, LS prevalence likely varies by population, and over 50 founder mutations in MMR genes have been recently identified in Icelandic, French Canadian, African American, Polish, and Latin American groups, among others. In Iceland, for example, due to three founder mutations (two in *MSH6*, one in *PMS2*), LS is more common than what was calculated from the CCFR data, with an estimated general population prevalence of 0.442% (1:226). Despite this higher prevalence, however, the frequency of CRC related to LS in this population is just 2.3%, again likely reflecting the lower penetrance of *MSH6* and *PMS2* in CRC.MMR-D has previously been theorized to be a late event in the development of CRC, whereby polyps in LS first develop similar to sporadic polyps (such as via an APC-mediated mechanism), with biallelic MMR loss then occurring afterward;30 the resultant MMR dysfunction leads to an accumulation of somatic mutations (i.e. MSI) which, in turn, accelerates progression to invasive cancer. This model is supported by the finding that in pre-malignant polyps in LS patients, the likelihood of MMR-D was associated with increased polyp size (suggesting that the smaller – and presumably earlier – polyps have not yet had the necessary 'second hit' to become MMR-D). Advances in histopathology and sequencing, however, have led to other potential models of LS-associated colorectal carcinogenesis. For example, Ahadova et al. found MMR-D crypt foci (histologically normal and non-neoplastic intestinal crypts with absent MMR protein expression) adjacent to MMR-D adenomas, suggesting a role for MMR-D in adenoma initiation. These investigators have proposed a novel and provocative pathway for LS-associated colorectal neoplasia that completely bypasses adenomatous precursors altogether. Their data suggest that the MMR-D crypt foci, known to be reasonably common in the intestinal epithelium of healthy cancer-free LS carriers, may acquire somatic mutations in TP53 or CTNNB1 that could lead to immediate invasive cancer growth, and that this direct process may explain interval colorectal cancers that develop between short-interval screening colonoscopies. Symptoms of Lynch syndrome vary from person to person based on the severity of their diagnosis. People diagnosed with Lynch syndrome have symptoms like those of the cancers they cause, the most common being colon and rectal cancer. [13]

Common symptoms of Lynch syndrome that relate to colon or rectal cancer include:

- Blood in your stool.
- Constipation.
- Cramps in your stomach or abdomen.
- Diarrhea or stool smaller than normal.
- Fatigue.
- Feeling full or bloated.
- Nausea or vomiting.

There are several management options, but the strength of evidence varies across types of interventions.

A. *Immunotherapy*

In the recent update of immunotherapy, they found out that neoepitopes offer new possibilities to enhance the immune system's ability to recognize and destroy the tumor.[15] The real benefit of such neoantigens as vaccines for the treatment of both lynch syndrome-colorectal cancer patients as well as lynch syndrome mutation carriers offers a

promising approach to treating and preventing the tumor from recurring.[16] this approach involves the use of a neoantigen-specific effector and memory T-cell response to get rid of the tumor tissue. recent studies showed that mismatch-repair status predicted the clinical benefit of immune checkpoint blockade.[17] according to that, it has come to light that the tumor microenvironment plays a vital role in modulating the response of checkpoint blockade therapy and eventually to patient outcomes. In an environment where hostile immune cells are actively engaged in immune surveillance and tumor clearance, intratumorally heterogeneity caused by genetic changes favors tumor survival. Tumor growth and heterogeneity are known to be driven by immune-editing processes, which impede recognition and destruction of antigen-expressing tumor cells by CTLs.[18] a strong inverse correlation between the highly immunogenic PIGO and MSH6 peptides was observed, which recalled a potent CTL response in the patient and the low expression levels of these transcripts. This inverse relationship strongly suggests a mechanism by which highly immunogenic neoepitope expression is downregulated by tumor cells to avoid immune attack.[19]

A second mechanism that tumor cells follow to inhibit immune attack is by down-regulating their antigen-presenting machinery including reducing expression of the HLA, β-macroglobulin, and/or peptide transporter genes.[20] A clinical trial (NCT02060188) concluded that nivolumab plus ipilimumab provides a promising new treatment option for patients with dMMR/MSI-H mCRC, with an investigator-assessed ORR of 55% (95% CI, 45.2 to 63.8) and a disease control rate at $\geq$ 12 weeks of 80%.[21] also, a recent study indicated that the degree of microsatellite instability can predict a patient's response to anti-PD-1 immunotherapy, and high microsatellite instability was an independent predictor of longer PFS in dMMR/MSI-H CRCs.[22] This tumor displays loss of nuclear staining of MSH6 (A), whereas staining is retained for MSH2 (B), MLH1 (C), and PMS2 (D) (magnification, ×20).

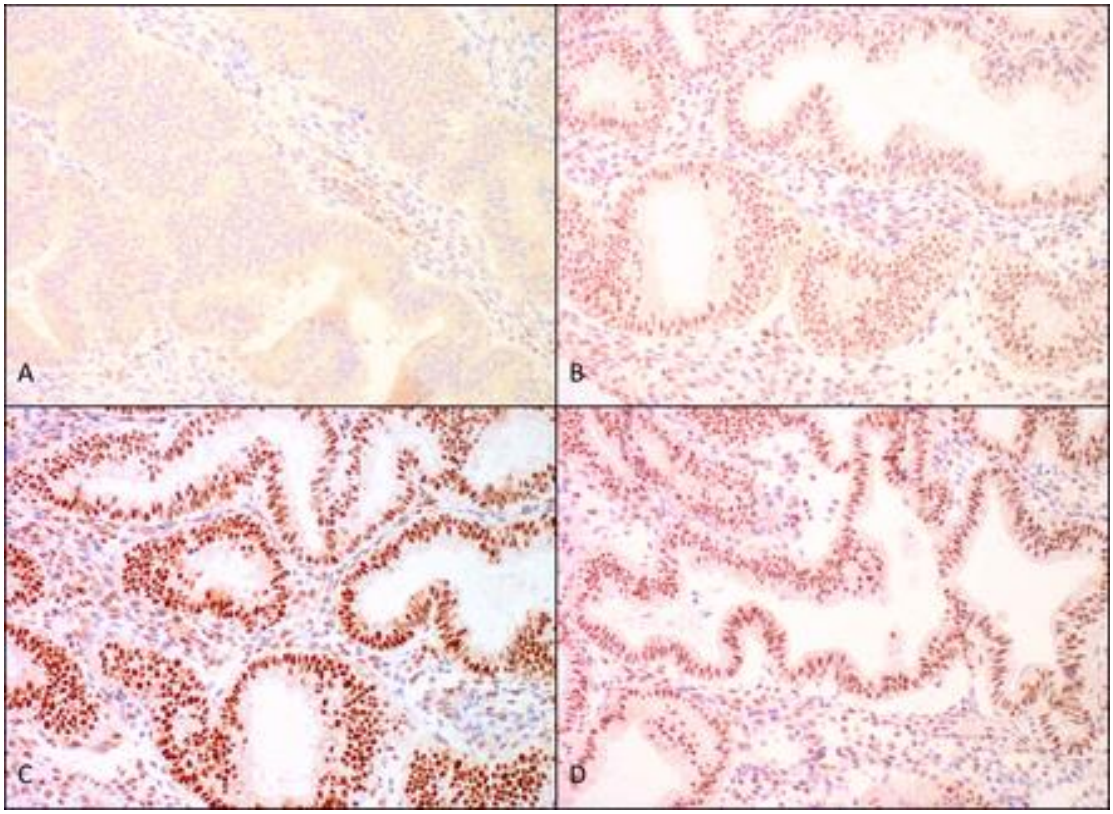

Fig. 4. Immunohistochemistry of the 4 MMR proteins: MLH1, MSH2, MSH6, and PMS2.This tumor displays loss of nuclear staining of MSH6 (A), whereas staining is retained for MSH2 (B), MLH1 (C), and PMS2 (D) (magnification, ×20).

B. *Surgery*

According to studies, people with Lynch syndrome are more likely to develop multiple colorectal cancers (CRCs) at various colorectal segments. For these patients, routine total colonoscopies are therefore required before colon tumor resection. At the same time, individuals with Lynch syndrome have a risk of developing a second colorectal cancer after resection of primary colorectal cancer. Therefore, Clinicians must decide whether to perform a total colectomy or segmental resection on these patients. According to the US Multi-Society Task Force on Colorectal Cancer, extended

colectomy is highly advised for patients with colon cancer and Lynch syndrome [23], but it is weakly recommended by the Mallorca group (a European group) [24] A subtotal colectomy performed at a young age (47 years) has been shown to increase life expectancy by up to 2.3 years.[25].

C. *Chemotherapy*

A clinical trial (ISRCTN59521990) showed that the long-term use of aspirin (600 mg/day, at least 2 years) has been shown to significantly lower CRC risk and extracolonic LS-associated tumors by the Colorectal Adenoma/Carcinoma Prevention Program (CAPP2).[26] Fewer CRCs reacted to 5-FU than expected, and many studies have reported resistance to commonly used chemotherapeutic agents, such as 5-FU and cisplatin. patients with LS or with the acquired form of MSI caused by the methylation-induced silencing of MLH1 should not be offered adjuvant chemotherapy with a 5-FU-based regimen. For patients with LS or MSI/acquired MSI, 5-FU-based regimens shouldn't be advised due to methylation-induced MLH1 silencing, according to both in vitro predictions and empirical observations.[27] Only a small number of studies have evaluated the effectiveness of chemotherapy in treating MSI-H or HNPCC tumor patients, and most of the studies found that 5-FU treatment could not improve the prognosis of these patients.[28] One study reported that oxaliplatin could improve prognosis in stage III colon cancer with MSI-H. More studies are still needed to recommend chemotherapy for CRC patients with LS. Another case reported that dabrafenib alone or combined with trametinib would benefit the therapy of MSI-H BRAF V600E-mutated endometrial adenocarcinoma.[29]

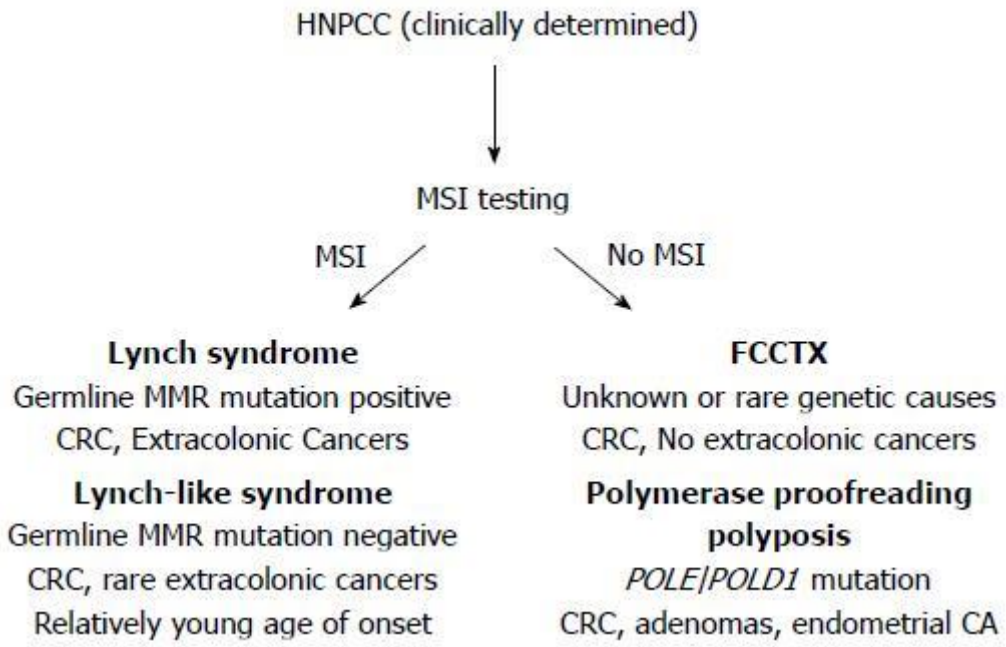

Fig. 5 Hereditary non-polyposis colorectal cancer conditions can be dichotomized via microsatellite instability testing and/or DNA mismatch repair protein

The use of exogenous hormones to lower the risk of endometrial cancer in Lynch syndrome-affected women has also been the subject of numerous studies that looked at potential preventive advantages. In one large observational study, women with Lynch syndrome who had used hormonal contraceptives for at least a year were found to have a significantly lower risk of developing endometrial cancer (HR 0.39; 95 percent CI, 0.23-0.64). In addition, nulliparity and earlier menarche were associated with a slightly lower risk of endometrial cancer, according to the same study. A small prospective biomarker study showed that the use of progestin-containing oral contraceptives and depo-medroxyprogesterone acetate led to significantly less endometrial proliferation in pre- and postintervention biopsies, though more conclusive prospective data are needed to confirm these findings.[30]

According to both observational data and several randomized prevention trials, aspirin and other cyclooxygenase-2 inhibitors may have a small impact on the risk of colorectal cancer and adenomas. [31-32] The international Colorectal Adenoma/Carcinoma Prevention Program 2 (CAPP2) study, which enrolled people with Lynch syndrome and randomly

assigned them to receive either a placebo or 600 mg/day of aspirin (participants were also randomly assigned to take 30 g/day of resistant starch vs. in this study, a placebo was used as a second intervention. Although the initial analysis after a mean of 29 months revealed no significant difference in colorectal adenoma or carcinoma risk among those with Lynch syndrome in CAPP2 who received aspirin compared with placebo,[33] a preplanned long-term analysis ultimately revealed a significant reduction in colorectal cancer incidence among participants who took aspirin for 2 or more years compared with those who were randomly assayed (incidence rate ratio, 0.37; 95 percent confidence interval, 0.18 [26] Surprisingly, participants who took aspirin for two or more years experienced a significant decrease in the incidence of any Lynch syndrome-related cancer (incidence rate ratio, 0.59; 95 percent confidence interval, 0.39-0.90). This finding raises the possibility that aspirin's preventive effects may go beyond the colorectum. Although the ideal dosage and duration of use are still unknown, daily aspirin is now accepted as a standard component of Lynch syndrome cancer prevention due to these compelling data. In a prospective, randomized trial of patients with Lynch syndrome, the ongoing CAPP3 study is evaluating 100 mg/day, 300 mg/day, or 600 mg/day of aspirin. It is interesting to note that a subgroup analysis of CAPP2 participants revealed a link between obesity and a higher risk of colorectal cancer and also suggested that aspirin's potential for preventing Lynch syndrome may only apply to obese people. The interaction of aspirin, obesity, and dietary/lifestyle factors on cancer risk in Lynch syndrome requires further research, according to study number [34]. Ibuprofen, calcium supplements, and multivitamin use may have cancer-preventive benefits in Lynch syndrome patients, though these interventions should not be regarded as standard in the absence of confirmatory prospective randomized clinical trials. Ibuprofen may also reduce the risk of colorectal cancer. [35]

We have made significant progress in the treatment of these tumors because of the studies conducted over the years on the molecular mechanisms underlying the onset of LS-related colorectal cancer. Immune checkpoint inhibitors have recently been developed as antitumor medications, and they show promise, particularly in sporadic CRC patients with MSI. We could say that Lynch syndrome patients are prime candidates for immunotherapeutic therapy because, in 95% of cases, MSI-H is present in tumor tissue. As recently reported by studies using the preclinical mouse model (62), we hope soon it will be possible in the context of this research to establish a preventive cancer vaccine for Lynch syndrome.[36]

A. *Colorectal Cancer*

Large cohort studies of continuously enrolled, unselected patients were initially investigated for specific information on cases of Lynch syndrome because they were thought to be less biased by publication. Following immune checkpoint-based therapy, Lynch syndrome patients had an ORR between 46 and 71 percent, according to three studies that looked at colorectal cancer response rates. [16,21] In two of the articles, data from the MK-3475 study, which involved three to six centers in the US (NCT01876511), were presented. Lynch syndrome-associated ORR was determined in the study by Le et al.25, and data on specific Lynch syndrome cases could be extrapolated from the study by Le et al. Pembrolizumab was used to treat eight Lynch syndrome patients with colorectal cancer in Le et al. [21],19 of whom two demonstrated PR, giving an ORR of 25%, and six demonstrated SD, reaching disease control in 100% of the patients. The ORR associated with Lynch syndrome had risen to 46% in the 2017 update. [37] Although the percentage of Lynch syndrome cases that initially had disease control was not stated, 23 percent of the entire cohort (covering 86 patients) revealed SD reaching disease control in 77 percent of the unselected MSI/dMMR cohort. Furthermore, it took an average of 21 weeks to respond, and it took 42 weeks to receive a full response. The paper from 2015 only mentioned corresponding data from the sporadic MSI/dMMR cohort with two colorectal cancer patients who both showed PR (ORR=100%). Although comparable information was missing in the paper's 2017 update,25 statistical analyses failed to find a significant difference between colorectal cancers with Lynch syndrome and those with sporadic MSI/dMMR (the ORR for the entire study cohort was 52%). There were 35 patients with Lynch syndrome in the CheckMate-142 study, which Overman et al. presented. Of these 35 patients, 25 displayed an objective response (ORR=71%). The study was a multicenter study involving 28 centers in eight countries. MSI/dMMR colorectal cancers that were sporadic (not Lynch syndrome) had an ORR of 48%. Due to a lack of individual data, no comparison was made between the two groups. Lynch syndrome and sporadic MSI cancers were not specified for Lynch syndrome and neither clinical trial had sufficient follow-up to calculate PFS and OS.[38]

IV. Experimental results and discussion

Scientific experiments have proven that There is no cure for Lynch syndrome yet, after testing If the cancer is initially found to be small, the chance of successful treatment increases but sometimes cancer can be prevented by removing certain organs before they develop into cancer. Fortunately, there are risk management guidelines for carriers of Lynch syndrome that are associated with lower cancer-related deaths. The recommended monitoring for carriers of Lynch syndrome is described as Cancer screening for people with Lynch syndrome. however, after the correct diagnosis of the type of cancer resulting from Lynch syndrome is made, it can be cured According to both observational data and several randomized prevention trials, a pre-planned long-term analysis finally confirmed a significant reduction in the incidence of colorectal cancer among participants who took aspirin for two or more years compared with those tested randomly (incidence ratio, 0.37; 95 percent confidence interval, 0.18 Surprisingly, these people had a significantly lower incidence of anyLynchSyndrome-related cancer (incidence rate ratio, 0.59; 95 percent confidence interval, 0.39-0.90). Based on this result, it was found that aspirin has protective effects against colon cancer. Despite the optimal dose and duration of use still unknown, aspirin intake has now been accepted as an effective way to prevent Lynch syndrome cancer, and the ongoing CAPP3 study evaluates 100 mg/day. or 300 mg/day or 600 mg/day of aspirin. The analysis carried out by CAPP2 on the subgroup of participants revealed that there is a link between colorectal cancer and obesity. Aspirin can be applied for prevention only to obese patients. Here are some of the factors affecting the increased risk of cancer associated with Lynch syndrome, such as the interaction of aspirin Obesity, and dietary/lifestyle factors require. According to Study Number. [36]. ibuprofen, calcium supplements, and multivitamin use may have cancer-preventive benefits in patients with Lynch syndrome and Ibuprofen may also reduce the risk of colorectal cancer.

Studies conducted over the years on the molecular mechanisms underlying the emergence of LS-related Colorectal cancer have made great progress in treating these tumors and Immune checkpoint inhibitors have recently been developed as antitumors, which shows that immunotherapy can be applied to patients with Lynch syndrome as a means of treatment because, in 95% of cases, MSI-H is present in tumor tissue. As recently reported by studies Using a preclinical mouse model (62), and in the context of this research, there are attempts to establish a protective cancer vaccine for Lynch syndrome. The data showed that frequent and early colonoscopy of healthy individuals with Lynch syndrome significantly reduces the incidence of colorectal cancer and overall mortality and is therefore considered a preventative method.[39] Recent data from a prospective multicenter European registry, Recent data suggest that some Lynch syndrome-associated colorectal cancers may develop as directly invasive malignancies rather than through the traditional adenoma-to-carcinoma pathway.[40] At this stage, some surgical operations can be performed, such as Endoscopic therapy, Surgical Therapy, Total Proctocolectomy with Brooke Ileostomy (with pouch), Colectomy with Ileorectostomy, and Restorative Proctocolectomy (Ileoanal Pouch Procedure). that endoscopic Therapy is used If the appendix is food, removal through a colonoscope may be sufficient, although surgery may be recommended for some patients. If cancer is found on examination. Surgical Therapy includes Removing the entire colon as the only way to completely prevent the development of colon cancer or to treat existing cancer. These three operations are the most common for the treatment of HNPCC and All three operations involve the removal of all or most of the colon, these operations can also be performed on women with also in the surgical removal of the uterus, ovaries, and fallopian tubes.

The choice of the above-described therapeutic approaches for LS-associated colon cancer depends on the evaluation of the clinical and genomic features of the tumors. Considering the side of the colon in which the primary tumor originates, and the locations and burden of metastatic disease, by the mutational status of some genes, such as KRAS and BRAF (41) and the status of MSI on tumor DNA (43). Because that affects the therapeutic method. With Lynch syndrome, endometrial cancer and ovarian cancer represent the second and third most common malignancies. Many screening attempts have been made for this cancer, but in the end, they do not show high sensitivity to detect this type, so risk-reducing surgery was resorted to with hysterectomy and sapling-oophorectomy because they are effective Notable for preventing endometrial and ovarian cancer in women with Lynch syndrome. Benefits have also emerged and developed for MMR proteins with new roles (such as preventing compensatory recombination, promoting meiotic connectivity, expanding repeat triplets, and modulating microRNA biogenesis). Immunoglobulin (Ig) diversification based on the 'somatic hypermutation' process is included. (SHM) after it was limited to post-replicative repair, and this process is regulated by the MutSα-MutLα complex, in association with two other proteins, AID (activation-induced cytidine deaminase) and Polμ (‘error-prone’ DNA Polymerase) (42); In particular, MutSα deficiency is associated with the neoplastic transformation of T lymphocytes (43). MMR maintains stability throughout the genome but is responsible for up to 60% of mutations in the V and S regions of the Ig site that are important for antibody diversification (44). Therefore, a good understanding of the complex signaling sequences that govern antibody diversity may

help reveal associations between the maintenance of genomic integrity and tumorigenesis in the adaptive immune response. From the colorectal cancer immune response to LS and MMR proteins, MMR-deficient cells accumulate an abundance of mutations encoding microsatellites, also present in tumor-related genes. These mutations may lead to the loss of function of the respective proteins but may also lead to the translation of new immune framework peptides or antigens (FSPs) (45).

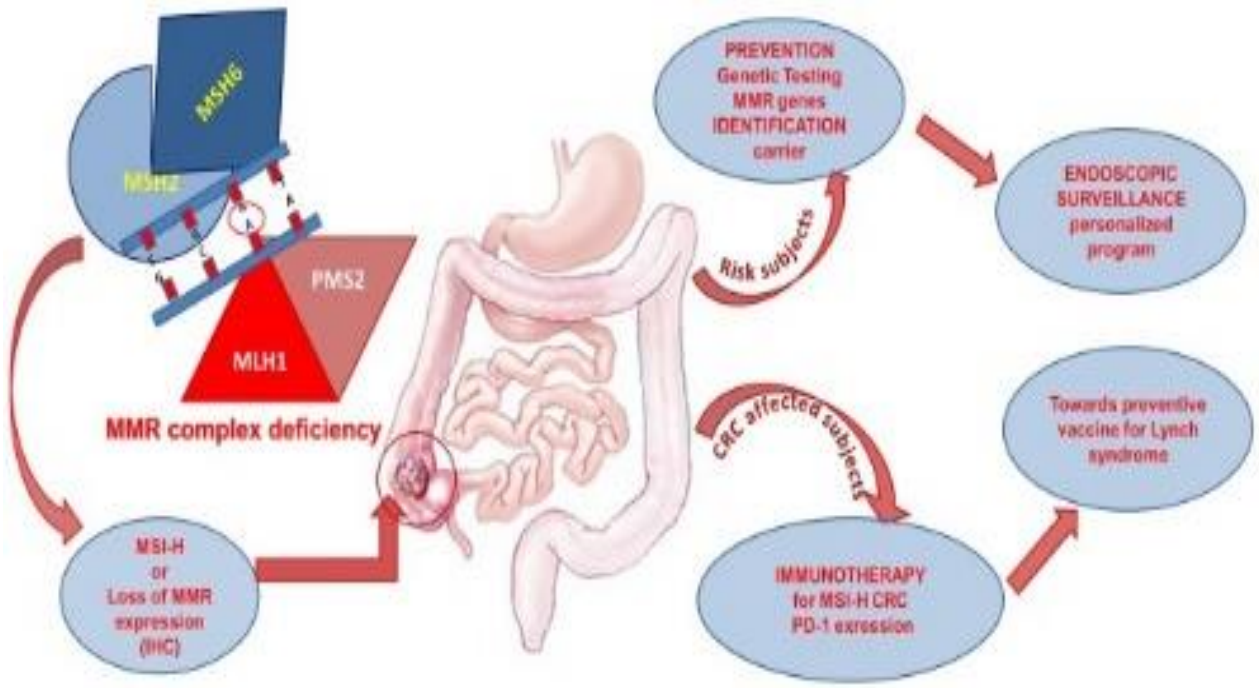

Fig. 6

Classification of MMR genetic variant is an essential item for selecting the time for internal colonic surveillance and for advancing towards personalized medicine as a critical point is represented by the correct identification of the pathogenicity of specific MMR gene variants in mutation detection analysis because it contributes significantly to the Improve relevant LS cancer prevention programs. This is because more recently, carriers of the MSH6 and PMS2 mutation have been reported to have a lower risk of CRC with later advancing age (46). Literature data may support a move to initiate colonoscopy surveillance in MSH6 and PMS2 mutation carriers at ages older than 30 years, provide no new indication for CRC, and extend the period to 2 years. Therefore, the classification of genetic variants is very important and effective the most applied protocol of adjuvant chemotherapy for colorectal cancer not metastatic (stage II) involves the administration of 5-fluorouracil (5FU). Instead in some metastatic CRC cases (stage III), systemic therapy with a FOLFOX- or CAPOX (capecitabine and oxaliplatin) regimen is the standard of care in these patients. Patients with left-sided and RAS wild-type tumors receive anti-epidermal growth factor receptor (EGFR)-directed therapy, while patients with right-sided tumors or those with RAS mutations receive bevacizumab. It is worth to be mentioned, in patients with tumors showing microsatellite instability or deficient mismatch repair, adjuvant chemotherapy with 5-fluorouracil did not result in a survival benefit in subgroup analyzes of patients with colon cancer without metastasis. While in patients with metastatic colon cancer who received treatment with capecitabine and oxaliplatin, survival was significantly longer among those with incomplete mismatch repair compared to those with good mismatch repair, we can point to this difference to the lymphatic sequence characteristic of MM deficient tumors because it determines the anti-tumor immune response that can be abrogated by the immunosuppressive effects of chemotherapy. However, T cells are unable to eradicate these tumors, due to the Most likely to overexpress immune checkpoint proteins that can interfere with checkpoint inhibitors fortunately, Recently, immune checkpoint inhibiting agents have been developed as antitumor drugs and appear promising, especially in sporadic CRC patients with MSI. Pembrolizumab (P) is an anti-PD-1 antibody that blocks the interaction between PD-1 on T-cells, and PD-L1 and PD-L2 on tumor cells. The antibody pembrolizumab has been evaluated in patients with metastatic colorectal cancer and MSI in whom previous treatment with cytotoxic agents had failed. The response to treatment was similar in patients with LS-related CRC and those with sporadic CRC. Moreover, the combination of

nivolumab, another anti-PD-1 antibody, plus ipilimumab, an anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibody, resulted in response rates and disease-control rates that were higher than those previously reported with nivolumab alone. In this context, it is interesting to note that these drugs show good results in the treatment of tumors with MSI.

From the above, we conclude that the earlier the disease is diagnosed, the better and spares us exposure to somewhat harsh treatment methods, because, despite the existence of treatment for cancers associated with Lynch syndrome there is no real definitive treatment for Lynch syndrome itself. For example, early detection of CRC development by LS is promising to improve the quality of care for patients and families with any genetic condition that leads to tumors of the gastrointestinal tract such as Lynch syndrome. Carriers of related predisposition alleles (47) to reduce mortality from hereditary colorectal cancer. Presumably, persons who are carriers of the disease-causing mutation in the MMR gene have been recommended annual colonoscopy monitoring starting at age 25. In the end, there are some measures recommended by doctors to prevent these cancers first, followed by the family medical history, as it is an effective way to predict cancers according to the studies conducted on cancer family G (2. Warthin AS (1925) The further study of a cancer family Accordingly, if one of the parents suffers from Lynch syndrome, then with a rate of 25%, children and future generations after them will be affected. And if you notice any of these symptoms, you should hurry up for an examination like Blood in your stool, Constipation, Cramps in your stomach or abdomen, Diarrhea, or stool smaller than normal, Fatigue, feeling full or bloated, and Nausea or vomiting.
Lynch syndrome is the most common genetic syndrome that predisposes patients to colorectal cancer. Advances in molecular diagnostics in the past 15 years have changed the nature of Lynch syndrome. It is now common to identify a germline mutation in one of the mismatch repair genes. The most prevalent mutations are found in MLH1 and MSH2. Microsatellite instability testing and immunohistochemistry are useful tools to determine if a patient is a candidate for testing for mutations in mismatch repair genes. Lynch syndrome patients are diagnosed with a germline mutation in one of the MMR genes, MLH1 on chromosome 3p21, MSH2 on chromosome 2p16, MSH6 on chromosome 2p16, PMS2 on chromosome 7p22, MLH3 on chromosome 2p16 and MSH3 on chromosome 5q11.so DNA MMR system imbalance leads to an increase in the rate of mutations that make cells more susceptible to mutations in genes that control cell growth. Microsatellites are mutations that frequently occur in small repetitive DNA strands if an imbalance occurs in the MMR system. in cancer with In an MMR-deficient cancer cell, some nucleotide repeat units in microsatellites can move away from the corresponding normal DNA. The number of repetitions usually decreases, but sometimes it increases as in (Fig 2). This difference in repeat units and thus the length or size of microsatellites is called MSI. Because approximately 95% of all cancers associated with Lynch syndrome show MSI. MSI serves as a credible phenotypic marker of MMR deficiency that eases assessment for the preselection of patients for germline mutation analysis of MMR genes.

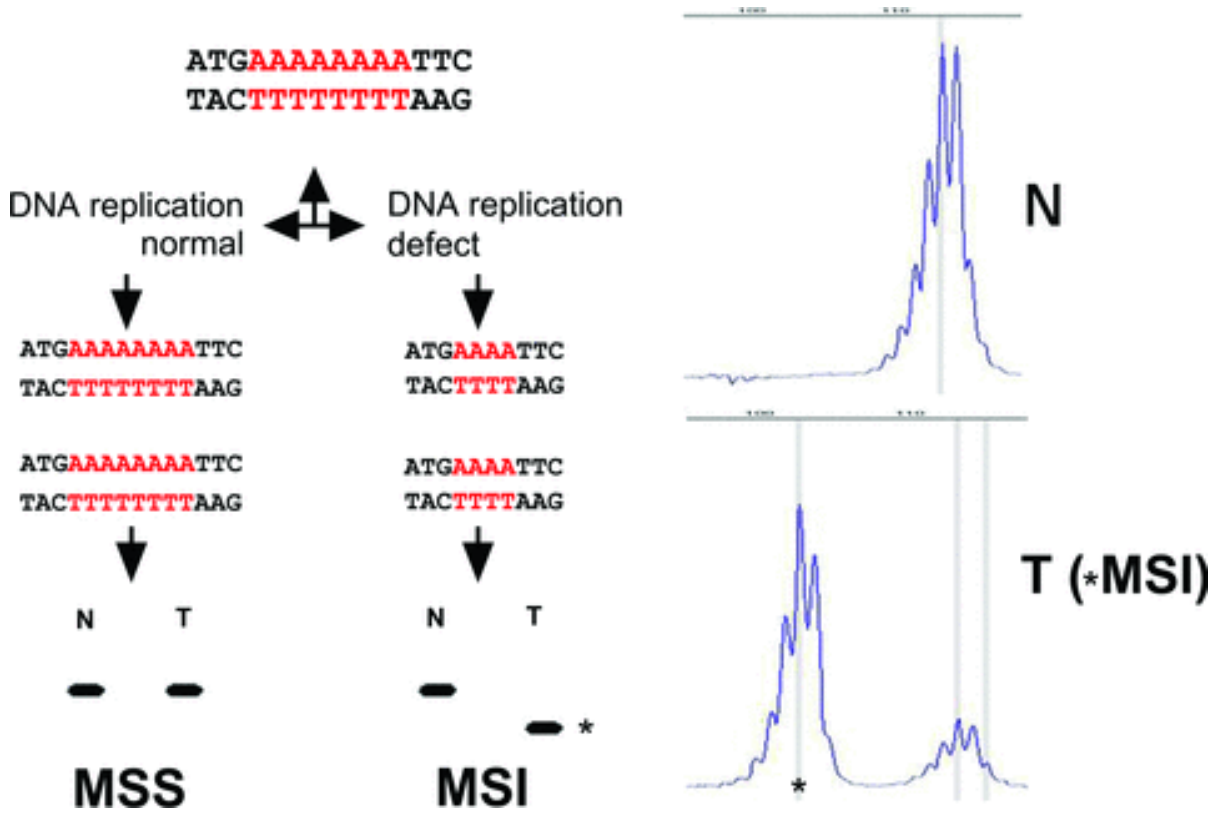

Fig. 7 MSI. A schematic microsatellite is indicated (poly A track). If the cancer cells contain a healthy MMR system the size of the microsatellite will be the same in DNA isolated from normal (N) and from tumor (T) cells: microsatellite stable (MSS) tumor. In case of a defect in MMR the size of the microsatellite can change when comparing N with T DNA: microsatellite unstable (MSI) tumor. Asterisks indicate the microsatellite's unstable tumor DNA fragment

V. Conclusion and Future Work

Lynch syndrome occurs due to a specific mutation in the MMR genes that leads to an increase in the rate of mutations that make cells more susceptible to mutations in genes that control cell growth. That causes the body to develop cancer tissue in multiple places with high-level microsatellite instability.

And because it's a genetic condition, it can be transmitted to the offspring through genetic material. Lynch syndrome follows an autosomal dominant inheritance pattern, in which a mutation needs to happen in only 1 copy of the gene for the person to have an elevated chance of getting that disease. Therefore, a child who has a parent with a mutation has a 50% chance of inheriting that mutation. A sibling or parent of a person who has a mutation also has a 50% chance of having the same mutation. So, the lynch syndrome mutation carriers have limited options in case of having children. To overcome this, people with lynch syndrome mutation have one option. Preimplantation genetic diagnosis (PGD) is a medical procedure done in conjunction with in-vitro fertilization (IVF). It allows people who carry a specific known genetic mutation to reduce the likelihood that their children will inherit the mutation. A person's eggs are removed and fertilized in a laboratory. This procedure can prevent the mutation from passing through the genetic material to the next generation creating healthy mutation-free children.

Lynch syndrome hasn't a defined treatment as it's a genetic disorder, but we can lower the risks associated with Lynch syndrome. Patients with a family history of lynch syndrome should be advised to perform regular screening for colorectal cancer and to perform a genetic test to confirm the lynch syndrome diagnosis. Patients with lynch syndrome have resistance to commonly used chemotherapeutic agents such as 5-FU and cisplatin. So, the right treatment course would be immunotherapy to enhance the immune system's ability to recognize and destroy the tumor. Few researchers refer to immunotherapy as a promising hope for lynch syndrome patients. Some of them are trying to produce a vaccine for lynch syndrome using neoantigen-specific effectors and memory T-cells.

A few clinical trials reported that there are a few methods to prevent cancer in lynch syndrome mutation carriers. A study conducted in a cancer research center in the United Kingdom showed that the regular use of aspirin can prevent lynch syndrome-associated cancer despite the uncertain dose and the unknown duration of use. The trial also reported that this method can be more beneficial to patients who suffer from obesity. Like aspirin, ibuprofen, calcium supplements, and multivitamin also have prevented effects on cancer associated with Lynch syndrome.

Future studies need to be conducted to show whether therapeutic vaccination with FSPs can have a beneficial effect on the outcome of MSI-H CRC, opening the perspective for the development of an FSP-based vaccination approach that might be applied to prevent tumor initiation or outgrowth in Lynch syndrome mutation carriers.

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