Chapter 3
New Insights into Lynch Syndrome Diagnosis

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Abstract Colorectal cancer (CRC) is the third most common cancer worldwide. Lynch syndrome accounts for 1–3 % of patients developing colorectal cancer. This autosomal dominant disorder is caused by germline mutations in the DNA mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2. A mutation in one of these genes is characterised by the development of CRC and various other associated cancers at an early age. The diagnosis of Lynch syndrome has evolved over the last two decades to include family history, tumour histopathological characteristics, immunohistochemistry, testing for microsatellite instability as well as germline genetic testing as modalities for making the diagnosis. By identifying families and individuals with Lynch syndrome, individuals can be enrolled in focussed screening programmes that have been shown to decrease mortality from colorectal cancer. In this chapter we define the terms "HNPCC", "Lynch syndrome" and "Familial colorectal cancer syndrome X" and discuss the different diagnostic modalities. We propose a logical and cost-effective algorithm to diagnose Lynch syndrome, by appropriately using all the diagnostic modalities in the at-risk individual.

Keywords Lynch Syndrome • HNPCC • Diagnosis • Mismatch repair • Immunohistochemistry • Genetic testing

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3.1 Introduction

Colorectal cancer (CRC) is the third most common cancer and cause of cancer-related death worldwide [1]. Although the majority of individuals who develop CRC have sporadic disease, up to 20 % may have inherited a predisposition to develop it [2]. Lynch syndrome is the most common form of hereditary CRC and accounts for between 1 and 3 % of patients with these tumours [3]. This autosomal dominant disorder is due to germline mutations in DNA mismatch repair (MMR) genes. It is characterised by the development of colorectal cancer as well as endometrial cancer and various other cancers at a young age [4]. MMR genes implicated in Lynch syndrome include MLH1, MSH2, MSH6 and PMS2 [3, 5]. Abnormalities in the function of these MMR genes lead to errors during DNA replication, in particular microsatellite instability (MSI) [6]. MSI can be found in over 90 % of tumours in individuals with Lynch syndrome, but can also be found in approximately 15 % of sporadic cases of CRC [5]. In almost all sporadic cases of MSI, a mutation in the MLH1 gene due to hypermethylation in the MLH1 promoter is present, and is not related to any inherited factor. Patients with a germ line mutation should be distinguished from those with a sporadic form of CRC. Methods to identify patients with a germ line mutation will be discussed in this chapter.

It is important to identify individuals with germ line mutations as these individuals can be enrolled in screening programmes to allow for polyp and early cancer detection. Intensive screening for colorectal cancer by colonoscopy as well as prophylactic gynaecological surgery reduces the incidence of Lynch syndrome related tumours and mortality [7, 8]. Family history and clinical criteria suggest Lynch syndrome the definitive diagnosis requires confirmation with germ line testing [9].

3.2 Nomenclature

The terms HNPCC, Lynch syndrome and Familial CRC Type X are often confused and used inappropriately in the literature.

Hereditary non-polyposis colorectal cancer (HNPCC) was originally defined by the Amsterdam 1 criteria to distinguish this form of inherited CRC from familial adenomatous polyposis (FAP) [10]. The term HNPCC was therefore used before the molecular aetiology of this disease was discovered.

Germline mutations are identified in only about 50 % of individuals who meet the Amsterdam criteria and many of the tumours from individuals who meet the Amsterdam criteria also do not show features of MSI [11–13].

The term Lynch syndrome is reserved for individuals with a known mutation in one of the MMR genes. Familial Colorectal Cancer Type X should be the term used to refer to those families who meet the Amsterdam Criteria, but do not have MSI-H tumours [14]. HNPCC should be used as an umbrella term including both these groups, although calls have been made to retire the term [15].

3.3 Detection Methods

3.3.1 Methods Based on Family History

3.3.1.1 Amsterdam Criteria

In 1990, the International Collaborative Group on HNPCC (ICG-HNPCC), comprising 30 experts from eight countries, met in Amsterdam and proposed a set of criteria to identify families who were likely to have an autosomal dominant inherited colon cancer predisposition [16]. The criteria generated (known as the Amsterdam criteria) were not intended for diagnosis, but rather to identify families that should be referred for mutation analysis, thereby allocating resources to an appropriate at-risk population. The criteria are listed in Table 3.1.

These criteria provided a basis for uniformity in collaborative studies and most investigators made use of them. The criteria were criticized for excluding extra-colonic Lynch syndrome associated cancers, therefore excluding many families from being offered genetic testing.

These shortcomings were recognised and a new set of criteria were drawn up at a meeting held in Coimbra, Portugal, in 1998. This resulted in a definition of HNPCC (Table 3.2) and the revised criteria listed in Table 3.3 [10].

When setting the new criteria, the ICG-HNPCC decided the criteria should be simple and not differ too much from the original criteria. The criteria should be clinical and accurate to ensure that families meeting these criteria would have a high likelihood of having HNPCC. The main difference between the new criteria (known as the Amsterdam II Criteria) and the Amsterdam I criteria was the inclusion of extra-colonic HNPCC-related tumours. Among all these tumours, cancer of the endometrium, ureter and renal pelvis and small bowel cancers have the highest relative risk [10].

3.3.1.2 Bethesda Criteria and Revised Bethesda Criteria

The use of the Amsterdam II criteria to identify patients with HNPCC is limited because the sensitivity is 78 % [12]. Improved understanding of the clinical and histological manifestations led the National Cancer Institute (NCI) to hold an

Table 3.1 Amsterdam criteria

At least three relatives with colorectal cancer, one of whom should be a first degree relative to the other two
At least two successive generations should be involved
At least one colorectal cancer should be diagnosed before the age of 50
FAP should be excluded
Tumours should be verified by pathological examination

Table 3.2 Definition of HNPCC (Lynch syndrome)

Familial clustering of colorectal and/or endometrial cancer
Associated cancers: Cancer of the stomach, ovary, ureter/renal pelvis, brain, small bowel, hepatobiliary tract and skin (sebaceous tumours)
Development of cancer at an early age
Development of multiple cancers
Features of colorectal cancers:
1. Predilection for proximal colon
2. Improved survival
3. Multiple colorectal cancers
4. Increased portion of mucinous tumours
5. Poorly differentiated tumours
6. Tumours with marked host-lymphocytic infiltration and lymphoid aggregation at the tumour margin
Features of colorectal adenoma
1. Numbers vary from one to few
2. Increased proportion of adenomas with villous growth pattern
3. High degree of dysplasia
4. Rapid progression from adenoma to carcinoma
High frequency of MSI
Immunohistochemical loss of MLH1, MSH2 or MSH6 protein expression
Germline mutation in MMR genes (MSH2, MLH1, MSH6, PMS1, PMS2)

Table 3.3 Amsterdam 2 criteria

At least three relatives with HNPCC-related cancer (CRC, cancer of the endometrium, small bowel, ureter or renal pelvis)
One should be a first degree relative of the other two
At least two successive generation should be affected
At least one should be diagnosed before the age of 50
Familial adenomatous polyposis should be excluded
Tumours should be verified by pathological examination

international workshop on HNPCC in 1996. The aim of this meeting was to clarify the role of genetics in the pathology of HNPCC and to develop a set of criteria for the identification of colorectal tumours that should be tested for the presence of microsatellite instability (MSI) [17].

A set of guidelines, called the Bethesda Guidelines (Table 3.4) were proposed [18]. It was estimated that the guidelines would potentially apply to 15–20 % of all colorectal cancers. Elements of the Bethesda Guidelines included both criteria for assessing tumours in families meeting the Amsterdam Criteria as well as other characteristics. The criteria would provide a sensitive set of guidelines that would include almost all HNPCC-associated colorectal cancers as well as many sporadic cancers. MSI-testing would then be used to exclude the individuals lacking microsatellite instability, who are highly unlikely to have Lynch syndrome. Tumours testing MSI-high (MSH-H) could then be further tested with immunohistochemistry and the patients with tumour that displayed loss of one of the MMR proteins should then be offered genetic testing.

Table 3.4 Bethesda guidelines

1. Individuals with cancer in families that meet the Amsterdam criteria
2. Individuals with two HNPCC-related cancers, including synchronous and metachronous colorectal cancers or associated cancers
3. Individuals with colorectal cancer and a first degree relative with colorectal cancer and/or HNPCC-related extracolonic cancer and/or a colorectal adenoma; one of the cancers diagnosed at the age <45 years, and the adenoma diagnosed <40 years.
4. Individuals with colorectal cancer or endometrial cancer diagnosed at the age <45 years
5. Individuals with right-sided colorectal cancer with an undifferentiated pattern (solid/cribiform) on histopathology diagnosed at age <45 years
6. Individuals with signet-ring-cell-type colorectal cancer diagnosed at age <45
7. Individuals with adenomas diagnosed at age <40

Table 3.5 Revised Bethesda guidelines [19]

Tumours from individuals should be tested for MSI in the following situations:
1. Colorectal cancer diagnosed in a patient less than 50 years of age
2. Presence of synchronous or metachronous colorectal, or other HNPCC-associated tumours, regardless of age
3. Colorectal cancer with MSI-H histology, diagnosed in a patient less than 60
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumour, with one of the cancers being diagnosed under the age of 50
5. Colorectal cancer diagnosed in two or more first- or second-degree relatives with HNPCC-related tumours, regardless of age

Resources would therefore be allocated to test only tumours with a high likelihood of having MSI.

Even though the Bethesda guidelines are used to identify tumours to be tested for MSI, the goal is to identify patients with Lynch syndrome [19]. It was therefore important to test how well the Bethesda guidelines did in identifying patients with MLH1 and MSH2 mutations. Data from these trials suggested that the criteria needed to be updated [12]. For this reason the Revised Bethesda Guidelines (Table 3.5) were drawn up, after a meeting held in Bethesda in 2002.

In a multicentre prospective study the revised Bethesda guidelines were shown to identify patients at risk for HNPCC with a sensitivity of 81 %, specificity of 98 % and positive predictive value of 29 %. It would, therefore, be reasonable to use these criteria to identify those patients who should have MSI tested [20].

3.4 Laboratory Methods

3.4.1 Histopathological Identification

Studies have suggested that MSI-H tumours may share morphologic characteristics that differ from non-MSI-H tumours [21, 22]. These tumours are more

likely to be mucinous type or have a signet ring cell component, have a solid cribiform growth pattern, and show increased tumour-infiltrating lymphocytes [2, 17, 22].

The features on histology should alert both the pathologist and clinician to test the tumour for MSI. The pathological features of undifferentiated (solid/cribiform) growth pattern and signet-ring type have been included in the Bethesda criteria. However, the exact role of histopathology for screening for MSI-H tumours remains unclear. The sensitivity for signet-ring type histology or an undifferentiated (solid/cribiform) growth pattern is low for patients over the age of 45 [10, 17]. Sensitivities of features, such as increased tumour-infiltrating lymphocytes, proved promising in some studies [22, 23], but not in others [21]. Currently, histopathology is used as adjunct to the Bethesda criteria to select those tumours to be tested for MSI.

3.4.2 Immunohistochemistry (IHC)

In Lynch syndrome, there is an inherited mutation in the gene coding for one of the mismatch repair (MMR) genes MLH1, MSH2, MSH6 and PMS2. Tumours of patients with these mutations have a functional loss of one of these mismatch repair proteins or gene products, and more than 90 % of these tumours will lack the expression of the involved protein [24–26].

Monoclonal antibodies to mismatch repair proteins are commercially available. When the specific gene product is expressed, the stain is positive and the MMR gene is present. When the protein is not expressed, the stain will be negative, indicating a mutation in the MMR gene. If all the MMR gene products are present on IHC, the patient is very unlikely to have Lynch syndrome and further genetic testing should not be offered.

IHC is less labor intensive, does not require a skilled molecular geneticist and has a shorter turnaround time than MSI testing. IHC can also aid in identifying the specific mismatch repair gene that is not expressed, therefore directing genetic testing. Studies validating IHC however, were performed with different patient populations, and with different aims. There are also numerous other biological, technical and clinical factors that affect the interpretation of these studies, all influencing validation of IHC as a universally accepted test.

In a review of the published literature on the sensitivity and specificity of IHC for MLH1 and MSH2 in predicting MSI in general, the sensitivity of IHC in predicting MSI was 90 % and the specificity greater than 99 % [27]. When the accuracy of IHC from different laboratories was tested, most laboratories produced similar results when staining for MSH2, but there was significant inter-laboratory variability when staining for MLH1. Factors influencing the accuracy and reproducibility of IHC include biological as well as technical factors.

3.4.2.1 Biological Factors

Gene mutations Different gene mutations have different variations of protein expression. For example, most MSH2 mutations are protein truncating; therefore most tumours from patients with MSH2 germline mutations will have absence of MSH2 protein when stained for by IHC. Conversely, approximately half of the mutations in MHL1 genes are missense mutations, resulting in expression of proteins that are catalytically inactive but antigenically intact [26, 28, 29]. These findings may explain the lower sensitivity in predicting germline mutations in MLH1 as well as the focal weak staining that is sometimes observed [30].

Antibodies MLH1 and MSH2 antibodies are most commonly used for IHC staining. Although more infrequently, Lynch syndrome is caused by mutations in the mismatch repair genes MSH6 or PMS2. These mutations would therefore be missed if IHC using antibodies from MLH1 and MSH2 are used [27].

MMR Protein interactions Interactions among mismatch repair proteins can affect the sensitivity of IHC. MMR proteins are only stable when they are in heterodimer pairs. It has been observed that MSH2 forms heterodimers with MSH3 and MSH6, forming a functional complex MutSα [31]. MSH6 however, can only dimerize with MSH2. The result of this pairing is that if there is a mutation in MSH2, MSH6 has no heterodimer partner and that tumour will stain negative for both MSH2 and MSH6 proteins. If there is a mutation in the MSH6 MMR, MSH2 can still dimerize with MSH3 and is therefore stable. Tumour tissue, in this instance, will stain positive for MSH2, but MSH6 will be absent [32]. MLH1 dimerizes with PMS2 and forms a functional complex MutLα [33–35]. MLH1 can also pair with PMS1 and MLH3. PMS2, however, can only pair with MLH1. If there is a germline mutation in the MLH1 gene, PMS is unstable and both MLH1 and PMS2 will be absent on staining. When there is a mutation in PMS2, the MLH1 will pair with PMS1 or MSH3 and will therefore be stable. In such a tumour PMS2 will stain absent, but MLH1 will stain positive [32].

In some MHL1 mutations, missense mutations results in proteins that is catalytically inactive but antigenically intact. The IHC staining for MLH1 in these tumours will also show presence of the MLH1 protein, but PMS2 staining will be absent. Additional staining with MSH6 and PMS2 antibodies therefore increases sensitivity of IHC.

3.4.2.2 Technical Factors

Protocols The importance of standardized IHC laboratory protocols has been evaluated in studies, and such protocols should be implemented at all laboratories offering IHC testing [36].

Antibody Clones Accurate and successful staining depends on the specific clone for a particular protein that is used. Differences in reproducibility and sensitivity of different clones were shown by some authors [37].

Adequate tissue sampling Adequate tissue sampling cannot be overemphasized. Identical samples will yield similar results. Discordant samples often yield inaccurate results. For example, frozen tissue used for MSI testing and paraffin block of different tumour areas used for IHC has been shown to yield different results. The most accurate results between IHC and MSI testing have been demonstrated using identical tissue samples for both methods using microdissection techniques [38].

3.4.3 MSI Testing

Microsatellite instability is the responsible carcinogenic pathway in approximately 15 % of all sporadic cases of colorectal cancer and all of the cancers associated with Lynch syndrome [39]. Microsatellites are repetitive short DNA sequences occurring throughout the genome. The majority of these sequences are non-coding. The even spacing between microsatellites is a sign of a healthy genome.

MSI is defined as altered lengths between microsatellites due to deletions or insertions and is associated with heterozygosity of loss of mismatch repair genes [40]. Tumour tissue is tested for MSI with a PCR-based test and this is compared to normal tissue from the same patient. Extra-colonic tumours associated with Lynch syndrome can also be tested for MSI [41]. MSI is reported as either MSI-high (MSI-H) or MSI-low (MSI-L). MSI-H is defined as instability of more than 30 % of the loci compared to that of normal tissue [42]. If there is no MSI in tumour tissue, it is referred to as microsatellite stable (MS-S). Tumours with MSI-L behave very similar to MS-S tumours [43]. For individuals with a tumour that is either MS-S or MSI-L, the likelihood of having a mutation in a MMR gene is very low and these individuals should not be offered germline testing [41, 44].

MSI determination is the current "gold standard" for testing tumour tissue for mismatch repair competency and is sensitive and highly reproducible [45]. The test is labour intensive, time consuming and requires a skilled molecular geneticist [43]. The result of the MSI test can be important in surgical decision making, because it might influence the extent of colonic resection. Unfortunately, the MSI test results are often not available at the time of surgical resection.

When tumour tissue tests MSI-H, IHC, will also be required to identify the specific mismatch repair gene mutation that is involved. For these reasons, several studies have compared MSI testing to IHC [3, 20, 28, 43, 46–54]. Shia comprehensively reviewed these studies [46]. The studies were divided into 2 groups: the first group included studies assessing IHC testing for MLH1 and MSH2 (with or without MSH6), whereas the second group included studies assessing IHC for MLH1, MSH2, MSH6 and PMS2.

The sensitivity for IHC with MLH1 and MSH2 antibodies was 85 %, compared to the sensitivity of 93 % of MSI testing. The low sensitivity of IHC in this group was largely attributed to the low rate of MLH1 mutation detection of 74 %. When

all four antibodies were used in IHC (group 2) the sensitivity of IHC was 92 %, equivalent to MSI testing. This improvement in sensitivity is due to the ability of PMS2 in predicting MLH1 missense mutations [46].

MSI is currently still regarded as the gold standard screening test for MMR mutations. When comparing MSI versus IHC as screening of Lynch syndrome, IHC is a feasible tool to use, but only if all four proteins are stained for. The advantages of being a simpler, more inexpensive test with shorter turn-around times makes IHC an attractive option. It also helps to identify the mutated gene, therefore directing genetic testing [46].

3.4.4 Genetic Testing

Ten to fifteen percent of sporadic colorectal cancers express MSI, and therefore MSI is not specific for Lynch syndrome [45, 55]. The deficient MMR in sporadic CRC cases is almost always due to MLH1 deficiency secondary to hepermethylation of the 5′ CpG Island in the MLH1 promoter, leading to transcriptional silencing [56]. The V600E mutation in BRAF is associated with MSI-H colorectal cancers but not associated with Lynch syndrome [57–60]. The presence of BRAF V600E mutation therefore excludes Lynch syndrome in a patient with a tumour that has loss of MLH1 on IHC with specificity of ~100 % [45].

When MSI and/or IHC suggests that there is a mutation in one of the mismatch repair genes and BRAF mutation testing is negative for MLH1 deficient tumours, the patient should be offered genetic testing on a blood sample [55, 60]. Mutations in MLH1 and MSH2 account for 70–90 % of all cases of Lynch syndrome. MLH1 is situated on chromosome 3p21 and MSH2 on 2p22. The genes for MLH6 and PMS2 are situated on chromosomes 2p16 and 7q11 respectively. Commercial testing is available for MLH1, MSH2, MSH6 and PMS2 and is done by gene sequencing or by in vitro synthesized protein assays [61]. These tests are very expensive and should therefore be done only on individuals where there is strong suspicion of a germline mutation. Genetic testing for the first member of the family is known as mutation detection and costs around $1,500.

When testing for MMR genes in the index patient, it should include full gene sequencing and large re-arrangement testing. Large re-arrangements account for 20 % of the known mutations [32]. Identification of a germline mutation is diagnostic for Lynch syndrome. Once a mutation is identified in a family, the other members of the family can be tested only for that mutation. Testing for only one mutation is much more straight forward and less expensive.

Hundreds of different mutations in the MMR genes in Lynch syndrome have been reported, with the incidence of different mutations varying in different populations. MLH1 is by far the most common MMR gene involved, followed by MSH2. MLH6 and PMS2 mutations are rarer [4, 44, 62].

IHC helps to direct germline testing. Loss of MSH6 or PMS2 on IHC suggests a mutation in the corresponding gene and testing for the specific gene should be

undertaken [32, 63]. With the loss of MLH1 on IHC, the decision making is more complex. Genetic testing is preceded by testing for the BRAF mutation. If the BRAF mutation is not present, genetic testing for MLH1 is pursued. In this situation, even if no MLH1 germline mutation can be found, the diagnosis of Lynch syndrome due to an undetectable mutation can be made. When IHC demonstrates absence of both MLH1 and PMS2 gene product, genetic testing for PMS2 is not indicated [14].

If IHC shows absence of MSH2 and MSH6, genetic testing should be started by analyzing the MSH2 gene, as Lynch syndrome is more frequently associated with a mutation in the MSH2 gene. Another germline mutation in a gene called the EpCAM gene, has recently been identified in a subset of families with Lynch syndrome with loss of MSH2 on IHC [64]. The incidence of an EpCAM mutation may be as high as 30 % when IHC shows absence of MSH2 [65]. Many laboratories now include EpCAM testing as part of the analysis for MLH2. If a mutation in the MSH2 gene is not identified, the MSH6 gene should be analyzed. Loss of MSH2/MSH6 on IHC is strongly associated with a germline defect of the MMR. If genetic testing does not detect a germline mutation in MSH2, EpCAM or MSH6 in an individual with loss of MSH2/MSH6 on IHC, the diagnosis of Lynch syndrome due to an undetectable mutation should be made [14].

Germline gene testing should only be done after adequate genetic counseling in a multidisciplinary environment. Genetic counseling is discussed in detail elsewhere in this book. If a member of a family test positive for the identified mutation, that member should be enrolled into a surveillance program. Family members who do not have the mutation can be discharged from further surveillance.

In cases where genetic testing is negative for a mutation or a mutation of undetermined significance is detected, genetic tests are considered indeterminate or uninformative [66]. Families with a history in keeping with Lynch syndrome, but without a detected mutation are at a lower risk for development of colorectal cancer than individuals with Lynch syndrome [67].

3.5 Familial Colorectal Cancer Syndrome X

Families who meet the Amsterdam II criteria with no identifiable deficiency in one of the mismatch repair genes should be considered to have Familial colorectal cancer syndrome X. The risk for developing colorectal cancer in these individuals are lower than in families diagnosed with Lynch syndrome, and they are not at increased risk for extra-colonic malignancies [68].

The gene(s) responsible in these families have not been identified yet, but seems to be inherited in an autosomal dominant fashion. Because the gene(s) are not identified, clinical testing is not available and all family members should be subjected to surveillance [32].

3.6 Algorithm for the Diagnosis of Lynch Syndrome

As part of the work-up for any patient with malignancy, a detailed family history should be obtained [4]. The clinician dealing with colorectal cancer should also enquire about family history of Lynch syndrome-associated malignancies. It is the duty of the treating physician to draw up pedigrees, thereby identifying at-risk first- and second degree relatives. This information must be clearly documented and all tumours from patients from families meeting the Amsterdam II and Revised Bethesda criteria should be further investigated. Genetic counsellors and nurses are often better equipped than surgeons to identify and contact relatives who are at risk. In certain centres, genetic counsellors and nurses receive in-depth training in genetics and are trained to help people at-risk or affected by diseases with a genetic component. Genetic nurses can:

- Perform risk assessment
- Analyse the genetic contribution to disease risk
- Discuss the impact of risk on health care management
- Provide genetic education
- Nursing care to patients and families and
- Conduct research in genetics

Genetic nurse counselors are a cost effective alternative to clinical geneticists [69]. They add another dimension of skills, but also a level of empathy and understanding, often lacking in a busy surgical out-patient department. If available, the genetic counsellor or genetic nurse counsellor should be involved very early in the management of a patient suspected to have Lynch syndrome. The formulation and maintenance of family trees would be a start of a cancer registry.

Tumour histopathology from an individual without a significant family history that meets the Revised Bethesda criteria should be subjected to further testing. MSI or IHC testing, using all four MMR proteins, can be used as first line screening test to diagnose Lynch syndrome. It seems reasonable and cost effective to use IHC as initial screening. If MSI is used as initial screening test, all tumours that are reported as MSI-H should undergo IHC testing to help identify the MMR that may be responsible.

Patients with tumours that show absence of one of the MMR proteins on IHC should be offered germline genetic testing. Genetic testing should be tailored to the IHC results (see Fig. 3.1).

If a germline mutation is identified on genetic testing, the diagnosis of Lynch syndrome is confirmed. Family members of such an individual should be offered genetic counselling and testing for that specific mutation. If a family member tests positive for the mutation, that individual should be enrolled in a surveillance program. Family members without the mutation can be discharged from surveillance. A co-ordinated predictive testing and colonoscopic surveillance program has been shown to extend the life of a compliant individual with Lynch syndrome, by about 20 years [7].

If no germline mutation is identified, the diagnosis of Familial Colorectal Cancer Syndrome X should be entertained. All at-risk family members of such an individual should be enrolled in a surveillance programme.

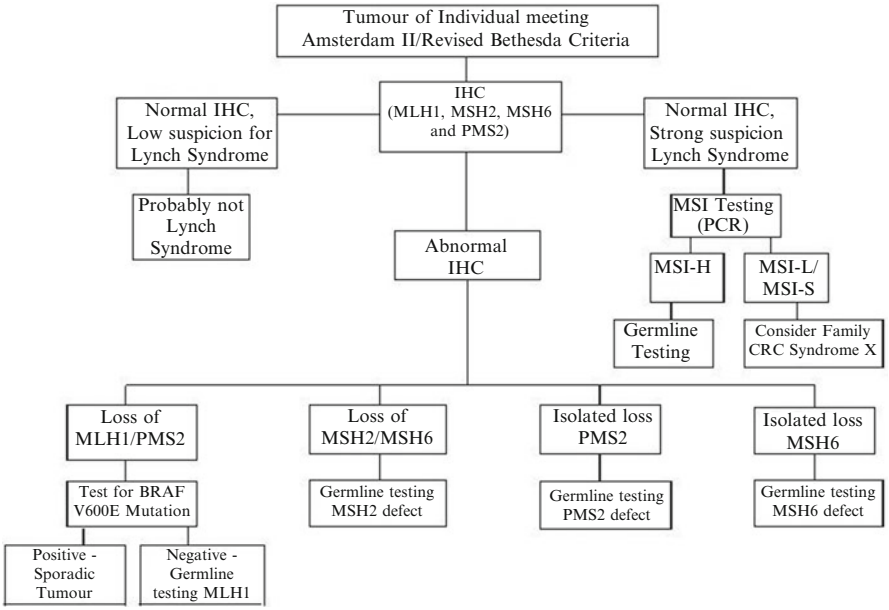

Fig. 3.1 Algorithm for the diagnosis of Lynch syndrome [40, 70]

3.7 Summary and Future Directions

The integration of molecular biology in the diagnosis of inherited colorectal cancer has become part of everyday practice when managing patients with a familial predisposition to colorectal cancer. Identifying patients with mutations in MMR genes has resulted in directed surveillance programmes that include prophylactic surgery when indicated, resulting in improved outcomes for patients with Lynch syndrome. A simple and cost-effective algorithm for the diagnosis of Lynch syndrome is the cornerstone in identifying patients with this inherited disorder. The future in the diagnosis of Lynch syndrome will be directed in point-of-care tests identifying MSI or IHC, thereby influencing surgical decision-making and family surveillance strategies in a cost-effective manner.

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