SPECIAL REPORT

Enabling the Early Detection and Targeted Intervention of Patients at Risk of Hereditary Cancer Syndromes

Cancer Risk in Lynch Syndrome

PMS2 Mutation in Lynch Syndrome

Assessing Genetic Risk of Breast and Ovarian Cancer

Trends and Technologies in Genetic Testing for Oncology

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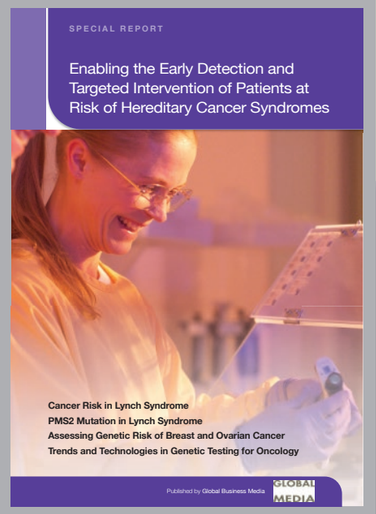

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Foreword

Cancer risk assessment has undergone a transformative evolution with the advent of advanced genetic testing, shedding light on hereditary syndromes such as Lynch syndrome and hereditary breast and ovarian cancer (HBOC). Among the key genetic anomalies linked to these conditions are mutations in mismatch repair (MMR) genes, which are causal in Lynch syndrome, and BRCA1/2 and PALB2 in HBOC.

Lynch syndrome, a hereditary condition predisposing individuals to colorectal and other cancers, is often associated with mutations in MMR genes, including PMS2. PMS2 pathogenic variants, although less common than mutations in other MMR genes such as MLH1 and MSH2, still present a significant risk for colorectal, endometrial, and other cancers. Understanding the specific risk profiles and mechanisms of PMS2-related cancers is crucial for developing tailored surveillance and prevention strategies. Challenges in accurately identifying PMS2 variants include discrimination of variants occurring in non-functional pseudogenes.

Breast and ovarian cancers, commonly associated with HBOC, are frequently linked to mutations in BRCA1 and BRCA2 genes. However, recent studies have expanded the list of genetic contributors, highlighting the importance of comprehensive genetic screening. Assessing genetic risk for breast and ovarian cancer involves evaluating a spectrum of gene mutations beyond BRCA1/2, including those in PALB2 and others, providing a more nuanced risk profile that can guide personalized prevention and treatment strategies.

Tumor genetics has become integral to the field of precision medicine. By analyzing the specific genetic mutations within a tumor, oncologists can tailor treatments to target those anomalies directly. This approach has revolutionized cancer therapy, allowing for more effective and less toxic treatment regimens. Precision medicine relies on detailed genetic information, which can be obtained through next-generation sequencing (NGS) technologies.

Advanced NGS kits have significantly improved the efficiency and accuracy of genetic testing for Lynch syndrome and HBOC. These kits simultaneously enable comprehensive screening of multiple genes, providing a thorough genetic profile, which is essential for risk assessment and management. For Lynch syndrome, NGS kits can detect mutations across all relevant MMR genes, including PMS2, offering a more complete picture of genetic predisposition. These kits can now also eliminate confounding results arising from pseudogenes. Similarly, for HBOC, NGS kits assess an array of susceptibility genes, enhancing the predictive power and enabling more precise interventions.

In summary, integrating genetic testing into cancer risk assessment and management has ushered in a new era of precision medicine. By understanding the specific genetic mutations that underlie conditions like Lynch syndrome and HBOC and utilizing advanced NGS assays, we can develop targeted strategies for prevention, early detection, and personalized treatment. This not only improves patient outcomes but also represents a significant leap forward in our fight against hereditary cancers.

Michael James
Editor

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ENABLING THE EARLY DETECTION AND TARGETED INTERVENTION OF PATIENTS AT RISK OF HEREDITARY CANCER SYNDROMES

Cancer Risk in Lynch Syndrome

Michael A James, PhD

How hereditary cancer syndromes such as Lynch syndrome can significantly increase patients' risk of developing colorectal cancer and other types of cancer.

Colorectal cancer is the 3rd most common cancer in worldwide, which accounts for 10% of cancer cases and the 2nd most cancer deaths,[1],[2]. These rates have not substantially improved since the 1990s. Diagnosis at an early stage is the biggest positive indicator of prognosis in colorectal cancer, as patients who benefit from detection and intervention while tumors remain localized and are resectable have a 90% 5-year survival rate[3]. Once not resectable, the 5-year survival rate drops to 10%[3].

While they are often undiagnosed, hereditary cancer syndromes are associated with around 10% of all cancers, as assessed by a 2020 multicenter study in Germany[4],[5]. Of all colorectal cancers, 5–10% are estimated to be hereditary[6]. Lynch syndrome is the most common hereditary colorectal cancer syndrome, sometimes referred to as hereditary nonpolyposis colorectal cancer syndrome and is caused by germline variants of one of several DNA mismatch repair (MMR) genes. This hereditary form of colorectal cancer can confer up to an 80% lifetime risk of developing colorectal cancer and a 60% lifetime risk of endometrial cancer in women[6]. Risk of other cancers, including gastric, ovarian, pancreatic, and glioblastoma, can also be associated with Lynch syndrome. Lynch syndrome is autosomal dominant, with the risk of cancer increasing upon loss of the functional allele. This gives first-degree relatives of a patient diagnosed with Lynch syndrome a 50% chance of being affected. The risk of developing colorectal cancer for someone who has been diagnosed with Lynch syndrome can depend on the particular underlying variant, and there can be variability in risk among patients with the same variant[7].

The Vital Importance of Hereditary Cancer Testing for Early Management of Lynch Syndrome

The identification of a pathogenic variant in a patient with hereditary cancer syndromes, including Lynch syndrome, can have substantial impacts on the treatment, prevention, and testing of family members. A 2020 US study reported that Lynch syndrome-associated MMR genes were among the 4 most common pathogenic germline variants found in cancer patients, along with BRCA1/2, MUTYH, and CHECK2[8]. These genes are MLH1, MSH2, MSH6 and PMS2. Deletions in the EPCAM gene, which cause decreased MSH2 expression, have also been found in Lynch syndrome[6].

Cascade family variant testing is the evaluation of family members most likely to inherit a mutation first and following up with additional family members according to those test results. Cascade testing rates are low in families in which a pathogenic variant of a Lynch mismatch repair gene is identified[8]. In a recent study at The Manchester Centre for Genomic Medicine, cascade testing for cancer predisposition gene variants resulted in the identification of 1 familial case per index case, leading to over 1000 surgeries and reducing the risk of cancer in hereditary breast and ovarian cancer and Lynch syndrome[9].

While they are often undiagnosed, hereditary cancer syndromes are associated with around 10% of all cancers, as assessed by a 2020 multicenter study in Germany

The Importance of Testing

Such testing is important because at-risk individuals can be identified early, even before symptoms appear. This can allow steps to be taken to prevent colorectal cancer or treat it early. Preventive steps can include the use of aspirin or other non-steroidal anti-inflammatory drugs. A 10-year follow-up to a clinical trial for the prevention of colorectal cancer using aspirin in patients with Lynch syndrome showed a significant reduction in risk over placebo (HR-0.56)[10].

Another preventive measure is the detection of adenomas using colonoscopy in patients with known Lynch syndrome, which can reduce colorectal cancer incidence and mortality[11]. Prophylactic surgery can be performed if adenomas are detected. Improved adenoma detection and reduced post-colonoscopy colorectal cancer incidence have been demonstrated with colonoscopy intervals of less than 3 years in patients with Lynch syndrome[11]. Models for the use of gene-specific variation

A 10-year follow-up to a clinical trial for the prevention of colorectal cancer using aspirin in patients with Lynch syndrome showed a significant reduction in risk over placebo

in Lynch syndrome to guide surveillance have supported recommendations for intensive colonoscopy surveillance (every 1–2 years) of patients with MLH1 or MSH2 variants and later initiation of surveillance (every 3 years at 35–40 years of age) for those with MSH6 or PMS2 variants[12]. The benefits of these surveillance approaches guided by MMR genotypes were based on clinical trial data, considering quality-adjusted life-years and cost-effectiveness.

The Role of Vaccines

With the advent of tumor antigen-specific vaccines to prevent or treat cancer, gene-specific information regarding MMR gene variants has the potential to guide personalized interventions for Lynch syndrome-associated colorectal cancer. Such vaccines are under investigation, such as peptide vaccines against a frame-shift mutant MLH1 identified in multiple Lynch syndrome families, which was immunogenic in vitro[13]. The tumor infiltrates in these patients revealed low activation of CD8 T cells, indicating possible immune suppression and encouraging a potential vaccine/checkpoint inhibitor combination as a personalized approach in such patients. Since MMR is deficient in Lynch syndrome, microsatellite instability, high mutational load, and presentation of neoantigens are expected, further encouraging immunotherapy approaches.

An Additional Benefit

Yet another benefit of testing for MMR variants in Lynch syndrome is the evaluation of risk in individuals since risk can depend on the specific variant and the existence of variability in risk within certain variants. For example, variability in risk was shown to be particularly evident in carriers of MLH1 or MSH2 variants and is hypothesized to be affected by unknown familial risk modifiers[7]. Differences in the associated risk and, potentially, differences in personalized therapy approaches among MMR variants may be affected by the unique molecular profiles that have been observed within groups of patients with specific germline MMR variants. An example of this is the observation of APC mutations and the absence of CTNNB1 mutations in PMS2 variant carriers with Lynch syndrome-associated colorectal cancer[14].

In summary, gene-specific testing for MMR gene variants associated with Lynch syndrome can enable valuable known preventive measures for patients affected by Lynch syndrome, including non-steroidal anti-inflammatory drugs, colonoscopic surveillance, and surgical removal of adenomas. In addition, gene-specific testing can facilitate more efficacious early treatment of Lynch syndrome-associated colorectal cancer and potentiate novel individualized approaches, such as neoantigen vaccines.

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PMS2 Mutation in Lynch Syndrome

Michael A James, PhD

The lifetime risk of colorectal cancer in a PMS2 pathogenic variant carrier has been estimated at 10–20% compared to 4% in the general population

Lynch syndrome is a major cause of familial cancers and the most common hereditary cancer syndrome in families affected by colorectal cancer. Germline variants in the *PMS2* gene are one underlying cause of Lynch syndrome. While they have been previously thought to be responsible for an estimated 8-15% of Lynch syndrome[1], *PMS2* variants are more common in the general population than in other MMR genes[1], and expanding knowledge of *PMS2* pathogenic variants and the associated penetrance of Lynch syndrome phenotypes and cancer is revealing a broader role in disease. Carriers of Lynch syndrome-associated pathogenic MMR gene variants, including those of *PMS2*, are at increased risk of developing cancers, most commonly colorectal cancer. Monoallelic carriers of a *PMS2* pathogenic variant inherit a 25–32% lifetime risk of any cancer[2]. The lifetime risk of colorectal cancer in a *PMS2* pathogenic variant carrier has been estimated at 10–20% compared to 4% in the general population[3]. Lynch syndrome is autosomal dominant, although it may go undiagnosed because of a lack of testing under stringent criteria, particularly with lower penetrance *PMS2* variant carriers. Constitutional mismatch repair deficiency (CMMRD) is an autosomal recessive childhood cancer syndrome, and the majority of cases have biallelic germline pathogenic variants of *PMS2*[1],[4]. CMMRD may not be detected in some patients because of cancer mortality early in life. Cancer risk varies with CMMRD and highly depends on genetic and environmental modifiers[5]. The contribution of *PMS2* to hereditary cancer syndromes may be underappreciated in terms of prevalence, particularly in the autosomal dominant form, Lynch syndrome. A new understanding of the clinical significance of *PMS2* variants and higher fidelity in testing for these variants is improving that deficiency.

The Need for Specific Analysis of the PMS2 Gene

The *PMS2* protein is an endonuclease that is required for 3' nick-directed mismatch repair[6]. While monoallelic germline variants of *PMS2* are less frequently identified in families that exhibit typical Lynch syndrome phenotypes because of lower penetrance, *PMS2* pathogenic variants do predispose to cancer, and biallelic germline variants of *PMS2* are the most common cause of constitutional mismatch repair deficiency[7]. This makes vigilance in testing for *PMS2* pathogenic variants particularly important, as there has been a lack of testing in families with low penetrance in regard to cancer[2]. More stringent criteria for diagnosing Lynch syndrome have more often led to the identification of germline variants in MLH1 or MSH2 MMR genes, to which 40% and 34% of Lynch syndrome cases have been attributed, respectively[8]. However, it is likely that with modified criteria for testing, a higher prevalence of *PMS2* variants with pathological significance may be found. Indeed, changing guidelines for testing have resulted in the identification of more families with Lynch syndrome[1]. Less stringent criteria that include all Lynch syndrome-associated cancers, including colorectal, endometrial, gastric, small bowel, ovarian, and ureter cancers, as well as the use of modern testing methods that can correctly identify *PMS2* pathogenic variants have the potential to capture previously unidentified familial cases. Updated guidelines can now consider colorectal cancer with high microsatellite instability and cases in second-degree relatives[1].

The testing criteria for identifying pathogenic variants in *PMS2* have been changing. More carriers of pathogenic mutations in *PMS2* can now be identified because of the fidelity of modern testing to the *PMS2* gene rather than its pseudogenes, discussed further in the following section. In addition, the clinical significance of more *PMS2* variants has been and is being determined through basic research into their functional consequences. It is important to note that, despite previous lack of knowledge regarding the prevalence of *PMS2* variants and the cancer risk in carriers, *PMS2* pathogenic variants do significantly contribute to Lynch syndrome and associated cancer risk. This calls for heightened surveillance and counselling efforts to identify and manage *PMS2* pathogenic variant carriers.

Challenges in Identifying Variants in PMS2 Versus PMS2CL During Genetic Testing for Lynch Syndrome

PMS2 comprises an ATPase domain and an endonuclease domain responsible for interaction with another MMR protein, MLH1.

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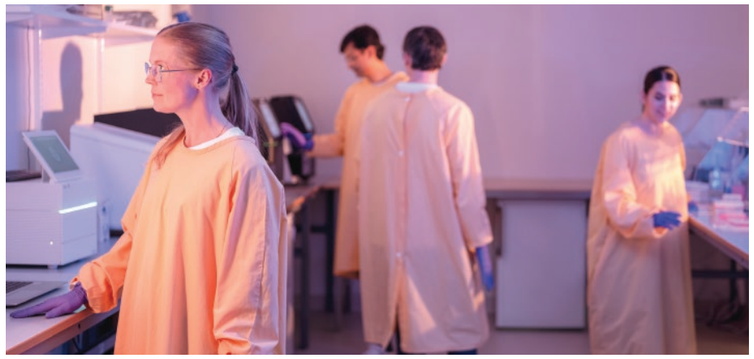

The endonuclease domain is required for MMR function[9]. Several pseudogenes homologous to *PMS2* have complicated accurate short-read gene sequencing using next-generation sequencing or Sanger sequencing[1]. In particular, the pseudogene *PMS2*CL has high homology to exons 9 and 11–15, comprising part of the ATPase domain and the entire endonuclease domain, compared to other *PMS2* pseudogenes that have homology to exons 1–5, representing a smaller portion of the protein in the N-terminus of the ATPase domain.

Gene conversion, or sequence transfer between *PMS2* and *PMS2*CL, can also occur, further complicating the detection of true *PMS2* variants by sequencing short fragments. A common gene conversion in *PMS2* exists in exons 13–15[10]. This represents a functional hybrid allele, present in up to 60% of the population. This can confound the significance of short sequence reads since they may compare differently to a gene conversion versus the non-hybrid allele.

These challenges to identifying pathogenic variants in the *PMS2* gene have been overcome by using modified long-range PCR[1]. This technique uses a primer within exon 10, which is not present in *PMS2* pseudogenes, followed by sequencing and comparison to the *PMS2* sequence[11]. Large-scale deletions of *PMS2* can also be detected by combining this method with multiplex ligation-dependent amplification. Such long-range PCR methods for discriminating between *PMS2* and *PMS2*CL had not been available in commercial kits until recently with kits such as Devyser LynchFAP* (Devyser), which tests for variants associated with Lynch syndrome and familial adenomatous polyposis. These modern assay methods have allowed the identification of true variants in the *PMS2* gene, providing more meaningful genetic risk assessment and advancing knowledge of clinically significant variants.

Gene conversion, or sequence transfer between PMS2 and PMS2CL, can also occur, further complicating the detection of true PMS2 variants by sequencing short fragments

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Assessing Genetic Risk of Breast and Ovarian Cancer

Michael A James, PhD

There are multiple germline variants in the BRCA genes that have been associated with the risk of breast and ovarian cancer, some of which are more common in certain populations

The Role of Mutations in BRCA1/2 And PALB2 in Breast and Ovarian Cancer Risk

Hereditary breast and ovarian cancer syndrome (HBOC) is characterized by a familial genetic predisposition to breast and ovarian cancers, early age of onset, and multiple or metachronous tumours. HBOC is most commonly caused by germline mutations in the *BRCA1* or *BRCA2* genes[1], the products of which are involved in homologous recombination repair of double-stranded DNA. While around 13% of women develop breast cancer in their lifetime[2], 45–72% of women with pathogenic variants in *BRCA1* or *BRCA2* will develop breast cancer by 70–80 years of age[3]. *BRCA1* variants are generally associated with a higher risk of breast and ovarian cancer than *BRCA2* variants. The CDC reports the risk for breast cancer with a pathogenic *BRCA* variant at 50% and that for ovarian cancer 30% by age 70[4]. Around 5–10% of breast cancers are associated with inherited variants[1]. Several other cancers have increased risk associated with *BRCA* variants, although to a lesser extent. These include the fallopian tube, primary peritoneal, prostate, and pancreatic cancers[3].

BRCA germline variant prevalence among ovarian cancer patients is higher in certain populations and is highest among Ashkenazi Jews in the United States, Canada, and Nordic countries[5]. There are multiple germline variants in the BRCA genes that have been associated with the risk of breast and ovarian cancer, some of which are more common in certain populations. Different germline variants can also affect the degree of risk differently[5]. For example, exon 11 mutations of BRCA1 were found to be associated with earlier age of diagnosis in both breast and ovarian cancers[6]. The ability to estimate risk based on the specific location of BRCA mutation is a work in progress but may enable better preventive approaches, such as determining the age to perform salpingo-oophorectomy to reduce risk, as discussed in more detail below.

While most cases of HBOC syndrome are caused by *BRCA* pathogenic variants, some are caused by other gene variants. Partner and localizer of *BRCA2* (*PALB2*) interacts with both *BRCA1* and *BRCA2* and is critical for key DNA repair functions of these proteins[7]. While not as common as *BRCA* variants in breast and ovarian cancer, *PALB2* pathogenic germline variants also confer a risk of developing these cancers. While earlier studies estimated a lower lifetime risk with *PALB2* variants for breast cancer of 20–30%, larger and later studies within the last ten years have indicated higher risks of 35% by age 70 and 53% by age 80[8]. In addition, grade 3 ER-positive HER-negative, grade 3, and triple-negative cancers were enriched in cases with pathogenic *PALB2* variants.

Loss-of-function variants of *BRCA* and *PALB2* genes cause significant risk and are frequently found in HBOC families. *PALB2* pathogenic variants have been found to carry risks that can overlap with *BRCA2* variants[9]. Therefore, knowing which genes and variants are at play in a patient or family can result in meaningful clinical guidance.

The Benefits of Targeted Sequencing for Breast and Ovarian Cancer Risk Assessment and Management

Genetic testing for hereditary breast and ovarian cancer is recommended for those with a strong family history or a moderate family history and Ashkenazi or Eastern European Jewish ancestry[1]. Sequencing of *BRCA1*, *BRCA2*, and *PALB2* variants can help provide crucial genetic information needed to assess patients' risk of developing breast and ovarian cancer and appropriate risk-ameliorating measures. In Western countries, *BRCA* germline mutation rates have been found to be high (35–40%) in ovarian cancer patients without family history, leading American institutions, such as the National Comprehensive Cancer Network (NCCN), to advocate for genetic testing of all ovarian cancer patients regardless of family history[10]. However, the European Society for Medical Oncology (ESMO) and the UK's National Institute for Health and Care Excellence (NICE) recommend that genetic testing be considered on the basis of a family history of breast or ovarian cancer[10]. Meanwhile, universal genetic testing has been shown to detect more inherited pathogenic variants that can guide clinical action than guideline-based approaches[11]. As with other hereditary cancer syndromes, such as Lynch syndrome, cascade testing, or the sequential testing of family members at risk based on positive index cases, can help identify family members who carry pathogenic variants causing HBOC. While HBOC families have shown higher rates of cascade testing than Lynch syndrome families, less than half of first-degree female relatives were found to participate in testing[12]. This highlights the need for more vigilant genetic testing in HBOC families.

A major benefit of *BRCA* testing in patients at risk with HBOC is the guidance of risk-reducing salpingo-oophorectomy (RRSO) and the timing of such a procedure. Guidelines recommend RRSO for patients with *BRCA* pathogenic variants aged 35 to 40 years[13]. Preventive surgery can reduce breast cancer risk by 50–60% and that of ovarian cancer by 80–90% in carriers of *BRCA* pathogenic variants[14]. For RRSO, specifically, a meta-analysis showed a reduction in ovarian cancer risk by 79% and in breast cancer by 51%[15].

Testing for pathogenic variants in homologous recombination repair genes also has the benefit of directing the use of PARP inhibitors[9]. Dysfunction in homologous DNA repair is sometimes termed *BRCA*ness given the similarities to *BRCA*-mutated cancers in phenotype. These cancers are often more sensitive to targeting DNA repair pathway factors, such as PARP. *BRCA* testing and homologous repair deficiency (HRD) testing are companions for evaluating potential response to PARP inhibitors. Since families with germline variants in *PALB2* may be deficient in similar DNA repair pathways, including testing for *PALB2* variants may help identify more familial cases of breast and ovarian cancer that would benefit from PARP inhibition.

In summary, the importance of testing for *BRCA* and *PALB2* variants in HBOC families and, in some cases, non-familial cancer is evident and can provide actionable results to guide risk assessment, preventive surgery, and targeted therapy.

Universal genetic testing has been shown to detect more inherited pathogenic variants that can guide clinical action than guideline-based approaches

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Trends and Technologies in Genetic Testing for Oncology

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Regardless of the terminology, there has been a great deal of progress in the development and implementation of precision medicine in oncology

Tumor Genetics in the Era of Precision Medicine

Precision medicine and personalized medicine are terms previously used interchangeably to describe medicine driven by knowledge of an individual's genetic and molecular profiles. This has included a targeted approach to treating cancer that is tailored to the individual, thereby creating the opportunity for safer therapy with a greater likelihood of eliciting a tumor response. Precision medicine is the term that is more often used in recent years, reflecting a targeted approach and a basis in specific genetics and molecular biology. Regardless of the terminology, there has been a great deal of progress in the development and implementation of precision medicine in oncology, which has been driven by advances in genetic and molecular research as well as genetic testing and diagnostics that allow patients with targetable alterations to be identified. While cytotoxic chemotherapies remain an important tool for cancer therapy, new generations of oncology therapeutics have followed the shift toward precision medicine, led by multidisciplinary approaches. These include synergistic combinations with immune checkpoint inhibitors for tumors that present neoantigens but have a dampened anti-tumor immune response. Precision medicine has become the standard of care for many clinically challenging cancers.

Immunotherapy approaches, such as the use of checkpoint inhibitors, can be indicated for tumors that are microsatellite instability (MSI)-high and/or have defects in mismatch repair (MMR) genes[1]. MMR deficiency is a characteristic of some hereditary cancers, such as in Lynch syndrome. Identifying such defects or pathogenic variants in MMR genes can indicate high mutational load and neoantigen presentation, which may direct the use of immunotherapies. Indeed, several approved checkpoint inhibitors, including pembrolizumab, durvalumab, avelumab, nivolumab, ipilimumab, and atezolizumab, have shown high objective response rates for Lynch syndrome-associated colorectal cancers (up to 71%) and noncolorectal cancers (up to 100%) with pathogenic MMR gene variants[2]. Some have been approved as first-line therapy for patients with unresectable or metastatic MSI-high or MMR-deficient colorectal cancer[3]. Other immunologic approaches can be effective in such cancers depending on identifying specific neoantigens. For example, Majumder et al. developed peptide vaccines against a specific MLH1 variant in Lynch syndrome, which showed immunogenic activity in vitro[4]. Tumors from the families that participated in the study showed low activation of CD8 T cells, which suggests immunosuppression that may be overcome by the addition of a checkpoint inhibitor.

Precision medicine based on genotype and phenotype has also targeted DNA repair mechanisms in those with defects in homologous recombination. For example, cancers with loss-of-function mutations or germline variants in BRCA1/2 or PALB2 have altered sensitivity to certain drugs. Sensitivity to genotoxic chemotherapeutic drugs, including platinum-based drugs, can be increased in tissues and tumors with BRCA1/2 or PALB2 mutations or variants[5],[6]. Colorectal cancer cells with defects in MMR genes have been found to be resistant to 5-fluorouracil but sensitive to irinotecan and mitomycin C[7]. These profiles that are dependent on genotype can help guide effective individualized therapy.

Deficiencies in BRCA1/2 or PALB can also render a tumor dependent on the function of poly (ADP-ribose) polymerase (PARP) in DNA repair[8], which has presented precision therapeutic opportunities with the use of PARP inhibitors. It has been established that breast and ovarian cancer patients carrying BRCA mutations or variants respond particularly well to both platinum-based and PARP inhibitor therapies[6],[9]. A meta-analysis showed significant progression-free survival benefit in breast and ovarian cancer patients that carry BRCA mutations or pathogenic germline variants. However, the overall survival benefit was sub-significant[10]. PARP inhibitors have proven to be a relatively effective and safe precision approach to treating breast and ovarian tumors with BRCA1/2 or PALB2 alterations, either as maintenance therapy or in combination with platinum-based chemotherapy[9].

Advanced Genetic Testing

Highly accurate diagnostic tests that provide fast, actionable results are key to supporting the drive towards individualized cancer therapies, such as those targeting homologous recombination- or MMR-deficient cancers. Testing has evolved from general assays for genomic alteration or repair deficiencies to sequencing and targeted gene-specific testing as knowledge of pathogenic variants and alterations has increased. Integrated testing for homologous repair or non-BRCA homologous recombination mutation can help predict PARP inhibitor response but is insufficient to guide the use of this targeted drug in many cases, such as in high-grade serous ovarian cancer[11]. Thus, ESMO recommendations include BRCA1/2 variant testing for all non-mucinous ovarian cancers at primary diagnosis to predict sensitivity to PARP inhibitors[11]. In ovarian cases where germline testing is indicated, testing for mutations/variants in MMR genes is recommended by ESMO and is strongly recommended where family history suggests Lynch syndrome. ESMO also recommends that MMR genetics and/or MSI testing be considered in all CRC patients[12]. The recommended follow-up and identification of hereditary versus sporadic cases depends on which MMR gene is altered. This highlights the need for accurate and efficient gene-specific testing to guide clinical courses and family risk assessment.

Targeted sequencing of hereditary cancer genes has evolved. Accurate identification of variants in genes that are associated with hereditary cancer syndromes, such as Lynch syndrome and hereditary breast and ovarian cancer, has improved and become easier with kits that offer simple workflow and single-tube formats. With these technologies, testing can be more repeatable, and handling time and the possibility of sample misidentification or cross-contamination can be minimized. Distinction of variants in these genes from interfering signals from pseudogenes and coverage of large deletions has been overcome with the incorporation of next-generation sequencing with long-range PCR. This represents a decided improvement over Sanger sequencing and multiplex ligation-dependent probe amplification for this reason and because of assay simplification.

Targeted approaches now exist that encompass multiple hereditary colorectal cancer syndromes, such as Lynch syndrome (MMR genes), Familial Adenomatous Polyposis (FAP), and MUTYH-Associated Polyposis. Guided by refined knowledge of pathogenic gene variants, these kits are focused enough to allow easy interpretation and comprehensive enough to optimize implicated gene coverage. For breast and ovarian cancers, single-tube testing for BRCA1, BRCA2, and PALB2 variants using next-generation sequencing approaches are now available that have minimal hands-on time and rapid turnaround time for sequencing results. These methods now allow for efficient coverage of high-penetrance genes using a targeted approach to identify clinically actionable variants for specific cancers. With trends toward testing even in the absence of family histories of hereditary cancer syndromes, e.g. ESMO recommendations for testing in all colorectal cancer patients, reliable but efficient testing using targeted sequencing kits becomes key to effective risk evaluation, prevention, and precision therapy.

For breast and ovarian cancers, single-tube testing for BRCA1, BRCA2, and PALB2 variants using next-generation sequencing approaches are now available that have minimal hands-on time and rapid turnaround time for sequencing results

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Notes

ENABLING THE EARLY DETECTION AND TARGETED INTERVENTION OF PATIENTS AT RISK OF HEREDITARY CANCER SYNDROMES

Notes

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