ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2023 February 24; 14(2): 40-98

Published by Baishideng Publishing Group Inc

World Journal of Clinical Oncology

Contents

Monthly Volume 14 Number 2 February 24, 2023

REVIEW

MINIREVIEWS

World Journal of Clinical Oncology

Monthly Volume 14 Number 2 February 24, 2023

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Oncology*, Budhi S Yadav, MD, (Radiation Oncology), Professor, Department of Radiotherapy & Oncology, Post Graduate Institute of Medical Education & Research, Chandigarh, 160012, India. drbudhi@gmail.com

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Oncology* (*WJCO*, *World J Clin Oncol*) is to provide scholars and readers from various fields of oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

INDEXING/ABSTRACTING

The *WJCO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Reference Citation Analysis, China National Knowledge Infrastructure, China Science and Technology Journal Database, and Superstar Journals Database. The 2022 edition of Journal Citation Reports® cites the 2021 Journal Citation Indicator (JCI) for *WJCO* as 0.35.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2218-4333/editorialboard.htm

PUBLICATION DATE
February 24, 2023

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2023 February 24; 14(2): 40-68

DOI: 10.5306/wjco.v14.i2.40

ISSN 2218-4333 (online)

REVIEW

Hereditary cancer syndromes

Evgeny N Imyanitov, Ekaterina S Kuligina, Anna P Sokolenko, Evgeny N Suspitsin, Grigoriy A Yanus, Aglaya G Iyevleva, Alexandr O Ivantsov, Svetlana N Aleksakhina

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A, A
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Stabellini N, United States; Zhang X, China

Received: November 17, 2022
Peer-review started: November 17, 2022
First decision: November 30, 2022
Revised: December 9, 2022
Accepted: February 14, 2023
Article in press: February 14, 2023
Published online: February 24, 2023

Evgeny N Imyanitov, Ekaterina S Kuligina, Anna P Sokolenko, Evgeny N Suspitsin, Grigoriy A Yanus, Aglaya G Iyevleva, Alexandr O Ivantsov, Svetlana N Aleksakhina, Department of Tumor Growth Biology, N.N. Petrov Institute of Oncology, St.-Petersburg 197758, Russia

Evgeny N Imyanitov, Ekaterina S Kuligina, Anna P Sokolenko, Evgeny N Suspitsin, Grigoriy A Yanus, Aglaya G Iyevleva, Alexandr O Ivantsov, Svetlana N Aleksakhina, Department of Clinical Genetics, St.-Petersburg Pediatric Medical University, St.-Petersburg 194100, Russia

Corresponding author: Evgeny N Imyanitov, DSc, Professor, Department of Tumor Growth Biology, N.N. Petrov Institute of Oncology, Pesochny, Leningradskaya Str. 68, St.-Petersburg 197758, Russia. evgeny@imyanitov.spb.ru

Abstract

Hereditary cancer syndromes (HCSs) are arguably the most frequent category of Mendelian genetic diseases, as at least 2% of presumably healthy subjects carry highly-penetrant tumor-predisposing pathogenic variants (PVs). Hereditary breast-ovarian cancer and Lynch syndrome make the highest contribution to cancer morbidity; in addition, there are several dozen less frequent types of familial tumors. The development of the majority albeit not all hereditary malignancies involves two-hit mechanism, *i.e.* the somatic inactivation of the remaining copy of the affected gene. Earlier studies on cancer families suggested nearly fatal penetrance for the majority of HCS genes; however, population-based investigations and especially large-scale next-generation sequencing data sets demonstrate that the presence of some highly-penetrant PVs is often compatible with healthy status. Hereditary cancer research initially focused mainly on cancer detection and prevention. Recent studies identified multiple HCS-specific drug vulnerabilities, which translated into the development of highly efficient therapeutic options.

Key Words: Hereditary cancer syndromes; Germline pathogenic variants; Cancer predisposition; Cancer treatment; Next-generation sequencing

Core Tip: There are many reviews describing particular types of hereditary cancer syndromes (HCSs) (*e.g.*, hereditary breast-ovarian cancer, Lynch syndrome, Li-Fraumeni syndrome, *etc.*). However, for the last 15-20 years there were no publications providing a general overview on familial cancers. Our paper describes mechanisms underlying genetic cancer predisposition, lists major types of HCSs, and comments on therapeutic advances in the management of hereditary tumors.

Citation: Imyanitov EN, Kuligina ES, Sokolenko AP, Suspitsin EN, Yanus GA, Iyevleva AG, Ivantsov AO, Aleksakhina SN. Hereditary cancer syndromes. *World J Clin Oncol* 2023; 14(2): 40-68
URL: https://www.wjgnet.com/2218-4333/full/v14/i2/40.htm
DOI: https://dx.doi.org/10.5306/wjco.v14.i2.40

INTRODUCTION

Hereditary cancer syndromes (HCSs) are a heterogeneous group of genetic diseases, which are associated with significantly increased risk of tumor development. There is a number of severe inborn disorders characterized by profound multiorgan failures, where cancer susceptibility constitutes only a part of clinical presentation of the disease (*e.g.*, Bloom syndrome, Fanconi anemia, Nijmegen breakage syndrome, ataxia-telangiectasia, *etc.*). Most of these syndromes involve biallelic inactivation of genes involved in DNA repair and are characterized by severe immune deficiency[1,2]. Subjects affected by "genuine" HCSs usually do not have any detectable phenotypic malfunctions, they differ from truly healthy people only by a highly elevated propensity to develop malignant disease in certain organs.

Hereditary cancers apparently represent the most common category of vertically transmitted disorders. Indeed, while the occurrence of the best known genetic diseases, *e.g.*, cystic fibrosis or phenylketonuria, usually falls below 1:10000, the population frequency of *BRCA1/2*-associated hereditary breast-ovarian cancer (HBOC) or *MLH1/MSH2*-linked Lynch syndrome is about 25-30 times higher and approaches approximately 1:300–1:400[3-6]. Collectively, at least 2% of presumably healthy subjects carry germline PVs associated with highly increased and often a nearly-fatal risk of a certain cancer type, and these estimates can be significantly higher in populations with pronounced founder effect[5,7].

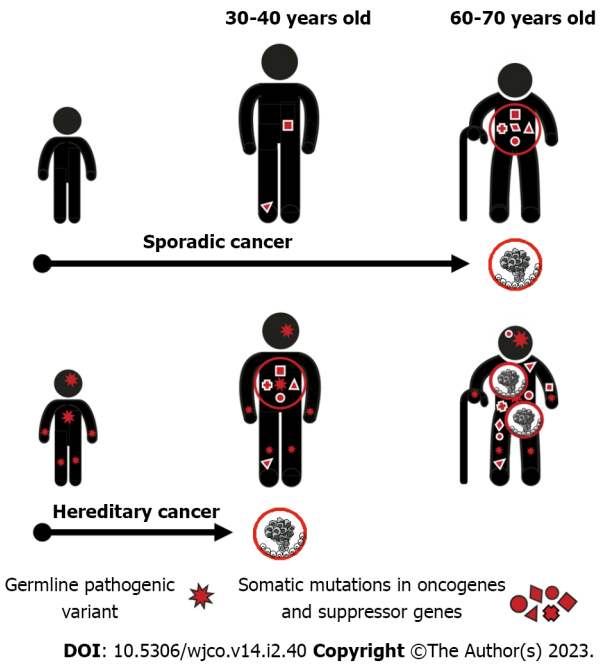
Earlier studies on HCSs usually assumed that almost all carriers of pathogenic alleles are destined to develop cancer, *i.e.* they considered mainly families and genes with almost 100% disease penetrance. The development of genetic technologies and the availability of large collections of cancer patients and healthy subjects resulted in the discovery of genes, whose alteration is associated with less pronounced but still medically relevant (2-3-fold) increase of cancer risk. These moderately penetrant alleles rarely cause familial clustering of malignancies and present a challenge for defining disease-preventive strategies. Furthermore, unbiased case-control studies revealed that earlier family-based HCS investigations overestimated disease risks for the majority of cancer genes; in fact, seemingly none of the well-established HCS genes has a complete penetrance, with the most of estimates falling within 40%–80% probability of tumor development for germline pathogenic variant (PV) carriers[4-6,8,9].

Virtually all HCSs are more or less organ-specific, *i.e.* they mainly manifest by cancers arising in particular anatomic sites or tissues. However, the development of hereditary cancer registries and large data sets led to the understanding that many HCSs are associated with a wider spectrum of cancers than was initially suggested, although most of the newly added tumor types are characterized only by a marginal increase of their lifetime risk. For example, *BRCA1* and *BRCA2* were discovered as breast-ovarian cancer genes. Recent data indicate that carriers of *BRCA1/2* PVs may have a borderline elevation of the probability of development for almost all major cancer types[10-16].

MECHANISMS OF HEREDITARY CANCER PREDISPOSITION

The acquisition of a single mutation in oncogene or suppressor gene is usually fully tolerable for a human cell due to the existence of multiple cancer-protecting biological mechanisms. The process of malignant transformation ultimately requires accumulation of several cancer-driving events in the same cell clone. Consequently, when a single cancer-associated PV is inherited from the parents, its carrier remains phenotypically healthy despite the presence of the pathogenic allele in every cell of the body. However, the number of additional events necessary for cancer manifestation decreases by one, therefore the probability of tumor development in this subject is manifold higher as compared to general population (Figure 1).

The majority of known HCS genes are suppressor genes, which require biallelic inactivation to exert their action. When inactivating PV in a single allele is inherited, the remaining copy of the gene retains its function and the normal health status is preserved. The process of malignant transformation is



DOI: 10.5306/wjco.v14.i2.40

Figure 1 Mechanisms of hereditary cancer predisposition. Single cancer-driving mutation is usually fully compensated, therefore carriers of germline pathogenic variants may remain healthy during a prolonged period of time. However, since every cell in the target organ already contains one alteration in cancer gene, the probability of accumulation of a critical mass of additional oncogenic mutations in any given cell clone is high, and cancer manifestation often occurs at a relatively young age.

usually triggered by the "second hit", *i.e.* by a somatic inactivation of the remaining allele occurring in any cell located within the target organ. This mechanism is highly characteristic for the best known HCS genes, *e.g.*, *RB1*, *BRCA1*, *BRCA2*, *MLH1*, *MSH2*, *etc*[4,17-19]. There are examples of mutated suppressor genes, which contribute to the development of hereditary cancers without mandatory inactivation of the remaining gene copy. It is suggested that the reduced gene dosage, so-called haploinsufficiency, is a primary cause of malignant transformation in these situations. Interestingly, some genes, *e.g.*, *PALB2* and *CHEK2*, may utilize both mechanisms: Indeed, instances of both monoallelic and biallelic inactivation of these genes in human tumors have been described in the literature, and there are clear biological differences between carcinomas associated with haploinsufficiency *vs* second-hit loss-of-function of the above genes[20,21].

A few human cancers are caused by the inheritance of activated oncogene. The best known example is the syndrome of multiple endocrine neoplasia (MEN) type 2A and 2B (now sometimes classified as MEN2 and MEN3, respectively), which is associated with gain-of-function PVs in *RET* receptor tyrosine kinase[22].

HCSs have a Mendelian mode of inheritance. Most of currently described hereditary cancers are transmitted by autosomal-dominant mechanisms. Recessive inheritance of cancer predisposition is more difficult to study, especially for common tumor types, therefore only a few examples of biallelic cancer-predisposing gene defects have been identified so far[23,24]. There are also reports describing instances of oligogenic inheritance, *i.e.* the combination of genetic variants resulting in significant increase of cancer risks[25-28].

Hereditary cancers usually have peculiar phenotypic characteristics attributed to their mechanisms of development[29]. Most of HCSs arising in adults manifest after the peak of reproductive activity, so cancer predisposition is transmitted through generations virtually without negative selection and HCS patients often describe multiple instances of the same disease in their relatives. Presence of the first cancer-predisposing mutation in every cell of the human organism ensures highly increased risk of cancer disease as long as target organs or their parts remain in the body. Consequently, HCSs often manifest by multiple primary malignancies[30]. Furthermore, given that the cancer development in PV carriers requires less additional somatic events as compared to genetically healthy subjects, hereditary cancers commonly demonstrate younger age at onset. The development of HCS usually involves gene-specific pathways, therefore these cancers are often distinguished by predetermined molecular portrait and histological appearance. For example, *BRCA1*-associated breast carcinomas are usually triple-negative, chromosomally unstable and carry somatic mutation in the *TP53* suppressor gene[31-34]. All these features, *i.e.*, family cancer history, presence of multiple primary tumors, young age at onset, and especial phenotypic characteristics, represent well-recognized clinical signs of HCSs[29].

MAJOR TYPES OF HCSs

Breast and ovarian carcinomas

It is difficult to discuss hereditary breast cancer (BC) and hereditary ovarian cancer (OC) as two separate disease entities, because the best known and the most frequent genetic causes for these diseases are represented by PVs located within the same genes, *BRCA1* and *BRCA2* (Figure 2). Nevertheless, there are essential differences between BC and OC, which may critically affect genetic investigations of these diseases. The lifetime risk for BC in Western countries is around 1:8, therefore about 1 out of 60-70 mother-daughter or sister-sister pairs would share this disease just by chance[35,36]. OC is significantly less common, with population occurrence approaching close to 1:60–1:70; therefore, the probability of "random" co-occurrence of OC in two female first-degree relatives is very low, falling within 1:3500–1:5000[36,37]. Furthermore, while two-thirds of OC cases belong to its major histological entity, *i.e.* high-grade serous ovarian carcinoma, breast carcinomas are characterized by significant biological diversity manifested by differences in their receptor status and other essential tumor features[38,39]. It appears that hereditary BC research has more confounding factors as compared to the analysis of OC familial clustering.

The causes of HBOC syndrome are considerably better understood than the genetic basis of hereditary BC alone. There are two major contributors to BC and OC predisposition, *BRCA1* and *BRCA2* (Table 1). Both these genes are involved in double-strand DNA repair by homologous recombination. *BRCA2*-associated cancers tend to have older age at onset as compared to *BRCA1*-driven malignancies. PVs in both *BRCA1* and *BRCA2* genes confer approximately 70% lifetime risk for BC; the cumulative risk for OC is estimated to be 44% and 17% for *BRCA1* and *BRCA2* genes, respectively[40]. Importantly, these collective calculations may somehow be misleading, because some PVs located within these genes predispose preferentially to BC, while others are associated with more pronounced OC risk; in fact, there are so-called BC and OC cluster regions located within these genes[41]. There are multiple genetic and non-genetic factors, which modify the risk of cancer disease in *BRCA1/2* PV carriers[42]. *BRCA1/2* make significant contribution to cancer morbidity: These PVs are observed in approximately 2%–5% of BC patients and up to 25%–30% of women diagnosed with high-grade serous OC[5,6,43-46]. In addition to *BRCA1* and *BRCA2*, some *RAD51* paralogs, namely *RAD51C* and *RAD51D*, predispose both to BC and OC[5,47,48]. Recent data also suggest the involvement of *RAD51B* germline PVs in breast- OC susceptibility[49]. The occurrence of PVs in newly described HBOC genes is an order of magnitude lower as compared to *BRCA1/2*[5,47].

PALB2 is the third most important BC-predisposing gene after *BRCA1* and *BRCA2*[50]. Its penetrance towards BC is similar to *BRCA2*, while the data regarding the role of *PALB2* PVs in OC predisposition are conflicting[47,51]. There are two middle-penetrance genes, *ATM* and *CHEK2*, which are associated with 2-3-fold elevation of the risk of BC development but are unlikely to contribute to increased OC susceptibility[47]. Moderate BC predisposing roles were also suggested for *NBN* (*NBS1*), *BLM*, *RECQL*, *FANCM*, *BARD1* and several other genes, but, contrary to the evidence obtained for *ATM* and *CHEK2*, these observations have not been uniformly reproduced across distinct data sets[5,6,47,52-54]. *BRIP1* is the only known gene, which is associated with hereditary OC but not with hereditary BC[47]. There are no mechanistic explanations, why some genes predispose to BC, others to OC, and a few to both BC and OC.

Many "novel" BC/OC-predisposing loci were discovered by candidate gene approach, where genes with similar to *BRCA1/2* functions, *i.e.*, the participants of DNA repair pathways, were selected for DNA testing in case-control studies. These functional considerations also influenced the interpretation of whole-exome studies, *i.e.*, the priority was given to genes involved in the maintenance of cellular genome[55,56]. Overall, exome sequencing studies largely failed to reveal novel BC predisposing genes whose contribution to BC morbidity is comparable with the impact of *BRCA1/2, PALB2* or *CHEK2* germline PVs[53,57,58].

BC may arise as a part of multiorgan cancer syndrome. Germline *TP53* PVs predispose to Li-Fraumeni syndrome, which is manifested by a wide spectrum of tumors. *TP53* PVs are particularly common in very young patients with BC[59]. Recent large-scale next-generation sequencing (NGS) studies suggest that mutated *TP53* can be found in non-selected BC patients, which do not have personal or family history of non-breast tumors[60-63]. A rare BC subtype, lobular BC, is associated with *CDH1* germline PVs predisposing to diffuse stomach cancer[47,64].

There are convincing data indicating that patients with Lynch syndrome, *i.e.*, hereditary predisposition to colorectal and endometrial cancer, develop OC more often than in general population[46,65-69]. Unlike *BRCA1/2*-driven tumors, Lynch syndrome associated OCs often have non-serous histology [68]. Several other multiorgan cancer syndromes also render marginally increased OC risk[46,70].

Exome sequencing studies of OC families identified several promising OC-predisposing candidates, *e.g.*, *ANKRD11* and *POLE* genes[71]. Some data indicate that protein-truncating germline PVs in the *ERCC3* gene may confer increased OC risk[72]. Validation of these findings is complicated due to rarity of *BRCA1/2*-independent familial OC clustering.

Small cell carcinomas of the ovary, hypercalcemic type (SCCOHTs) constitute a rare variety of OC. SCCOHTs are associated with germline PV in the *SMARCA4* gene, which plays a role in chromatin remodeling[70].

Table 1 Health impact of major hereditary cancer genes: Frequency of pathogenic variants in non-selected subjects and oncological patients

Gene	Frequency of pathogenic variants in population	Contribution in cancer morbidity	Ref.
BRCA1	Approximately 0.1%; > 1% in some founder populations	Breast cancer: 1%-3%; High-grade serous ovarian cancer: 15%-30%	[5,6,45,230-233]
BRCA2	Approximately 0.3%; > 1% in some founder populations	Breast cancer: 1%-3%; High-grade serous ovarian cancer: 7%-12%; Prostate cancer: 2%-4%; Pancreatic cancer: 2%-3%	[5,6,45,99,102,112,232,233]
PALB2	Approximately 0.1%	Breast cancer: Approximately 0.5%-1%	[5,6,45]
CHEK2	0.5%-0.7%	Breast cancer: 0.5%-2%; Moderately elevated frequencies across several cancer types	[5,6,25,113,234,235]
ATM	0.3%-0.5%	Breast cancer: 0.5%-0.8%; Moderately elevated frequencies across several cancer types	[5,6,45,99,102,113]
MLH1, MSH2, MSH6, PMS2, EPCAM	0.02%-0.05% for *MLH1, MSH2, MSH6, EPCAM* each; approximately 0.1% for *PMS2*	Colorectal cancer: 1%-6%; Endometrial cancer: 2%-6%	[5,6,76,236-238]
CDH1	< 0.005%	Diffuse gastric cancer: 7%; Lobular breast cancer: 0.3%	[5,6,92]
TP53	< 0.01%	Breast cancer in women < 30 years old: 2%-6%; Pediatric cancers: 8%; Osteosarcoma: 4%	[161,239,240]
HOXB13	0.2%-0.4%	Prostate cancer: Approximately 1%	[112,117,241]

Colorectal tumors

The accumulation of multiple cases of colorectal cancer (CRC) in pedigrees was systematically described in 1967 by Lynch *et al*[73]. Lynch syndrome, also called hereditary non-polyposis colorectal cancer (HNPCC), is the best-known genetic cause of CRC predisposition. HNPCC is associated with heterozygous germline inactivation of genes involved in DNA mismatch repair (MMR), namely *MLH1*, *MSH2*, *MSH6* or *PMS2* (Table 1). In addition, some Lynch syndrome patients carry deletion of the last portion of epithelial cell adhesion molecule (*EPCAM*), a gene located upstream to the *MSH2* genomic segment. This deletion results in the loss of transcription of the termination polyadenylation signal at the end of *EPCAM* and consequent emergence of the read-through *EPCAM-MSH2* fusion RNA message; furthermore, cells expressing the *EPCAM-MSH2* chimera demonstrate methylation of the *MSH2* promoter and failure to produce functional MSH2 protein[74]. The genetic causes of Lynch syndrome are apparently limited to the germline inactivation of *MLH1*, *MSH2*, *MSH6* or *PMS2* genes, as attempts to link this disease with PVs in other participants of MMR were unsuccessful[4]. The lifetime risk of CRC for the carriers of pathogenic alleles falls within 40%–70% for *MLH1* and *MSH2* genes, however it reaches only 10%–20% for *MSH6* and *PMS2* heterozygous individuals. Lynch syndrome contributes approximately to 3% of CRC morbidity in Western countries, however this estimate is significantly lower in some other populations[3,4,75-79]. In addition to CRC, Lynch syndrome is associated with a highly elevated risk of endometrial cancer as well as increased susceptibility to gastric, small bowel, biliary, urothelial, ovarian, brain, and some other malignancies. The spectrum and the risk of extracolonic and extraendometrial cancers varies depending on the gene involved[4,77,80]. The development of tumors in Lynch syndrome patients involves somatic second-hit inactivation of the remaining copy of the disease-causing gene[4].

Malfunction of MMR in HNPCC-associated tumors results in a high tumor mutation burden (TMB). Short repetitive sequences, so-called microsatellites, are particularly prone to MMR defects. Consequently, Lynch syndrome tumors have high-level microsatellite instability (MSI-H) diagnosed by electrophoretic detection of multiple changes in the length of mononucleotide repeats. Electrophoretic equipment is not a component of the standard morphological laboratory; therefore, many hospitals chose to use immunohistochemical (IHC) detection of MMR deficiency (MMR-D). Indeed, tumors arising in carriers of *MLH1* PVs lack the expression of MLH1 and PMS2 proteins, while *MSH2*-related CRCs show concomitant loss of MSH2 and MSH6 staining. Germline heterozygosity for *MSH6* or *PMS2* genes is accompanied by tumor-specific IHC negativity for *MSH6* or *PMS2*, respectively[77,81]. Importantly, only a minority of tumors with MSI-H/MMR-D phenotype are hereditary cancers. MSI-H/MMR-D is also highly characteristic for sporadic colorectal, gastric and endometrial carcinomas, especially for malignancies occurring in elderly patients. Inactivation of MMR in sporadic tumors is usually attributed to the down-regulation of the *MLH1* gene *via* promoter hypermethylation[81]. For the time being, MSI-H/MMR-D screening is recommended for all patients with CRC[82]. The selection of patients with MSI-H/MMR-D phenotype for subsequent germline testing may include consideration of age, family history of cancer, tumor location, and, in some instances, molecular characteristics of cancer cells. For example, Lynch syndrome related CRCs usually do not have mutation in the *BRAF* oncogene and demonstrate lack of methylation in the *MLH1* gene promoter[81]. Increasing availability of NGS is

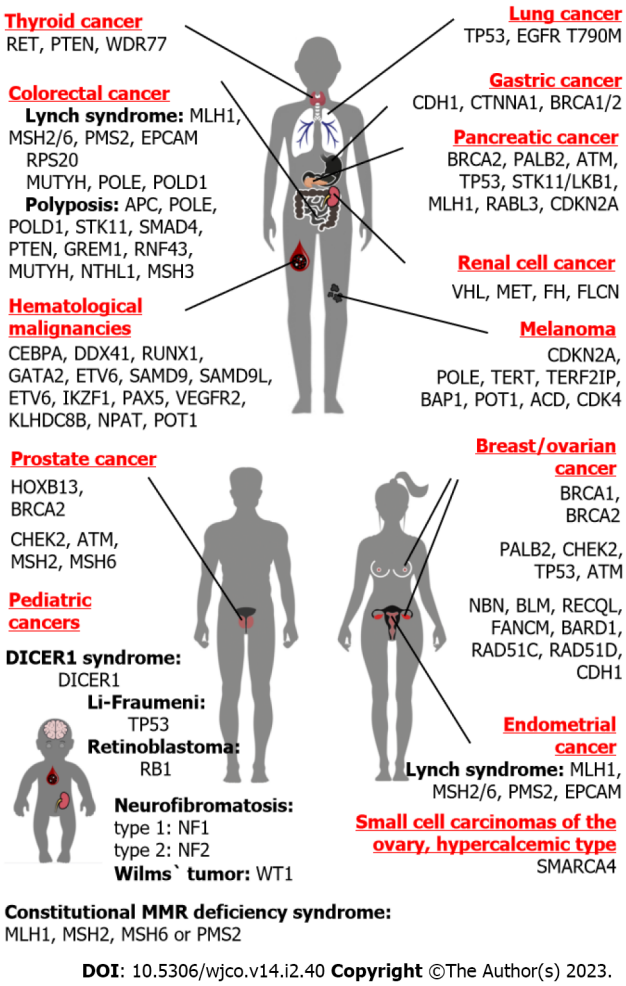


Figure 2 Main hereditary cancer genes and organs at risk. This figure illustrates major hereditary cancer types observed in females, males, adults of both genders, and children.

likely to result in the acceptance of uniform germline testing for all patients with microsatellite unstable colorectal and endometrial cancer, therefore the significance of procedures applied for the patient selection may diminish in the near future.

CRC familial clustering commonly occurs irrespective of MSI-H/MMR-D and Lynch syndrome. Surprisingly, the attempts to identify other than Lynch syndrome hereditary *CRC* genes were largely unsuccessful. Besides *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM*, there is only one hereditary CRC gene with proven significance, *RPS20*. However, *RPS20* is altered only in a minority of multi-case CRC families and its impact is limited to a few selected populations[4,76,79].

Some germline PVs predispose to polyposis of gastrointestinal tract and increased risk of malignant transformation. There is a number of polyposis-related genes, which are associated with several scenarios of the disease development, *e.g.*, either the emergence of CRC in combination with the presence of multiple polyps, or, alternatively, the appearance of CRC in the absence of benign colon lesions. Some polyposis syndromes are transmitted by autosomal-dominant mode (*APC*, *POLE*, *POLD1*, *STK11*, *SMAD4*, *BMPR1A*, *PTEN*, *GREM1*, *RNF43*), while others involve recessive inheritance and biallelic gene inactivation in affected patients (*MUTYH*, *NTHL1*, *MSH3*, *MBD4*)[23,24,83].

The most known polyposis gene, adenomatous polyposis coli (*APC*), is associated with very severe impairment of gastrointestinal tract, although some hypomorphic *APC* variants cause an attenuated form of this disease. *APC* is a tumor suppressor gene, its inactivation results in up-regulation of the WNT signaling pathway. The incidence of APC is around 1:10000, and approximately 30% of detected *APC* PVs are de novo mutations. In addition to colon polyposis and CRC, there are some common extracolonic features of this disease, in particular, duodenal polyps and carcinomas, stomach polyps, osteomas, desmoid tumors and congenital hypertrophy of the retinal pigmented epithelium[84].

MUTYH-associated polyposis (MAP) has a somewhat lower incidence than APC, with estimates approaching approximately 1:20000. *MUTYH* gene is involved in base excision repair (BER), therefore its biallelic deficiency is associated with increased risk of accumulation of oncogenic mutations. MAP is usually characterized by a moderate number of polyps and relatively late disease onset. However, the probability of CRC development in MAP patients is high and approaches approximately 80%. *MUTYH*-

driven CRCs often contain *KRAS G12C* substitution. Approximately 5% of patients with *KRAS G12C*-mutated CRC are biallelic carriers of *MUTYH* pathogenic alleles, therefore somatic *KRAS* status may be used as an indicator for MAP screening in CRC patients. Extracolonic manifestations of MAP are relatively uncommon, with the exception of highly increased risk for kidney cancer[83]. Most patients of European ancestry with genetic MAP diagnosis are homozygotes or compound heterozygotes for founder *MUTYH* alleles, *Y165C* and/or *G382D*[3,84-86].

NTHL1-related polyposis is similar to MAP, as it is caused by germline biallelic inactivation of the gene involved in BER. It is exceptionally rare, with estimated incidence falling below 1:100000. Various extracolonic tumors are highly characteristic for this syndrome, with a particularly elevated risk for BC [24]. A recent study identified *MBD4*, another participant of BER pathway, as a genetic cause of polyposis and multiorgan cancer predisposition[83].

Heterozygous germline PVs in *POLE* and *POLD1* genes predispose to gastrointestinal polyposis, CRC, endometrial carcinomas and some other malignancies. Inactivation of these genes results in failure of proofreading activities of DNA polymerases, therefore tumors arising in carriers of *POLE* and *POLD1* pathogenic alleles contain ultrahigh number of somatic mutations[24,76,85,87].

Gastric cancer

Gastric cancer (GC) is among the most common malignancies worldwide. Its incidence is highly influenced by environmental and behavioral factors: GC risk is significantly associated with Helicobacter pylori infection, low hygienic standard, high consumption of salt, "Northern" diet, alcohol abuse, *etc.*[88]. Consequently, family clustering of GC is not necessarily attributed to genetic factors, but may also be observed due to sharing of some GC-predisposing attitudes.

Strong evidence for the role of heredity is obtained only for diffuse GC, a histological variety of GC characterized by poor differentiation and presence of signet-ring cells[9,89]. The causative gene, *CDH1*, was initially discovered in New Zealand Maori families characterized by an exceptionally high incidence of diffuse GC[90]. *CDH1* encodes E-cadherin, a protein involved in cell adhesion. *CDH1* germline PVs are uncommon in the majority of analyzed populations, with the frequency being around 1:5000–1:20000[5,6,91], while the proportion of *CDH1* heterozygotes in consecutive series of GC patients approaches approximately 7% for diffuse GC and 2% for non-selected GC[92]. A few hundred *CDH1*-related GC pedigrees have been described worldwide. Presence of *CDH1* germline PVs is also associated with high risk of lobular BC, a peculiar and relatively uncommon variety of BC disease. Family studies estimated penetrance of CDH1 PVs to be around 70% for GC and 40% for BC[9]. Unbiased NGS data sets revealed instances of *CDH1* germline PVs unrelated to clinically diagnosed diffuse GC, therefore, there are yet unknown factors modifying phenotypic consequences of *CDH1* heterozygosity[5,6,91]. Genetic analysis of *CDH1* PV-negative diffuse GC families led to the identification of subjects with inactivating PVs in *CTNNA1* gene, which encodes alpha-catenin and interacts with beta-catenin and E-cadherin[9].

There are studies suggesting the role of PVs in double-strand DNA repair genes in GC predisposition. For example, contribution of *PALB2* PVs has been suggested in some investigations[93,94], however the analysis of *PALB2*-related families did not confirm these findings[95]. GC is likely to be a part of *BRCA1/2* syndrome, as some GCs arise on *BRCA1/2*-mutated background and demonstrate somatic loss of the remaining allele of the involved gene[13,96,97]. Lynch syndrome and some hereditary polyposis syndromes may involve malignant transformation of stomach epithelia. The lifetime GC risk in carriers of *MLH1* or *MSH2* PVs approaches 7%–8%. Specific nucleotide substitutions located in the promoter 1B region of the *APC* gene cause a condition, which is called gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS). GAPPS is attributed to down-regulation of *APC* transcription in gastric mucosa; interestingly GAPPS patients do not have extensive involvement of the colon because *APC* expression in colonic epithelium is regulated by the promoter 1A[9,23,24,84,98].

Pancreatic cancer

Predisposition to pancreatic cancer (PanCa) is usually inherited as a part of multi-organ HCS. *BRCA2* is the best-established PanCa-predisposing gene (Table 1). PVs in *BRCA2* confer approximately 5%–10% lifetime risk of developing PanCa, which is an order of magnitude higher than in general population[99-102]. In contrast to *BRCA2*, the data on the contribution of *BRCA1* in PanCa morbidity are controversial [103]. It is safe to state that if *BRCA1* indeed plays a role in PanCa susceptibility, its penetrance towards this cancer type is significantly lower as compared to *BRCA2*[99-101].

The association of the *PALB2* gene with familial PanCa was initially demonstrated by exome sequencing analysis of a PanCa patient whose sister also suffered from this disease[104]. Family-based studies of *PALB2*-related pedigrees have confirmed this association, although the risk of PanCa associated with *PALB2* PVs is moderate[95]. Moderate-to-high elevation of PanCa risk is also characteristic for *ATM* heterozygotes[99,105-108].

PanCa may emerge as a part of Li-Fraumeni syndrome, a disease caused by *TP53* germline PVs, as well as a manifestation of Lynch syndrome[99,101,107]. Peutz-Jeghers syndrome (PJS) (attributed to PVs in *STK11/LKB1*) and *CDKN2A*-driven familial melanoma syndrome are associated with 20%–25% lifetime risk of PanCa[101,107,109].

Whole-genome sequencing study of a PanCa family revealed segregation of this disease with *RABL3* truncating PV[110]. *RABL3* is involved in the prenylation of KRAS protein. However, PVs in the *RABL3* gene appear to be exceptionally rare and are unlikely to significantly contribute to overall PanCa morbidity[111].

Prostate cancer

PVs in two genes, *HOXB13* and *BRCA2*, are associated with more than 5-fold elevation of prostate cancer (PrCa) risk, and, therefore, with almost 1:2 probability of developing this disease during lifetime. *HOXB13* is the only known gene specifically associated with PrCa (Table 1). It encodes a prostate-specific homeobox transcription factor. Its PVs are represented by several ethnicity-specific missense mutations, which affect the interaction between HOXB13 protein and MEIS homeobox cofactor. *HOXB13* PVs contribute to approximately 1% of PrCa incidence[112-114].

BRCA2 is apparently the most frequent cause of hereditary PrCa. Its penetrance towards PrCa in men is comparable to the risk estimates observed for BC in female *BRCA2* PV carriers[103,112,114,115]. Similar to pancreatic cancer, evidences regarding the contribution of *BRCA1* in PrCa morbidity are controversial, and associated risks are at best low-to-moderate[103,115,116]. The role of *ATM* PVs in PrCa predisposition is well established; *ATM*-heterozygous men have an approximately 2-fold elevation of the probability of PrCa development[112,114,117]. The impact of *PALB2* PVs has been suggested in some studies, although systematic investigations failed to validate these findings[95]. Lynch syndrome associated with PVs in *MSH2* and *MSH6* genes may also render an increased PrCa risk[118].

Renal cell cancer

Next-generation sequencing of DNA obtained from renal cell carcinoma (RCC) patients revealed an unexpectedly high frequency of germline PVs: Pathogenic or likely pathogenic alleles were detected in 41/254 (16%) analyzed subjects[119]. Approximately 5% of RCC incidence is associated with RCC-predisposing syndromes[119]. Von-Hippel-Lindau syndrome caused by germline PVs in the *von Hippel-Lindau* (*VHL*) gene renders approximately 30%–40% lifetime risk of RCC and is also associated with the development of pancreatic neuroendocrine tumors, pheochromocytomas and hemangioblastomas. PVs in the *fumarate hydratase* (*FH*) gene are responsible for hereditary leiomyomatosis and renal cell cancer. Germline PVs in *MET* receptor tyrosine kinase confer a fatal risk of papillary RCC. RCC is also characteristic for Birt-Hogg-Dubé syndrome, a disease caused by PVs in the *FLCN* gene and associated with slowly progressing renal lesions, skin fibrofolliculomas and lung cysts[120]. The risk of various types of RCC is increased in patients with tuberous sclerosis syndrome[121].

Lung cancer

Genuine hereditary lung cancer (LC) is an exceptionally rare disease. The best-described cause of familial LC is the inheritance of the *epidermal growth factor receptor (EGFR) T790M* variant[122,123]. *EGFR T790M* was initially discovered as a secondary somatic mutation acquired during the course of therapy by EGFR inhibitors[124,125]. Subsequent studies demonstrated that some subjects carry this missense substitution in germline. Inborn *EGFR T790M* allele is associated with the development of lung tumors, which contain tyrosine kinase inhibitor sensitizing mutations in exons 19 and 21 of the *EGFR* gene[126]. Only a few dozen subjects carrying germline *EGFR T790M* allele have been described worldwide[123]. The frequency of the *EGFR T790M* allele in consecutive LC series is vanishingly low[127,128]. In addition to *EGFR T790M*, a few unique LC families with other germline pathogenic *EGFR* variants have been described[123,128]. LC may also arise as a part of Li-Fraumeni syndrome, being attributed to germline *TP53* pathogenic allele[8,129].

Melanoma

Germline PVs in the *CDKN2A* gene have been detected in 20%–40% of families with multiple instances of cutaneous melanoma. *CDKN2A* PV carriers are at risk of development of other tumor types, particularly pancreatic cancer[130,131]. *CDKN2A* pathogenic alleles are associated with a more aggressive superficial spreading subtype, however there are controversial data with regard to their impact on melanoma-specific survival[132]. There are several described pedigrees where melanoma incidence is segregated with pathogenic alleles in *CDK4*, *POT1* or *TERT* genes[133].

Multiple endocrine neoplasia

Multiple endocrine neoplasia (MEN) type 1 affects parathyroid glands, pancreatic islet cells and the anterior pituitary. It is caused by heterozygous inactivation of the *MEN1* tumor suppressor gene, which encodes menin, a protein involved in regulation of a spectrum of biological processes. The prevalence of MEN1 syndrome is approximately 1:30000[22], although the population frequency of *MEN1* PVs may be slightly higher[5]. Most of MEN1 patients demonstrate primary hyperparathyroidism caused by parathyroid hyperplasia. This condition is accompanied by hypercalcemia with varying degrees of its consequences. Duodeno-pancreatic neuroendocrine tumors of pancreas are represented by gastrinomas, non-functioning tumors, insulinomas, glucagonomas and vasoactive intestinal peptide producing tumors. Anterior pituitary neoplasms include prolactinomas as well as somatropin-, adrenocorticotropic

hormone- and gonadotropin-secreting adenomas. In addition to the above three organs, MEN1 may manifest by adrenocortical, bronchopulmonary and thymic neuroendocrine tumors as well as by a number of non-endocrine neoplasms[134]. Unexpectedly, a strong association between *MEN1* heterozygosity and highly increased risk of acute pancreatitis has been demonstrated in a recent study[108]. Some patients, who have MEN1-related phenotype, but lack PVs in the *MEN1* gene, carry *CDNK1B* pathogenic alleles. *CDNK1B*-related MEN is now classified as MEN4 syndrome[22].

MEN2A (MEN2) and MEN2B (MEN3) syndromes are caused by activating PVs in *RET* receptor tyrosine kinase. Both these conditions are strongly associated with the development of medullary thyroid carcinoma (MTC). MTC is a relatively rare subtype of thyroid cancer, however germline *RET* pathogenic alleles make a very significant contribution to the incidence of this disease being detected in about a quarter of MTC patients. Besides MTC, approximately half of subjects with MEN2A syndrome develop pheochromocytomas, and up to a third of MEN2A cases are characterized by hyperparathyroidism. The prevalence of MEN2A is similar to the one for MEN1. MEN2A is caused by *RET* PVs in codon 634, or less, frequently, in codons 609, 611, 618, 620 or 630. These PVs, being located in the extracellular domain and resulting in replacements of cysteines, induce conformational changes in RET protein, which facilitate dimerization and cross-phosphorylation of this receptor. There are some other point mutations, which do not affect cysteines and generally cause a milder disease phenotype, *i.e.* the development of MTC in the absence of other endocrine tumors; isolated MTC may also be associated with cysteine mutations involving other than 634 codons of the *RET* oncogene. MEN2B (MEN3), being an order of magnitude less common than MEN2A, is a significantly more aggressive disease manifested in the first or second decade of life with highly metastatic and potentially fatal MTC. Patients with MEN2B also often develop pheochromocytomas as well as some non-endocrine features, *e.g.*, neuromas and musculoskeletal abnormalities. MEN2B is usually caused by *RET M918T* allele or, in less than 5% of cases, *A883F* substitution. These amino acid substitutions are located in the kinase domain and render dimerization-independent activation of RET receptor. Overall, the distinction between familial MTC, MEN2A and MEN2B may look counter-intuitive, as these maladies are all related to *RET* activating alleles and differ from each other mainly by the disease severity but not by underlying biological mechanisms[22,135,136].

Carney complex manifests with adrenocortical disease, pituitary adenomas, gonadal and thyroid tumors, spotty skin pigmentation, cardiac and cutaneous myxomas, and some other non-endocrine neoplasms. This condition is caused by *PRKAR1A* germline PVs[137]. There is a number of genes, associated with isolated endocrine cancers. Germline PVs in the *WDR77* gene have been recently shown to predispose to papillary subtype of thyroid cancer. *WDR77* is a component of a transmethylase complex responsible for posttranslational modification of histone H4[138]. Genetic susceptibility to pheochromocytoma and/or paraganglioma may be rendered by PVs affecting *SDHAF2*, *SDHB*, *SDHC*, *SDHD*, *MAX*, *TMEM127* or some other genes[139]. There are instances of familial pituitary adenoma associated with *AIP* germline PVs[140,141].

Li-Fraumeni syndrome

Li-Fraumeni syndrome is caused by PVs in the *TP53* gene. *TP53* is apparently the best-studied tumor suppressor gene, which is involved in the regulation of DNA damage response, programmed cell death, cell cycle and several other biological processes. Population occurrence of *TP53* germline heterozygosity is well below 1:10000, although some communities demonstrate a noticeable frequency of founder hypomorphic *TP53* variants[5,6,142]. Earlier family-based studies suggested nearly-fatal penetrance for *TP53* germline PVs, although recent data indicate that some carriers of *TP53* pathogenic alleles manage to achieve late adulthood without being affected by cancer disease[8].

TP53 PVs render a highly increased risk of childhood cancers. Li-Fraumeni syndrome-associated pediatric malignancies include adrenal cortical carcinomas, choroid plexus carcinomas, rhabdomyosarcomas and medulloblastomas. Adult cancers are mainly represented by very-young-onset BC in females as well as lung carcinomas, osteosarcomas, soft-tissue sarcomas and brain tumors[8,63,143]. Breast carcinomas arising in *TP53* PV carriers frequently carry *HER2* amplification[144]. Li-Fraumeni syndrome related lung carcinomas are characterized by an exceptionally high frequency of *EGFR* somatic mutations[129,145]. Carriers of *TP53* PVs also have highly elevated risk of hematological malignancies[146]. The analysis of specific groups of consecutive patients revealed that Li-Fraumeni syndrome is a significant contributor to the incidence of pediatric cancers, very-young-onset breast carcinomas and osteosarcomas[142,146-150].

PTEN hamartoma tumor syndrome

PTEN hamartoma tumor syndrome (PHTS) is manifested by multiple benign and malignant tumors affecting breast, thyroid, endometrium, skin, kidney, colon and some other organs[151-153]. It is caused by heterozygous inactivating PVs in the *PTEN* gene, which is involved in the negative regulation of phosphatidylinositol 3-kinase/AKT/mechanistic target of rapamycin (mTOR) pathway and plays a role in the regulation of cell survival, proliferation, apoptosis and various metabolic processes[152,154]. *PTEN*-related syndrome is commonly known as Cowden syndrome, however the PHTS is a more preferable definition as it includes some other *PTEN*-associated maladies, *e.g.*, Bannayan-Riley-Ruvalcaba syndrome and Lhermitte–Duclos disease[151,152]. Patients with PHTS often have a wide

range of skin and mucosal manifestations and frequently present with macrocephaly[151]. Based on clinical considerations, the reported frequency of PHTS is approximately 1:200000[154], although unbiased NGS studies suggest that approximately 1:10000 healthy people are *PTEN* heterozygotes[5,6]. Activating germline PVs in the *WWP1* gene, which encodes E3 ubiquitin ligase and negatively regulates PTEN, were detected in some *PTEN*-wild-type patients with PHTS-associated tumors[155].

PJS

PJS manifests *via* characteristic mucocutaneous pigmentations and various polyp-related complications. Multiple gastrointestinal hamartomatous polyps in the affected patients are located mainly in the small bowel. The disease is caused by heterozygous inactivating PVs in tumor suppressor kinase *STK11/LKB1*. *STK11/LKB1* is involved in the regulation of cell cycle, apoptosis and cell metabolism. Population occurrence of PJS is estimated to be within 1:50000–1:200000, however as many as 1 out of 10000 apparently healthy subjects may carry *STK11/LKB1* PVs[5,156]. *STK11/LKB1* is a highly-penetrant cancer-predisposing gene. This genetic condition is associated with highly elevated risk of breast, colon, stomach, pancreatic and some other malignancies[156]. In addition, there are rare tumor subtypes specifically linked to PJS, *e.g.*, so-called sex cord tumors with annular tubules affecting ovaries[157]. Clinical presentation of PJS may depend on the type of *STK11/LKB1* PVs[158].

Gorlin syndrome

Gorlin syndrome [nevoid basal cell carcinoma (BCC) syndrome] is characterized by the appearance of BCCs and the development of odontogenic keratocysts. This disease is also associated with increased risk of medulloblastoma. In addition, various developmental abnormalities are frequently seen in patients with this condition. Gorlin syndrome is a rare disease, being observed in approximately 1:30000–1:300000 subjects. The most frequent cause of Gorlin syndrome is a heterozygous inactivating PV in the *PTCH1* gene. *SUFU* or *PTCH2* pathogenic alleles have been identified in the affected subjects, who are mutation-negative for *PTCH1*. Tumor development in Gorlin syndrome patients involves upregulation of the Hedgehog signaling pathway due to loss of its negative regulation by *PTCH1*, *SUFU* or *PTCH2*[159]. BCC predisposition may also be rendered by heterozygous inactivating PVs in the *PTPN14* tumor suppressor gene[160].

Pediatric cancers

It is difficult to draw a strict distinction between "pediatric" and "adult" hereditary cancers because many HCSs may present with various manifestations both in childhood and in the middle of life. Relevant examples include Li-Fraumeni syndrome, Cowden syndrome, PJS, neurofibromatosis, *RET*-related malignancies, *etc.* Expectedly, NGS analysis of non-selected patients with pediatric cancers revealed elevated frequency of PVs in known cancer-predisposing genes[161,162].

Retinoblastoma was the first pediatric tumor for which the genetic origin was convincingly established and the causative gene was identified. Hereditary retinoblastoma is caused by germline inactivation of the *RB1* gene. *RB1*, being the first cloned tumor suppressor gene, is implicated in the negative regulation of the cell cycle[19]. *RB1* germline alterations are observed in all patients with familial and/or bilateral retinoblastoma as well as in 14% of subjects with sporadic unilateral appearance of this disease[163]. Retinoblastoma survivors are at high risk of developing other neoplasms, particularly sarcomas[164]. Spliceosome dysfunction has been recently shown to underlie the emergence of bone malignancies in *RB1* heterozygotes[165].

Wilms` tumor (nephroblastoma, WT) is a relatively common pediatric cancer. The most frequent genetic cause of WT is a mutation in the *WT1* gene, which can be associated either with isolated WT, or with its combination with aniridia, nephrotic syndrome and/or abnormal genitalia. WT can also be a part of so-called overgrowth syndromes (Beckwith-Wiedemann syndrome, Sotos syndrome, Simpson–Golabi–Behmel syndrome, Perlman syndrome) or several syndromes associated with a wide spectrum of cancers (Li-Fraumeni syndrome, Bloom syndrome, Fanconi anemia, *etc.*)[166].

Neurofibromatosis type 1 is caused by inactivating heterozygous PVs in the *NF1* gene. NF1 is a negative regulator of the RAS signaling pathway. *NF1* heterozygosity is estimated to occur in 1:3500 newborns and is manifested by *cafe au lait* spots, axillary freckles, Lisch nodules and neurofibromas. This syndrome is associated with a high risk of development of gliomas, hematological malignancies, pheochromocytomas and some other tumors. Neurofibromatosis type 2 is ten times less common than the type 1 disease. The *NF2* gene encodes merlin, its inactivation is associated with the development of schwannomas and meningiomas in adolescence or adulthood[167].

DICER1 syndrome has been described relatively recently[168]. It is associated with heterozygous germline inactivation of the *DICER1* gene. DICER1, a ribonuclease III family enzyme, is responsible for the maturation of microRNA. The pathogenesis of *DICER1*-related malignancies usually involves somatic alteration of the remaining gene allele. *DICER1* PVs are characterized by incomplete penetrance. Carriers of *DICER1* PVs are at risk of developing pleuropulmonary blastomas, gynandroblastomas, sarcomas, Sertoli-Leydig cell tumors and some other neoplasms[169,170].

PVs in the *SMARC* family genes, which regulate chromatin remodeling, are responsible for the rhabdoid tumor predisposition syndrome[171]. *SMARCB1* pathogenic alleles are associated with the

development of malignant rhabdoid tumors of the central nervous system and kidneys. Hypomorphic *SMARCB1* PVs are also implicated in familial schwannomatosis where the development of schwannomas involves concomitant down-regulation of both *SMARCB1* and *NF2* genes[172]. *SMARCE1* PVs predispose to the development of meningiomas. *SMARCA4* pathogenic alleles are associated with rhabdoid tumors as well as small-cell OC, hypercalcemic type[171].

Constitutional mismatch repair deficiency syndrome (CMMRD) is an autosomal-recessive disorder caused by biallelic inactivation of *MMR* genes[4]. This condition has characteristic cutaneous manifestations and renders a high probability of developing brain, gastrointestinal and hematological malignancies at a young age[173].

Hematological malignancies

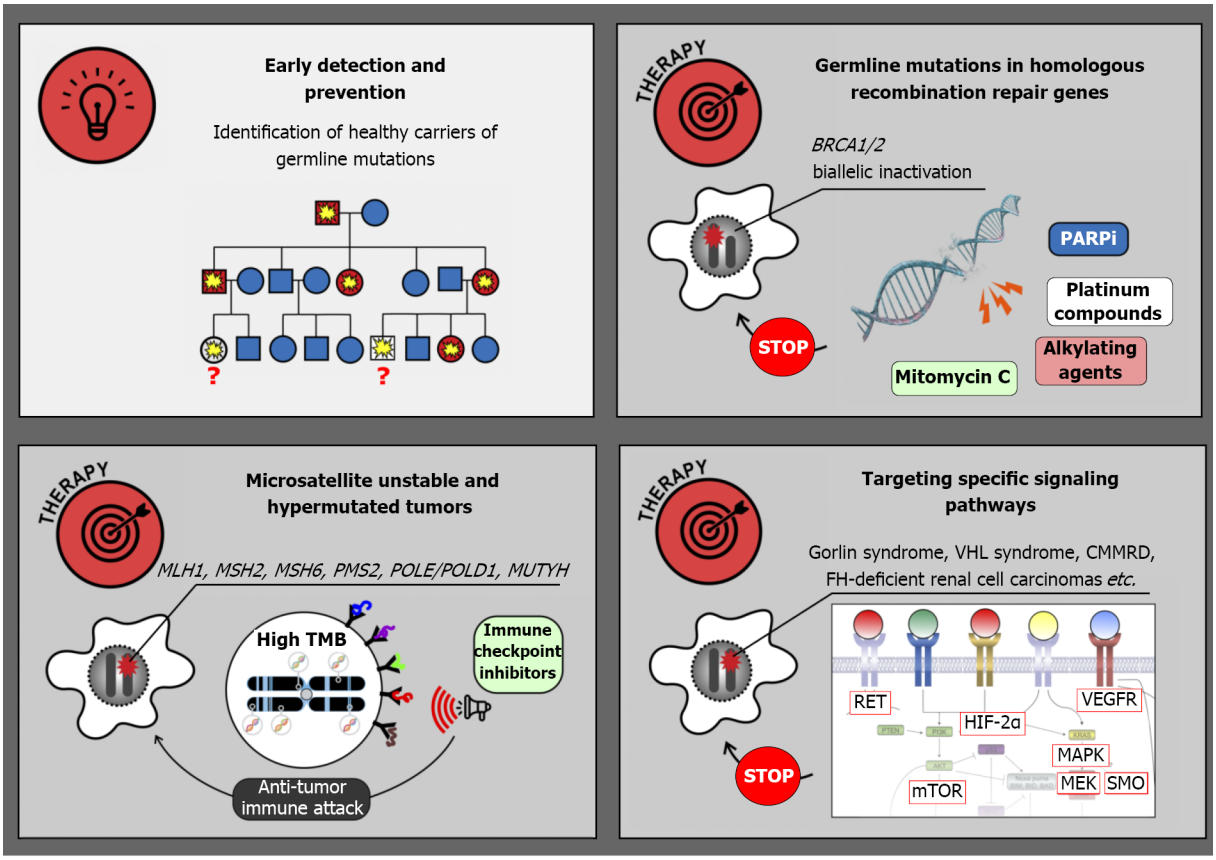
Hematological malignancies often manifest as a part of a syndromic condition. Various abnormalities of hematopoiesis resulting in the depletion of some cell lineages are frequently accompanied by myeloid-derived neoplasms. Immune deficiencies render an increased risk of development of lymphomas[174]. Familial clustering of acute myeloid leukemia may be attributed to germline PVs in *CEBPA*, *DDX41*, *RUNX1*, *GATA2*, *ETV6*, *SAMD9*, *SAMD9L* and some other genes. Hereditary acute lymphoblastic leukemia is related to germline PVs in *ETV6*, *IKZF1* or *PAX5* genes and may as well be a part of clinical manifestation of Li-Fraumeni syndrome[175]. Alterations in the *KDR* (vascular endothelial growth factor 2) receptor tyrosine kinase are the most frequent cause of hereditary Hodgkin lymphoma; high risk of this disease may also be rendered by germline PVs located in *KLHDC8B*, *NPAT* or *POT1* genes [176].

MANAGEMENT OF HEREDITARY TUMORS

Cancer detection and prevention

The research on HCSs was initially viewed mainly as a part of prophylactic medicine. Indeed, there is a strong emphasis on the identification of yet healthy people, who are carriers of tumor-predisposing PVs and may significantly benefit from early cancer detection and prevention (Figure 3). Diagnostic surveillance strategies have been articulated for all major cancer syndromes. For example, female carriers of *BRCA1*, *BRCA2* and some other pathogenic alleles are advised to start breast self-examination from 18 years old; regular clinical breast examination and magnetic resonance imaging are usually added beginning from 25 years, and they are supplemented by annual mammography in women aged 30–75 years. OC screening includes annual transvaginal ultrasound examination and CA-125 serum marker measurement starting at 30–35 years[84]. Clinical efficacy of surveillance is considerably higher in patients with Lynch syndrome. The adherence to colonoscopy performed every 1–2 years beginning from 20–25 years of age, upper endoscopy every 3–5 years starting at 30–35 years as well as endometrial cancer screening, significantly reduces individual risk of cancer death[84]. Effective surveillance is more complicated in subjects with multiorgan cancer predisposition. In particular, carriers of *TP53* germline PVs are advised to begin cancer screening in early childhood and, wherever possible, to abstain from potentially mutagenic diagnostic procedures, *e.g.*, X-ray examination[146]. The development of screening recommendations for subjects with HCSs is a continuous process, which is usually coordinated by international and national healthcare professional societies or initiative groups, involves interaction of a high number of experts working in different areas of medicine, requires significant research efforts aimed at collection of real-world data and is a subject of regular updates[84,146,177,178]. There is a multitude of published guidelines, which generally suggest similar diagnostic algorithms but differ from each other in many nuances. The detailed discussion on existing recommendations is beyond the scope of this review.

Prophylactic risk-reducing surgery has become a standard medical intervention, being particularly well investigated in subjects with the HBOC syndrome, hereditary diffuse GC, hereditary medullary thyroid cancer, *etc.*[9,22,146,179-181]. It is self-explanatory that surgical removal of the organ(s) at-risk may be applied only in situations when this procedure is not associated with life-threatening adverse effects or disproportional decrease of the quality of life, and only for syndromes with insufficient reliability of early cancer diagnosis. Carriers of highly-penetrant BC-predisposing PVs (*BRCA1*, *BRCA2*, *PALB2*, *TP53*, *etc.*) are encouraged to undergo risk-reducing breast surgery, given that even high compliance with diagnostic check-ups does not fully warrant cancer detection at early stage or good treatment outcome[182]. *BRCA1/2* heterozygous women are strongly recommended to opt for prophylactic salpingo-oophorectomy at the age of 35–45 years (or after the completion of childbearing)[177,178,183]. This procedure is justified by the poor clinical efficacy of OC screening and dispensability of ovaries for women entering their second half of life. Prophylactic gastrectomy in *CDH1* PV carriers is associated with severe impairment of the quality of life, however the abstinence from this procedure is associated with a significant risk of death due to diffuse GC[9]. Risk-reducing thyroidectomy followed by hormone replacement therapy is a standard option for carriers of *RET* high-risk PVs. This surgery is usually performed in childhood, and the recommended age for intervention varies depending on the type of *RET* PV[184,185].



DOI: 10.5306/wjco.v14.i2.40 **Copyright** ©The Author(s) 2023.

Figure 3 Management of hereditary cancer syndromes. PARPi: Poly (ADP-ribose) polymerase inhibitors; TMB: Tumor mutation burden; HIF-2α: Hypoxia inducible factor-2α; VHL: von Hippel-Lindau; mTOR: Mechanistic target of rapamycin; MAPK: Mitogen-activated protein kinase signaling pathway; MEK: Mitogen-activated protein kinase; VEGFR: Vascular endothelial growth factor receptor; SMO: Smoothened; CMMRD: Constitutional mismatch repair deficiency syndrome.

Benefit from risk-reducing surgeries has been confirmed by real-world data, however this experience is mainly limited to healthy relatives of cancer patients, who were found to be heterozygous for a highly-penetrant pathogenic allele[184,186,187]. Recent large-scale genetic investigations have identified some carriers of tumor-predisposing variants, who do not have a family history of cancers associated with their genetic findings[5,6]. Apparently, these individuals should be advised to undergo full-scale diagnostic surveillance, whereas great caution must be taken while considering prophylactic surgical interventions in subjects with favorable pedigree data[23].

Advances in cytotoxic and targeted therapy

Despite substantial advances in early detection and prevention of malignant diseases, cancer genetics remained an "exotic" discipline for many practicing oncologists until the second decade of this century. This was due to relative rarity of familial tumors and limited impact of germline DNA testing on the treatment strategies. Several discoveries, which were made within the past 10–15 years and resulted in the recognition of specific drug vulnerabilities in hereditary cancers, have moved familial cancer studies to the frontline of medical oncology[188,189].

BRCA1/2-driven breast and ovarian carcinomas arise due to somatic inactivation of the remaining allele of the involved gene (Figure 3 and Table 2). Consequently, these tumors are deficient in DNA double-strand break repair and demonstrate pronounced sensitivity to platinum compounds, mitomycin C, bifunctional alkylating agents and poly (ADP-ribose) polymerase (PARP) inhibitors (PARPi). Several clinical studies involving cisplatin or carboplatin suggested that platinum-based regimens are highly effective in women with breast or ovarian *BRCA1/2*-associated cancer[190-192]. Combined administration of cisplatin and mitomycin C resulted in a remarkable improvement of treatment outcomes in patients with *BRCA1*-mutated carcinomas[193,194]. There are a number of successful clinical investigations, which resulted in the approval of PARPi for the treatment of hereditary breast, ovarian, pancreatic and prostate malignancies[195]. Interestingly, non-breast/ovarian carcinomas arising in *BRCA1/2* PV carriers often retain the second *BRCA1/2* allele and therefore do not have this drug vulnerability. Findings obtained on *BRCA1/2* PV carriers may or may not be applicable to other genes involved in homologous recombination, as not all of the latter trigger tumor development by the two-hit mechanism, and even biallelic defects in some genes, *e.g.*, *ATM* or *CHEK2*, are not

Table 2 Cytotoxic and targeted therapy for tumors arising in carriers of cancer-predisposing alleles

Tumor type	Target	Drugs	Ref.
BRCA1/2-driven carcinomas and their phenocopies	*BRCA1/2* inactivation resulting in the deficiency of DNA repair by homologous recombination	Platinum derivatives, Mitomycin C, Bifunctional alkylating agents, PARPi	[190-193, 195]
Hypermutated cancers (Lynch syndrome associated microsatellite unstable tumors; *POLD1/POLE*-deficient cancers; *MUTYH*-associated colorectal carcinomas; tumors in patients with CMMRD syndrome)	High tumor mutation burden resulting in excessive number of neoantigens	Immune checkpoint inhibitors	[199-206]
RET-associated malignancies	RET tyrosine kinase	RET inhibitors	[207-209]
Neurofibromatosis, type 1	Upregulation of RAS/RAF/MEK pathway due to NF1 inactivation	MEK inhibitors	[210, 211]
Basal cell carcinomas in patients with Gorlin syndrome	Hedgehog pathway	SMO inhibitors	[213]
Tumors arising in patients with tuberous sclerosis	mTOR pathway	mTOR inhibitors	[214, 215]
Renal cell carcinomas associated with von Hippel-Lindau syndrome	Up-regulation of HIF-2α due to *VHL* gene inactivation	HIF-2α inhibitors	[216]

HIF-2α: Hypoxia inducible factor-2α; PARPi: Poly (ADP-ribose) polymerase inhibitors; CMMRD: Constitutional mismatch repair deficiency syndrome; MEK: Mitogen-activated protein kinase; SMO: Smoothened; mTOR: Mechanistic target of rapamycin; VHL: von Hippel-Lindau.

necessarily associated with platinum or PARPi sensitivity[21,196-198].

Microsatellite-unstable cancers, including tumors arising due to Lynch syndrome, are characterized by an excessive number of somatic mutations, and, consequently, high tumor antigenicity. These malignancies can be managed by the administration of so-called immune checkpoint inhibitors, the drugs which antagonize immune suppressor molecules and restore proper antitumor immunity[199]. Clinical studies on microsatellite-unstable cancers involved both patients with Lynch syndrome and subjects with sporadic carcinomas. Pembrolizumab has been approved for the treatment of MSI-H tumors irrespective of their organ localization[200]. Interestingly, a small study comparing hereditary *vs* sporadic microsatellite-unstable endometrial carcinomas revealed that tumors associated with a germline pathogenic allele have higher TMB and are more responsive to this drug[201]. The results of available clinical trials support the use of pembrolizumab or a combination of nivolumab and ipilimumab in the first-line therapy of metastatic MSI-H CRC[199-202]. There are instances of successful utilization of immune checkpoint inhibitors for the treatment of *POLE/POLD1*- and *MUTYH*-related malignancies[203,204]. Several case studies reported clinical benefit from immune therapy in patients with CMMRD-associated tumors[205,206].

Some hereditary cancers are associated with the upregulation of specific signaling pathways. A multikinase inhibitor vandetanib, which has activity towards RET and several other tyrosine kinases, has demonstrated significant clinical activity in patients with hereditary MTCs[207]. Clinical studies on selective RET inhibitors, selpercatinib and pralsetinib, included subjects with both hereditary and sporadic *RET*-driven thyroid tumors, and demonstrated remarkable benefit from these drugs[136,208, 209].

Tumors arising in patients with neurofibromatosis type 1 are characterized by inactivation of *NF1* gene, which is a negative regulator of RAS/RAF/MEK pathway. Consequently, these malignancies are potentially sensitive to MEK inhibition[210,211]. MEK inhibitor selumetinib has been evaluated in 25 children with recurrent, refractory, or progressive pediatric low-grade *NF1*-related gliomas, which failed at least one prior therapy. Objective response was documented in 10 (40%) cases, and 24 (96%) patients experienced no progression of the disease within 2 years[210]. Another study included children with *NF1*-associated symptomatic inoperable plexiform neurofibromas. Objective responses were observed in 37/50 (70%) patients, with 28 instances of response lasting more than 1 year[211]. Activating mutations in RAS/RAF/MEK pathway are also characteristic for hypermutated cancers arising in CMMRD patients. Pronounced efficacy of selumetinib or trametinib has been demonstrated in several patients with heavily pretreated CMMRD-related brain tumors[212].

Gorlin syndrome related BCCs can be managed by down-regulation of G-protein coupled receptor smoothened (SMO), which is involved in the activation of the Hedgehog pathway. Vismodegib, a selective SMO inhibitor, has been evaluated in placebo-controlled trial involving 46 patients, who had at least ten tumors each. All subjects receiving this drug experienced the decrease of existing tumor burden. Furthermore, the use of vismodegib slowed the emergence of new cancer lesions in patients with Gorlin syndrome[213].

Cancers associated with tuberous sclerosis are responsive to mTOR targeted drugs. Clinical efficacy of everolimus has been repeatedly demonstrated in angiomyolipomas and subependymal giant cell astrocytomas associated with this syndorme[214,215]. There are promising results of the treatment of

VHL syndrome related tumors by hypoxia-inducible factor-2α inhibitor belzutifan[216]. FH-deficient RCCs often respond to the combination of anti-vascular endothelial growth factor therapy and mTOR antagonists or to multitargeted tyrosine kinase inhibitors[217,218].

Drug vulnerabilities detected in hereditary cancer often have clinical relevance to their sporadic phenocopies. For example, platinum/PARPi sensitivity was initially described in *BRCA1/2*-driven carcinomas, but subsequent research revealed that tumors with *BRCA1/2*-like (BRCAness) properties, *e.g.*, a specific pattern of chromosomal instability, are also sensitive to these compounds[219,220].

CONCLUSION

Increasing involvement of healthy people in whole exome or multigene sequencing will certainly identify a huge number of subjects, who have a potentially severe disease according to a genetic test, but continue to remain unaffected until the elderly age. We are already witnessing that virtually all updated penetrance estimates are significantly lower than the ones observed by earlier studies, and, *vice versa*, the population frequency of some presumably "fatal" germline PVs is manifold higher than the observed incidence of corresponding genetic diseases[4-6,8,9]. The distinction between genetic health and disease is likely to be reconsidered in the near future.

Earlier cancer genetic studies produced rather straightforward gene-disease interactions, where all relevant genes and associated diseases could be easily presented in a table-like format. Systematic large-scale investigations carried out in the last decade revealed substantial promiscuity in genotype-phenotype interactions, thus complicating the clinical diagnosis of HCSs and interpretation of genetic findings[4,17,103,108,119,149,161,162,221]. The unbiased cataloging of patient data may help to account for the diversity of HCS manifestations.

Most of the known non-cancer genetic diseases are recessive, while most of the already identified cancer predisposition syndromes are dominant. This difference is unlikely to be related to genuine biological reasons, but is rather attributed to difficulties in the genetic studies of common cancer types. Virtually all "classic" genetic pathologies are orphan maladies (*e.g.*, cystic fibrosis or phenylketonuria), so the appearance of even 2-3 patients with a unique phenotype in the same family/pedigree, or in the same neighborhood, is immediately recognizable by practicing physicians or clinical investigators. However, if we consider a recessive mechanism for say, conventional breast, lung, or colorectal carcinomas, *i.e.*, the situation when both parents are asymptomatic heterozygous carriers of a recessive tumor-predisposing allele, and the disease is manifested only in subjects with biallelic gene involvement, there is little if any chance to distinguish these subjects from sporadic phenocopies[222]. Indeed, already known recessive tumor-predisposing syndromes include mainly rare diseases with very characteristic phenotypic manifestation, *e.g.*, some hereditary polyposis syndromes[84]. Systematic germline sequencing of cancer patients and the analysis of accumulated "big data" may eventually identify some examples of recessive predisposition to common cancer types. Focus on large communities with pronounced founder effect may facilitate the research in this direction.

The critical mass of advances in clinical genetics, including studies on HCSs, has been achieved due to efforts of scientists working mainly in North America, Western Europe, Japan, and several other parts of the world distinguished by the combination of an exceptionally high level of technological development and strong dedication to biomedical research. Consequently, current knowledge on pathogenic alleles and corresponding familial diseases mainly reflects the genetic background of Western European populations and some Eastern Asian communities. It is self-explanatory that each ethnic group has its own ancestors, who have a unique composition of pathogenic gene variants. Consequently, the distribution of genetic diseases is a subject of major interethnic variations, with a number of maladies observed only in selected populations. It is important to encourage ethnicity-specific cataloging of pathogenic alleles and corresponding phenotypes in order to support proper practical implementation of gene-based tests. Furthermore, analysis of "novel" populations is likely to result in the discovery of new medically relevant genes and corresponding genetic diseases[36,223-226].

Most of cancer studies rely mainly on the identification of protein-truncating variants. The clarification of functional/pathogenic significance for missense mutations is complicated, and there is a need for robust bioinformatic and laboratory pipelines supporting the distinction between disease-causing and neutral amino acid substitutions[227,228]. Current research is mainly focused on the coding regions of the genome; however other genetic loci, to be studied by whole genome cataloging, are also very likely to be a source of disease-predisposing variations[229].

Identification of cancer-predisposing genes is an example of triumph of translational medicine. The development of methods of non-surgical prevention of tumor progression in carriers of disease-associated pathogenic alleles is an obvious priority for future studies in this field.

FOOTNOTES

Author contributions: Imyanitov EN and Kuligina ES wrote the article draft; Kuligina ES prepared the illustration; Sokolenko AP, Suspitsin EN, Yanus GA, Iyevleva AG, Ivantsov AO, Aleksakhina SN acquired the literature data and analyzed the results; All authors approved the final version of the article.

Supported by The Russian Science Foundation, No. 17-75-30027.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Russia

ORCID number: Evgeny N Imyanitov 0000-0003-4529-7891; Ekaterina S Kuligina 0000-0002-2396-6540; Anna P Sokolenko 0000-0001-6304-1609; Grigoriy A Yanus 0000-0002-9844-4536; Svetlana N Aleksakhina 0000-0002-2149-7728.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Walsh MF**, Chang VY, Kohlmann WK, Scott HS, Cunniff C, Bourdeaut F, Molenaar JJ, Porter CC, Sandlund JT, Plon SE, Wang LL, Savage SA. Recommendations for Childhood Cancer Screening and Surveillance in DNA Repair Disorders. *Clin Cancer Res* 2017; **23**: e23-e31 [PMID: 28572264 DOI: 10.1158/1078-0432.CCR-17-0465]
2 **Sharma R**, Lewis S, Wlodarski MW. DNA Repair Syndromes and Cancer: Insights Into Genetics and Phenotype Patterns. *Front Pediatr* 2020; **8**: 570084 [PMID: 33194896 DOI: 10.3389/fped.2020.570084]
3 **Valle L**, de Voer RM, Goldberg Y, Sjursen W, Försti A, Ruiz-Ponte C, Caldés T, Garré P, Olsen MF, Nordling M, Castellvi-Bel S, Hemminki K. Update on genetic predisposition to colorectal cancer and polyposis. *Mol Aspects Med* 2019; **69**: 10-26 [PMID: 30862463 DOI: 10.1016/j.mam.2019.03.001]
4 **Peltomäki P**, Olkinuora A, Nieminen TT. Updates in the field of hereditary nonpolyposis colorectal cancer. *Expert Rev Gastroenterol Hepatol* 2020; **14**: 707-720 [PMID: 32755332 DOI: 10.1080/17474124.2020.1782187]
5 **Breast Cancer Association Consortium**, Dorling L, Carvalho S, Allen J, González-Neira A, Luccarini C, Wahlström C, Pooley KA, Parsons MT, Fortuno C, Wang Q, Bolla MK, Dennis J, Keeman R, Alonso MR, Álvarez N, Herraez B, Fernandez V, Núñez-Torres R, Osorio A, Valcich J, Li M, Törngren T, Harrington PA, Baynes C, Conroy DM, Decker B, Fachal L, Mavaddat N, Ahearn T, Aittomäki K, Antonenkova NN, Arnold N, Arveux P, Ausems MGEM, Auvinen P, Becher H, Beckmann MW, Behrens S, Bermisheva M, Białkowska K, Blomqvist C, Bogdanova NV, Bogdanova-Markov N, Bojesen SE, Bonanni B, Børresen-Dale AL, Brauch H, Bremer M, Briceno I, Brüning T, Burwinkel B, Cameron DA, Camp NJ, Campbell A, Carracedo A, Castelao JE, Cessna MH, Chanock SJ, Christiansen H, Collée JM, Cordina-Duverger E, Cornelissen S, Czene K, Dörk T, Ekici AB, Engel C, Eriksson M, Fasching PA, Figueroa J, Flyger H, Försti A, Gabrielson M, Gago-Dominguez M, Georgoulias V, Gil F, Giles GG, Glendon G, Garcia EBG, Alnæs GIG, Guénel P, Hadjisavvas A, Haeberle L, Hahnen E, Hall P, Hamann U, Harkness EF, Hartikainen JM, Hartman M, He W, Heemskerk-Gerritsen BAM, Hillemanns P, Hogervorst FBL, Hollestelle A, Ho WK, Hooning MJ, Howell A, Humphreys K, Idris F, Jakubowska A, Jung A, Kapoor PM, Kerin MJ, Khusnutdinova E, Kim SW, Ko YD, Kosma VM, Kristensen VN, Kyriacou K, Lakeman IMM, Lee JW, Lee MH, Li J, Lindblom A, Lo WY, Loizidou MA, Lophatananon A, Lubiński J, MacInnis RJ, Madsen MJ, Mannermaa A, Manoochehri M, Manoukian S, Margolin S, Martinez ME, Maurer T, Mavroudis D, McLean C, Meindl A, Mensenkamp AR, Michailidou K, Miller N, Mohd Taib NA, Muir K, Mulligan AM, Nevanlinna H, Newman WG, Nordestgaard BG, Ng PS, Oosterwijk JC, Park SK, Park-Simon TW, Perez JIA, Peterlongo P, Porteous DJ, Prajzendanc K, Prokofyeva D, Radice P, Rashid MU, Rhenius V, Rookus MA, Rüdiger T, Saloustros E, Sawyer EJ, Schmutzler RK, Schneeweiss A, Schürmann P, Shah M, Sohn C, Southey MC, Surowy H, Suvanto M, Thanasitthichai S, Tomlinson I, Torres D, Truong T, Tzardi M, Valova Y, van Asperen CJ, Van Dam RM, van den Ouweland AMW, van der Kolk LE, van Veen EM, Wendt C, Williams JA, Yang XR, Yoon SY, Zamora MP, Evans DG, de la Hoya M, Simard J, Antoniou AC, Borg Å, Andrulis IL, Chang-Claude J, García-Closas M, Chenevix-Trench G, Milne RL, Pharoah PDP, Schmidt MK, Spurdle AB, Vreeswijk MPG, Benitez J, Dunning AM, Kvist A, Teo SH, Devilee P, Easton DF. Breast Cancer Risk Genes - Association Analysis in More than 113,000 Women. *N Engl J Med* 2021; **384**: 428-439 [PMID: 33471991 DOI: 10.1056/NEJMoa1913948]
6 **Hu C**, Hart SN, Gnanaolivu R, Huang H, Lee KY, Na J, Gao C, Lilyquist J, Yadav S, Boddicker NJ, Samara R, Klebba J, Ambrosone CB, Anton-Culver H, Auer P, Bandera EV, Bernstein L, Bertrand KA, Burnside ES, Carter BD, Eliassen H, Gapstur SM, Gaudet M, Haiman C, Hodge JM, Hunter DJ, Jacobs EJ, John EM, Kooperberg C, Kurian AW, Le Marchand L, Lindstroem S, Lindstrom T, Ma H, Neuhausen S, Newcomb PA, O'Brien KM, Olson JE, Ong IM, Pal T, Palmer JR, Patel AV, Reid S, Rosenberg L, Sandler DP, Scott C, Tamimi R, Taylor JA, Trentham-Dietz A, Vachon CM, Weinberg C, Yao S, Ziogas A, Weitzel JN, Goldgar DE, Domchek SM, Nathanson KL, Kraft P, Polley EC, Couch FJ. A Population-

Based Study of Genes Previously Implicated in Breast Cancer. *N Engl J Med* 2021; **384**: 440-451 [PMID: 33471974 DOI: 10.1056/NEJMoa2005936]

7 **Roa BB**, Boyd AA, Volcik K, Richards CS. Ashkenazi Jewish population frequencies for common mutations in BRCA1 and BRCA2. *Nat Genet* 1996; **14**: 185-187 [PMID: 8841191 DOI: 10.1038/ng1096-185]

8 **Amadou A**, Achatz MIW, Hainaut P. Revisiting tumor patterns and penetrance in germline TP53 mutation carriers: temporal phases of Li-Fraumeni syndrome. *Curr Opin Oncol* 2018; **30**: 23-29 [PMID: 29076966 DOI: 10.1097/CCO.0000000000000423]

9 **van der Post RS**, Oliveira C, Guilford P, Carneiro F. Hereditary gastric cancer: what's new? *Fam Cancer* 2019; **18**: 363-367 [PMID: 30989426 DOI: 10.1007/s10689-019-00127-7]

10 **Reckamp KL**, Behrendt CE, Slavin TP, Gray SW, Castillo DK, Koczywas M, Cristea MC, Babski KM, Stearns D, Marcum CA, Rodriguez YP, Hass AJ, Vecchio MM, Mora P, Cervantes AE, Sand SR, Mejia RM, Tsou TC, Salgia R, Weitzel JN. Germline mutations and age at onset of lung adenocarcinoma. *Cancer* 2021; **127**: 2801-2806 [PMID: 33858029 DOI: 10.1002/cncr.33573]

11 **Oh M**, McBride A, Yun S, Bhattacharjee S, Slack M, Martin JR, Jeter J, Abraham I. BRCA1 and BRCA2 Gene Mutations and Colorectal Cancer Risk: Systematic Review and Meta-analysis. *J Natl Cancer Inst* 2018; **110**: 1178-1189 [PMID: 30380096 DOI: 10.1093/jnci/djy148]

12 **de Jonge MM**, Ritterhouse LL, de Kroon CD, Vreeswijk MPG, Segal JP, Puranik R, Hollema H, Rookus MA, van Asperen CJ, van Leeuwen FE, Smit VTHBM, Howitt BE, Bosse T; HEBON Group. Germline BRCA-Associated Endometrial Carcinoma Is a Distinct Clinicopathologic Entity. *Clin Cancer Res* 2019; **25**: 7517-7526 [PMID: 31492746 DOI: 10.1158/1078-0432.CCR-19-0848]

13 **Avanesyan AA**, Sokolenko AP, Ivantsov AO, Kleshchev MA, Maydin MA, Bizin IV, Raskin GA, Shelekhova KV, Gorodnova TV, Bessonov AA, Anisimova EI, Volynshchikova OA, Romanko AA, Ni VI, Broyde RV, Tkachenko OB, Whitehead AJ, Scherbakov AM, Imyanitov EN. Gastric Cancer in BRCA1 Germline Mutation Carriers: Results of Endoscopic Screening and Molecular Analysis of Tumor Tissues. *Pathobiology* 2020; **87**: 367-374 [PMID: 33161400 DOI: 10.1159/000511323]

14 **Kim H**, Choi DH, Park W, Im YH, Ahn JS, Park YH, Nam SJ, Kim SW, Lee JE, Yu JH, Lee SK, Jung BY. The association between non-breast and ovary cancers and BRCA mutation in first- and second-degree relatives of high-risk breast cancer patients: a large-scale study of Koreans. *Hered Cancer Clin Pract* 2019; **17**: 1 [PMID: 30622657 DOI: 10.1186/s13053-018-0103-3]

15 **Ko JM**, Ning L, Zhao XK, Chai AWY, Lei LC, Choi SSA, Tao L, Law S, Kwong A, Lee NP, Chan KT, Lo A, Song X, Chen PN, Chang YL, Wang LD, Lung ML. BRCA2 loss-of-function germline mutations are associated with esophageal squamous cell carcinoma risk in Chinese. *Int J Cancer* 2020; **146**: 1042-1051 [PMID: 31396961 DOI: 10.1002/ijc.32619]

16 **Maccaroni E**, Giampieri R, Lenci E, Scortichini L, Bianchi F, Belvederesi L, Brugiati C, Pagliaretta S, Ambrosini E, Berardi R. BRCA mutations and gastrointestinal cancers: When to expect the unexpected? *World J Clin Oncol* 2021; **12**: 565-580 [PMID: 34367929 DOI: 10.5306/wjco.v12.i7.565]

17 **Jonsson P**, Bandlamudi C, Cheng ML, Srinivasan P, Chavan SS, Friedman ND, Rosen EY, Richards AL, Bouvier N, Selcuklu SD, Bielski CM, Abida W, Mandelker D, Birsoy O, Zhang L, Zehir A, Donoghue MTA, Baselga J, Offit K, Scher HI, O'Reilly EM, Stadler ZK, Schultz N, Socci ND, Viale A, Ladanyi M, Robson ME, Hyman DM, Berger MF, Solit DB, Taylor BS. Tumour lineage shapes BRCA-mediated phenotypes. *Nature* 2019; **571**: 576-579 [PMID: 31292550 DOI: 10.1038/s41586-019-1382-1]

18 **Hodgson D**, Lai Z, Dearden S, Barrett JC, Harrington EA, Timms K, Lanchbury J, Wu W, Allen A, Senkus E, Domchek SM, Robson M. Analysis of mutation status and homologous recombination deficiency in tumors of patients with germline BRCA1 or BRCA2 mutations and metastatic breast cancer: OlympiAD. *Ann Oncol* 2021; **32**: 1582-1589 [PMID: 34500047 DOI: 10.1016/j.annonc.2021.08.2154]

19 **Martínez-Sánchez M**, Hernandez-Monge J, Rangel M, Olivares-Illana V. Retinoblastoma: from discovery to clinical management. *FEBS J* 2022; **289**: 4371-4382 [PMID: 34042282 DOI: 10.1111/febs.16035]

20 **Preobrazhenskaya EV**, Shleykina AU, Gorustovich OA, Martianov AS, Bizin IV, Anisimova EI, Sokolova TN, Chuinyshena SA, Kuligina ES, Togo AV, Belyaev AM, Ivantsov AO, Sokolenko AP, Imyanitov EN. Frequency and molecular characteristics of PALB2-associated cancers in Russian patients. *Int J Cancer* 2021; **148**: 203-210 [PMID: 32997802 DOI: 10.1002/ijc.33317]

21 **Iyevleva AG**, Aleksakhina SN, Sokolenko AP, Baskina SV, Venina AR, Anisimova EI, Bizin IV, Ivantsov AO, Belysheva YV, Chernyakova AP, Togo AV, Imyanitov EN. Somatic loss of the remaining allele occurs approximately in half of CHEK2-driven breast cancers and is accompanied by a border-line increase of chromosomal instability. *Breast Cancer Res Treat* 2022; **192**: 283-291 [PMID: 35020107 DOI: 10.1007/s10549-022-06517-3]

22 **McDonnell JE**, Gild ML, Clifton-Bligh RJ, Robinson BG. Multiple endocrine neoplasia: an update. *Intern Med J* 2019; **49**: 954-961 [PMID: 31387156 DOI: 10.1111/imj.14394]

23 **Powers JM**, Ebrahimzadeh JE, Katona BW. Genetic testing for hereditary gastrointestinal cancer syndromes: Interpreting results in today's practice. *Curr Treat Options Gastroenterol* 2019; **17**: 636-649 [PMID: 31761969 DOI: 10.1007/s11938-019-00253-2]

24 **Magrin L**, Fanale D, Brando C, Fiorino A, Corsini LR, Sciacchitano R, Filorizzo C, Dimino A, Russo A, Bazan V. POLE, POLD1, and NTHL1: the last but not the least hereditary cancer-predisposing genes. *Oncogene* 2021; **40**: 5893-5901 [PMID: 34363023 DOI: 10.1038/s41388-021-01984-2]

25 **Sokolenko AP**, Bogdanova N, Kluzniak W, Preobrazhenskaya EV, Kuligina ES, Iyevleva AG, Aleksakhina SN, Mitiushkina NV, Gorodnova TV, Bessonov AA, Togo AV, Lubiński J, Cybulski C, Jakubowska A, Dörk T, Imyanitov EN. Double heterozygotes among breast cancer patients analyzed for BRCA1, CHEK2, ATM, NBN/NBS1, and BLM germ-line mutations. *Breast Cancer Res Treat* 2014; **145**: 553-562 [PMID: 24800916 DOI: 10.1007/s10549-014-2971-1]

26 **Hilbers FS**, van 't Hof PJ, Meijers CM, Mei H, Michailidou K, Dennis J, Hogervorst FBL, Nederlof PM, van Asperen CJ, Devilee P. Clustering of known low and moderate risk alleles rather than a novel recessive high-risk gene in non-BRCA1/2 sib trios affected with breast cancer. *Int J Cancer* 2020; **147**: 2708-2716 [PMID: 32383162 DOI:

10.1002/ijc.33039]
27 **Schubert SA**, Ruano D, Tiersma Y, Drost M, de Wind N, Nielsen M, van Hest LP, Morreau H, de Miranda NFCC, van Wezel T. Digenic inheritance of MSH6 and MUTYH variants in familial colorectal cancer. *Genes Chromosomes Cancer* 2020; **59**: 697-701 [PMID: 32615015 DOI: 10.1002/gcc.22883]
28 **Gao C**, Polley EC, Hart SN, Huang H, Hu C, Gnanaolivu R, Lilyquist J, Boddicker NJ, Na J, Ambrosone CB, Auer PL, Bernstein L, Burnside ES, Eliassen AH, Gaudet MM, Haiman C, Hunter DJ, Jacobs EJ, John EM, Lindström S, Ma H, Neuhausen SL, Newcomb PA, O'Brien KM, Olson JE, Ong IM, Patel AV, Palmer JR, Sandler DP, Tamimi R, Taylor JA, Teras LR, Trentham-Dietz A, Vachon CM, Weinberg CR, Yao S, Weitzel JN, Goldgar DE, Domchek SM, Nathanson KL, Couch FJ, Kraft P. Risk of Breast Cancer Among Carriers of Pathogenic Variants in Breast Cancer Predisposition Genes Varies by Polygenic Risk Score. *J Clin Oncol* 2021; **39**: 2564-2573 [PMID: 34101481 DOI: 10.1200/JCO.20.01992]
29 **Brown GR**, Simon M, Wentling C, Spencer DM, Parker AN, Rogers CA. A review of inherited cancer susceptibility syndromes. *JAAPA* 2020; **33**: 10-16 [PMID: 33234888 DOI: 10.1097/01.JAA.0000721648.46099.2c]
30 **Whitworth J**, Smith PS, Martin JE, West H, Luchetti A, Rodger F, Clark G, Carss K, Stephens J, Stirrups K, Penkett C, Mapeta R, Ashford S, Megy K, Shakeel H, Ahmed M, Adlard J, Barwell J, Brewer C, Casey RT, Armstrong R, Cole T, Evans DG, Fostira F, Greenhalgh L, Hanson H, Henderson A, Hoffman J, Izatt L, Kumar A, Kwong A, Lalloo F, Ong KR, Paterson J, Park SM, Chen-Shtoyerman R, Searle C, Side L, Skytte AB, Snape K, Woodward ER; NIHR BioResource Rare Diseases Consortium, Tischkowitz MD, Maher ER. Comprehensive Cancer-Predisposition Gene Testing in an Adult Multiple Primary Tumor Series Shows a Broad Range of Deleterious Variants and Atypical Tumor Phenotypes. *Am J Hum Genet* 2018; **103**: 3-18 [PMID: 29909963 DOI: 10.1016/j.ajhg.2018.04.013]
31 **Holstege H**, Joosse SA, van Oostrom CT, Nederlof PM, de Vries A, Jonkers J. High incidence of protein-truncating TP53 mutations in BRCA1-related breast cancer. *Cancer Res* 2009; **69**: 3625-3633 [PMID: 19336573 DOI: 10.1158/0008-5472.CAN-08-3426]
32 **Mavaddat N**, Barrowdale D, Andrulis IL, Domchek SM, Eccles D, Nevanlinna H, Ramus SJ, Spurdle A, Robson M, Sherman M, Mulligan AM, Couch FJ, Engel C, McGuffog L, Healey S, Sinilnikova OM, Southey MC, Terry MB, Goldgar D, O'Malley F, John EM, Janavicius R, Tihomirova L, Hansen TV, Nielsen FC, Osorio A, Stavropoulou A, Benítez J, Manoukian S, Peissel B, Barile M, Volorio S, Pasini B, Dolcetti R, Putignano AL, Ottini L, Radice P, Hamann U, Rashid MU, Hogervorst FB, Kriege M, van der Luijt RB; HEBON, Peock S, Frost D, Evans DG, Brewer C, Walker L, Rogers MT, Side LE, Houghton C; EMBRACE, Weaver J, Godwin AK, Schmutzler RK, Wappenschmidt B, Meindl A, Kast K, Arnold N, Niederacher D, Sutter C, Deissler H, Gadzicki D, Preisler-Adams S, Varon-Mateeva R, Schönbuchner I, Gevensleben H, Stoppa-Lyonnet D, Belotti M, Barjhoux L; GEMO Study Collaborators, Isaacs C, Peshkin BN, Caldes T, de la Hoya M, Cañadas C, Heikkinen T, Heikkilä P, Aittomäki K, Blanco I, Lazaro C, Brunet J, Agnarsson BA, Arason A, Barkardottir RB, Dumont M, Simard J, Montagna M, Agata S, D'Andrea E, Yan M, Fox S; kConFab Investigators, Rebbeck TR, Rubinstein W, Tung N, Garber JE, Wang X, Fredericksen Z, Pankratz VS, Lindor NM, Szabo C, Offit K, Sakr R, Gaudet MM, Singer CF, Tea MK, Rappaport C, Mai PL, Greene MH, Sokolenko A, Imyanitov E, Toland AE, Senter L, Sweet K, Thomassen M, Gerdes AM, Kruse T, Caligo M, Aretini P, Rantala J, von Wachenfeld A, Henriksson K; SWE-BRCA Collaborators, Steele L, Neuhausen SL, Nussbaum R, Beattie M, Odunsi K, Sucheston L, Gayther SA, Nathanson K, Gross J, Walsh C, Karlan B, Chenevix-Trench G, Easton DF, Antoniou AC; Consortium of Investigators of Modifiers of BRCA1/2. Pathology of breast and OCs among BRCA1 and BRCA2 mutation carriers: results from the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). *Cancer Epidemiol Biomarkers Prev* 2012; **21**: 134-147 [PMID: 22144499 DOI: 10.1158/1055-9965.EPI-11-0775]
33 **Hoyer J**, Vasileiou G, Uebe S, Wunderle M, Kraus C, Fasching PA, Thiel CT, Hartmann A, Beckmann MW, Lux MP, Reis A. Addition of triple negativity of breast cancer as an indicator for germline mutations in predisposing genes increases sensitivity of clinical selection criteria. *BMC Cancer* 2018; **18**: 926 [PMID: 30257646 DOI: 10.1186/s12885-018-4821-8]
34 **Breast Cancer Association Consortium**, Mavaddat N, Dorling L, Carvalho S, Allen J, González-Neira A, Keeman R, Bolla MK, Dennis J, Wang Q, Ahearn TU, Andrulis IL, Beckmann MW, Behrens S, Benitez J, Bermisheva M, Blomqvist C, Bogdanova NV, Bojesen SE, Briceno I, Brüning T, Camp NJ, Campbell A, Castelao JE, Chang-Claude J, Chanock SJ, Chenevix-Trench G, Christiansen H, Czene K, Dörk T, Eriksson M, Evans DG, Fasching PA, Figueroa JD, Flyger H, Gabrielson M, Gago-Dominguez M, Geisler J, Giles GG, Guénel P, Hadjisavvas A, Hahnen E, Hall P, Hamann U, Hartikainen JM, Hartman M, Hoppe R, Howell A, Jakubowska A, Jung A, Khusnutdinova EK, Kristensen VN, Li J, Lim SH, Lindblom A, Loizidou MA, Lophatananon A, Lubinski J, Madsen MJ, Mannermaa A, Manoochehri M, Margolin S, Mavroudis D, Milne RL, Mohd Taib NA, Morra A, Muir K, Obi N, Osorio A, Park-Simon TW, Peterlongo P, Radice P, Saloustros E, Sawyer EJ, Schmutzler RK, Shah M, Sim X, Southey MC, Thorne H, Tomlinson I, Torres D, Truong T, Yip CH, Spurdle AB, Vreeswijk MPG, Dunning AM, García-Closas M, Pharoah PDP, Kvist A, Muranen TA, Nevanlinna H, Teo SH, Devilee P, Schmidt MK, Easton DF. Pathology of Tumors Associated With Pathogenic Germline Variants in 9 Breast Cancer Susceptibility Genes. *JAMA Oncol* 2022; **8**: e216744 [PMID: 35084436 DOI: 10.1001/jamaoncol.2021.6744]
35 **Waks AG**, Winer EP. Breast Cancer Treatment: A Review. *JAMA* 2019; **321**: 288-300 [PMID: 30667505 DOI: 10.1001/jama.2018.19323]
36 **Fierheller CT**, Alenezi WM, Tonin PN. The Genetic Analyses of French Canadians of Quebec Facilitate the Characterization of New Cancer Predisposing Genes Implicated in Hereditary Breast and/or Ovarian Cancer Syndrome Families. *Cancers (Basel)* 2021; **13** [PMID: 34298626 DOI: 10.3390/cancers13143406]
37 **Jayson GC**, Kohn EC, Kitchener HC, Ledermann JA. Ovarian cancer. *Lancet* 2014; **384**: 1376-1388 [PMID: 24767708 DOI: 10.1016/S0140-6736(13)62146-7]
38 **Lheureux S**, Gourley C, Vergote I, Oza AM. Epithelial ovarian cancer. *Lancet* 2019; **393**: 1240-1253 [PMID: 30910306 DOI: 10.1016/S0140-6736(18)32552-2]
39 **Loibl S**, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. *Lancet* 2021; **397**: 1750-1769 [PMID: 33812473 DOI: 10.1016/S0140-6736(20)32381-3]
40 **Kuchenbaecker KB**, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, Jervis S, van Leeuwen FE, Milne

RL, Andrieu N, Goldgar DE, Terry MB, Rookus MA, Easton DF, Antoniou AC; BRCA1 and BRCA2 Cohort Consortium, McGuffog L, Evans DG, Barrowdale D, Frost D, Adlard J, Ong KR, Izatt L, Tischkowitz M, Eeles R, Davidson R, Hodgson S, Ellis S, Nogues C, Lasset C, Stoppa-Lyonnet D, Fricker JP, Faivre L, Berthet P, Hooning MJ, van der Kolk LE, Kets CM, Adank MA, John EM, Chung WK, Andrulis IL, Southey M, Daly MB, Buys SS, Osorio A, Engel C, Kast K, Schmutzler RK, Caldes T, Jakubowska A, Simard J, Friedlander ML, McLachlan SA, Machackova E, Foretova L, Tan YY, Singer CF, Olah E, Gerdes AM, Arver B, Olsson H. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA* 2017; **317**: 2402-2416 [PMID: 28632866 DOI: 10.1001/jama.2017.7112]

41 **Rebbeck TR**, Mitra N, Wan F, Sinilnikova OM, Healey S, McGuffog L, Mazoyer S, Chenevix-Trench G, Easton DF, Antoniou AC, Nathanson KL; CIMBA Consortium, Laitman Y, Kushnir A, Paluch-Shimon S, Berger R, Zidan J, Friedman E, Ehrencrona H, Stenmark-Askmalm M, Einbeigi Z, Loman N, Harbst K, Rantala J, Melin B, Huo D, Olopade OI, Seldon J, Ganz PA, Nussbaum RL, Chan SB, Odunsi K, Gayther SA, Domchek SM, Arun BK, Lu KH, Mitchell G, Karlan BY, Walsh C, Lester J, Godwin AK, Pathak H, Ross E, Daly MB, Whittemore AS, John EM, Miron A, Terry MB, Chung WK, Goldgar DE, Buys SS, Janavicius R, Tihomirova L, Tung N, Dorfling CM, van Rensburg EJ, Steele L, Neuhausen SL, Ding YC, Ejlertsen B, Gerdes AM, Hansen Tv, Ramón y Cajal T, Osorio A, Benitez J, Godino J, Tejada MI, Duran M, Weitzel JN, Bobolis KA, Sand SR, Fontaine A, Savarese A, Pasini B, Peissel B, Bonanni B, Zaffaroni D, Vignolo-Lutati F, Scuvera G, Giannini G, Bernard L, Genuardi M, Radice P, Dolcetti R, Manoukian S, Pensotti V, Gismondi V, Yannoukakos D, Fostira F, Garber J, Torres D, Rashid MU, Hamann U, Peock S, Frost D, Platte R, Evans DG, Eeles R, Davidson R, Eccles D, Cole T, Cook J, Brewer C, Hodgson S, Morrison PJ, Walker L, Porteous ME, Kennedy MJ, Izatt L, Adlard J, Donaldson A, Ellis S, Sharma P, Schmutzler RK, Wappenschmidt B, Becker A, Rhiem K, Hahnen E, Engel C, Meindl A, Engert S, Ditsch N, Arnold N, Plendl HJ, Mundhenke C, Niederacher D, Fleisch M, Sutter C, Bartram CR, Dikow N, Wang-Gohrke S, Gadzicki D, Steinemann D, Kast K, Beer M, Varon-Mateeva R, Gehrig A, Weber BH, Stoppa-Lyonnet D, Sinilnikova OM, Mazoyer S, Houdayer C, Belotti M, Gauthier-Villars M, Damiola F, Boutry-Kryza N, Lasset C, Sobol H, Peyrat JP, Muller D, Fricker JP, Collonge-Rame MA, Mortemousque I, Nogues C, Rouleau E, Isaacs C, De Paepe A, Poppe B, Claes K, De Leeneer K, Piedmonte M, Rodriguez G, Wakely K, Boggess J, Blank SV, Basil J, Azodi M, Phillips KA, Caldes T, de la Hoya M, Romero A, Nevanlinna H, Aittomäki K, van der Hout AH, Hogervorst FB, Verhoef S, Collée JM, Seynaeve C, Oosterwijk JC, Gille JJ, Wijnen JT, Gómez Garcia EB, Kets CM, Ausems MG, Aalfs CM, Devilee P, Mensenkamp AR, Kwong A, Olah E, Papp J, Diez O, Lazaro C, Darder E, Blanco I, Salinas M, Jakubowska A, Lubinski J, Gronwald J, Jaworska-Bieniek K, Durda K, Sukiennicki G, Huzarski T, Byrski T, Cybulski C, Toloczko-Grabarek A, Złowocka-Perłowska E, Menkiszak J, Arason A, Barkardottir RB, Simard J, Laframboise R, Montagna M, Agata S, Alducci E, Peixoto A, Teixeira MR, Spurdle AB, Lee MH, Park SK, Kim SW, Friebel TM, Couch FJ, Lindor NM, Pankratz VS, Guidugli L, Wang X, Tischkowitz M, Foretova L, Vijai J, Offit K, Robson M, Rau-Murthy R, Kauff N, Fink-Retter A, Singer CF, Rappaport C, Gschwantler-Kaulich D, Pfeiler G, Tea MK, Berger A, Greene MH, Mai PL, Imyanitov EN, Toland AE, Senter L, Bojesen A, Pedersen IS, Skytte AB, Sunde L, Thomassen M, Moeller ST, Kruse TA, Jensen UB, Caligo MA, Aretini P, Teo SH, Selkirk CG, Hulick PJ, Andrulis I. Association of type and location of BRCA1 and BRCA2 mutations with risk of breast and ovarian cancer. *JAMA* 2015; **313**: 1347-1361 [PMID: 25849179 DOI: 10.1001/jama.2014.5985]

42 **Milne RL**, Antoniou AC. Modifiers of breast and ovarian cancer risks for BRCA1 and BRCA2 mutation carriers. *Endocr Relat Cancer* 2016; **23**: T69-T84 [PMID: 27528622 DOI: 10.1530/ERC-16-0277]

43 **Sun J**, Meng H, Yao L, Lv M, Bai J, Zhang J, Wang L, Ouyang T, Li J, Wang T, Fan Z, Fan T, Lin B, Xie Y. Germline Mutations in Cancer Susceptibility Genes in a Large Series of Unselected Breast Cancer Patients. *Clin Cancer Res* 2017; **23**: 6113-6119 [PMID: 28724667 DOI: 10.1158/1078-0432.CCR-16-3227]

44 **Gorodnova T**, Sokolenko A, Ni V, Ivantsov A, Kotiv K, Petrik S, Amelina I, Berlev I, Imyanitov E. BRCA1-associated and sporadic ovarian carcinomas: outcomes of primary cytoreductive surgery or neoadjuvant chemotherapy. *Int J Gynecol Cancer* 2019; **29**: 779-786 [PMID: 30839285 DOI: 10.1136/ijgc-2018-000175]

45 **Kurian AW**, Ward KC, Howlader N, Deapen D, Hamilton AS, Mariotto A, Miller D, Penberthy LS, Katz SJ. Genetic Testing and Results in a Population-Based Cohort of Breast Cancer Patients and Ovarian Cancer Patients. *J Clin Oncol* 2019; **37**: 1305-1315 [PMID: 30964716 DOI: 10.1200/JCO.18.01854]

46 **Pietragalla A**, Arcieri M, Marchetti C, Scambia G, Fagotti A. Ovarian cancer predisposition beyond BRCA1 and BRCA2 genes. *Int J Gynecol Cancer* 2020; **30**: 1803-1810 [PMID: 32895312 DOI: 10.1136/ijgc-2020-001556]

47 **Colas C**, Golmard L, de Pauw A, Caputo SM, Stoppa-Lyonnet D. "Decoding hereditary breast cancer" benefits and questions from multigene panel testing. *Breast* 2019; **45**: 29-35 [PMID: 30822622 DOI: 10.1016/j.breast.2019.01.002]

48 **Yang X**, Song H, Leslie G, Engel C, Hahnen E, Auber B, Horváth J, Kast K, Niederacher D, Turnbull C, Houlston R, Hanson H, Loveday C, Dolinsky JS, LaDuca H, Ramus SJ, Menon U, Rosenthal AN, Jacobs I, Gayther SA, Dicks E, Nevanlinna H, Aittomäki K, Pelttari LM, Ehrencrona H, Borg Å, Kvist A, Rivera B, Hansen TVO, Djursby M, Lee A, Dennis J, Bowtell DD, Traficante N, Diez O, Balmaña J, Gruber SB, Chenevix-Trench G, Investigators K, Jensen A, Kjær SK, Høgdall E, Castéra L, Garber J, Janavicius R, Osorio A, Golmard L, Vega A, Couch FJ, Robson M, Gronwald J, Domchek SM, Culver JO, de la Hoya M, Easton DF, Foulkes WD, Tischkowitz M, Meindl A, Schmutzler RK, Pharoah PDP, Antoniou AC. Ovarian and Breast Cancer Risks Associated With Pathogenic Variants in RAD51C and RAD51D. *J Natl Cancer Inst* 2020; **112**: 1242-1250 [PMID: 32107557 DOI: 10.1093/jnci/djaa030]

49 **Setton J**, Selenica P, Mukherjee S, Shah R, Pecorari I, McMillan B, Pei IX, Kemel Y, Ceyhan-Birsoy O, Sheehan M, Tkachuk K, Brown DN, Zhang L, Cadoo K, Powell S, Weigelt B, Robson M, Riaz N, Offit K, Reis-Filho JS, Mandelker D. Germline RAD51B variants confer susceptibility to breast and ovarian cancers deficient in homologous recombination. *NPJ Breast Cancer* 2021; **7**: 135 [PMID: 34635660 DOI: 10.1038/s41523-021-00339-0]

50 **Antoniou AC**, Casadei S, Heikkinen T, Barrowdale D, Pylkäs K, Roberts J, Lee A, Subramanian D, De Leeneer K, Fostira F, Tomiak E, Neuhausen SL, Teo ZL, Khan S, Aittomäki K, Moilanen JS, Turnbull C, Seal S, Mannermaa A, Kallioniemi A, Lindeman GJ, Buys SS, Andrulis IL, Radice P, Tondini C, Manoukian S, Toland AE, Miron P, Weitzel JN, Domchek SM, Poppe B, Claes KB, Yannoukakos D, Concannon P, Bernstein JL, James PA, Easton DF, Goldgar DE, Hopper JL, Rahman N, Peterlongo P, Nevanlinna H, King MC, Couch FJ, Southey MC, Winqvist R, Foulkes WD, Tischkowitz M. Breast-cancer risk in families with mutations in PALB2. *N Engl J Med* 2014; **371**: 497-506 [PMID:

25099575 DOI: 10.1056/NEJMoa1400382]

51 **Song H**, Dicks EM, Tyrer J, Intermaggio M, Chenevix-Trench G, Bowtell DD, Traficante N; Group A, Brenton J, Goranova T, Hosking K, Piskorz A, van Oudenhove E, Doherty J, Harris HR, Rossing MA, Duerst M, Dork T, Bogdanova NV, Modugno F, Moysich K, Odunsi K, Ness R, Karlan BY, Lester J, Jensen A, Krüger Kjaer S, Høgdall E, Campbell IG, Lázaro C, Pujara MA, Cunningham J, Vierkant R, Winham SJ, Hildebrandt M, Huff C, Li D, Wu X, Yu Y, Permuth JB, Levine DA, Schildkraut JM, Riggan MJ, Berchuck A, Webb PM; Group OS, Cybulski C, Gronwald J, Jakubowska A, Lubinski J, Alsop J, Harrington P, Chan I, Menon U, Pearce CL, Wu AH, de Fazio A, Kennedy CJ, Goode E, Ramus S, Gayther S, Pharoah P. Population-based targeted sequencing of 54 candidate genes identifies PALB2 as a susceptibility gene for high-grade serous ovarian cancer. *J Med Genet* 2021; **58**: 305-313 [PMID: 32546565 DOI: 10.1136/jmedgenet-2019-106739]

52 **Sokolenko AP**, Iyevleva AG, Preobrazhenskaya EV, Mitiushkina NV, Abysheva SN, Suspitsin EN, Kuligina ESh, Gorodnova TV, Pfeifer W, Togo AV, Turkevich EA, Ivantsov AO, Voskresenskiy DV, Dolmatov GD, Bit-Sava EM, Matsko DE, Semiglazov VF, Fichtner I, Larionov AA, Kuznetsov SG, Antoniou AC, Imyanitov EN. High prevalence and breast cancer predisposing role of the BLM c.1642 C>T (Q548X) mutation in Russia. *Int J Cancer* 2012; **130**: 2867-2873 [PMID: 21815139 DOI: 10.1002/ijc.26342]

53 **Cybulski C**, Carrot-Zhang J, Kluźniak W, Rivera B, Kashyap A, Wokołorczyk D, Giroux S, Nadaf J, Hamel N, Zhang S, Huzarski T, Gronwald J, Byrski T, Szwiec M, Jakubowska A, Rudnicka H, Lener M, Masojć B, Tonin PN, Rousseau F, Górski B, Dębniak T, Majewski J, Lubiński J, Foulkes WD, Narod SA, Akbari MR. Germline RECQL mutations are associated with breast cancer susceptibility. *Nat Genet* 2015; **47**: 643-646 [PMID: 25915596 DOI: 10.1038/ng.3284]

54 **Neidhardt G**, Hauke J, Ramser J, Groß E, Gehrig A, Müller CR, Kahlert AK, Hackmann K, Honisch E, Niederacher D, Heilmann-Heimbach S, Franke A, Lieb W, Thiele H, Altmüller J, Nürnberg P, Klaschik K, Ernst C, Ditsch N, Jessen F, Ramirez A, Wappenschmidt B, Engel C, Rhiem K, Meindl A, Schmutzler RK, Hahnen E. Association Between Loss-of-Function Mutations Within the FANCM Gene and Early-Onset Familial Breast Cancer. *JAMA Oncol* 2017; **3**: 1245-1248 [PMID: 28033443 DOI: 10.1001/jamaoncol.2016.5592]

55 **Thompson ER**, Doyle MA, Ryland GL, Rowley SM, Choong DY, Tothill RW, Thorne H; kConFab, Barnes DR, Li J, Ellul J, Philip GK, Antill YC, James PA, Trainer AH, Mitchell G, Campbell IG. Exome sequencing identifies rare deleterious mutations in DNA repair genes FANCC and BLM as potential breast cancer susceptibility alleles. *PLoS Genet* 2012; **8**: e1002894 [PMID: 23028338 DOI: 10.1371/journal.pgen.1002894]

56 **Felicio PS**, Grasel RS, Campacci N, de Paula AE, Galvão HCR, Torrezan GT, Sabato CS, Fernandes GC, Souza CP, Michelli RD, Andrade CE, Barros BDF, Matsushita MM, Revil T, Ragoussis J, Couch FJ, Hart SN, Reis RM, Melendez ME, Tonin PN, Carraro DM, Palmero EI. Whole-exome sequencing of non-BRCA1/BRCA2 mutation carrier cases at high-risk for hereditary breast/ovarian cancer. *Hum Mutat* 2021; **42**: 290-299 [PMID: 33326660 DOI: 10.1002/humu.24158]

57 **Kuligina ES**, Sokolenko AP, Bizin IV, Romanko AA, Zagorodnev KA, Anisimova MO, Krylova DD, Anisimova EI, Mantseva MA, Varma AK, Hasan SK, Ni VI, Koloskov AV, Suspitsin EN, Venina AR, Aleksakhina SN, Sokolova TN, Milanović AM, Schürmann P, Prokofyeva DS, Bermisheva MA, Khusnutdinova EK, Bogdanova N, Dörk T, Imyanitov EN. Exome sequencing study of Russian breast cancer patients suggests a predisposing role for USP39. *Breast Cancer Res Treat* 2020; **179**: 731-742 [PMID: 31754952 DOI: 10.1007/s10549-019-05492-6]

58 **Koivuluoma S**, Tervasmäki A, Kauppila S, Winqvist R, Kumpula T, Kuismin O, Moilanen J, Pylkäs K. Exome sequencing identifies a recurrent variant in SERPINA3 associating with hereditary susceptibility to breast cancer. *Eur J Cancer* 2021; **143**: 46-51 [PMID: 33279852 DOI: 10.1016/j.ejca.2020.10.033]

59 **Shin SJ**, Dodd-Eaton EB, Peng G, Bojadzieva J, Chen J, Amos CI, Frone MN, Khincha PP, Mai PL, Savage SA, Ballinger ML, Thomas DM, Yuan Y, Strong LC, Wang W. Penetrance of Different Cancer Types in Families with Li-Fraumeni Syndrome: A Validation Study Using Multicenter Cohorts. *Cancer Res* 2020; **80**: 354-360 [PMID: 31719101 DOI: 10.1158/0008-5472.CAN-19-0728]

60 **Lolas Hamameh S**, Renbaum P, Kamal L, Dweik D, Salahat M, Jaraysa T, Abu Rayyan A, Casadei S, Mandell JB, Gulsuner S, Lee MK, Walsh T, King MC, Levy-Lahad E, Kanaan M. Genomic analysis of inherited breast cancer among Palestinian women: Genetic heterogeneity and a founder mutation in TP53. *Int J Cancer* 2017; **141**: 750-756 [PMID: 28486781 DOI: 10.1002/ijc.30771]

61 **Fortuno C**, James PA, Spurdle AB. Current review of TP53 pathogenic germline variants in breast cancer patients outside Li-Fraumeni syndrome. *Hum Mutat* 2018; **39**: 1764-1773 [PMID: 30240537 DOI: 10.1002/humu.23656]

62 **Rana HQ**, Gelman R, LaDuca H, McFarland R, Dalton E, Thompson J, Speare V, Dolinsky JS, Chao EC, Garber JE. Differences in TP53 Mutation Carrier Phenotypes Emerge From Panel-Based Testing. *J Natl Cancer Inst* 2018; **110**: 863-870 [PMID: 29529297 DOI: 10.1093/jnci/djy001]

63 **Kratz CP**, Freycon C, Maxwell KN, Nichols KE, Schiffman JD, Evans DG, Achatz MI, Savage SA, Weitzel JN, Garber JE, Hainaut P, Malkin D. Analysis of the Li-Fraumeni Spectrum Based on an International Germline TP53 Variant Data Set: An International Agency for Research on Cancer TP53 Database Analysis. *JAMA Oncol* 2021; **7**: 1800-1805 [PMID: 34709361 DOI: 10.1001/jamaoncol.2021.4398]

64 **Corso G**, Montagna G, Figueiredo J, La Vecchia C, Fumagalli Romario U, Fernandes MS, Seixas S, Roviello F, Trovato C, Guerini-Rocco E, Fusco N, Pravettoni G, Petrocchi S, Rotili A, Massari G, Magnoni F, De Lorenzi F, Bottoni M, Galimberti V, Sanches JM, Calvello M, Seruca R, Bonanni B. Hereditary Gastric and Breast Cancer Syndromes Related to CDH1 Germline Mutation: A Multidisciplinary Clinical Review. *Cancers (Basel)* 2020; **12** [PMID: 32560361 DOI: 10.3390/cancers12061598]

65 **Bonadona V**, Bonaïti B, Olschwang S, Grandjouan S, Huiart L, Longy M, Guimbaud R, Buecher B, Bignon YJ, Caron O, Colas C, Noguès C, Lejeune-Dumoulin S, Olivier-Faivre L, Polycarpe-Osaer F, Nguyen TD, Desseigne F, Saurin JC, Berthet P, Leroux D, Duffour J, Manouvrier S, Frébourg T, Sobol H, Lasset C, Bonaïti-Pellié C; French Cancer Genetics Network. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. *JAMA* 2011; **305**: 2304-2310 [PMID: 21642682 DOI: 10.1001/jama.2011.743]

66 **Therkildsen C**, Ladelund S, Smith-Hansen L, Lindberg LJ, Nilbert M. Towards gene- and gender-based risk estimates in

Lynch syndrome; age-specific incidences for 13 extra-colorectal cancer types. *Br J Cancer* 2017; **117**: 1702-1710 [PMID: 29065108 DOI: 10.1038/bjc.2017.348]

67 **Carnevali I**, Riva C, Chiaravalli AM, Sahnane N, Di Lauro E, Viel A, Rovera F, Formenti G, Ghezzi F, Sessa F, Tibiletti MG. Inherited cancer syndromes in 220 Italian ovarian cancer patients. *Cancer Genet* 2019; **237**: 55-62 [PMID: 31447066 DOI: 10.1016/j.cancergen.2019.06.005]

68 **Dominguez-Valentin M**, Sampson JR, Seppälä TT, Ten Broeke SW, Plazzer JP, Nakken S, Engel C, Aretz S, Jenkins MA, Sunde L, Bernstein I, Capella G, Balaguer F, Thomas H, Evans DG, Burn J, Greenblatt M, Hovig E, de Vos Tot Nederveen Cappel WH, Sijmons RH, Bertario L, Tibiletti MG, Cavestro GM, Lindblom A, Della Valle A, Lopez-Köstner F, Gluck N, Katz LH, Heinimann K, Vaccaro CA, Büttner R, Görgens H, Holinski-Feder E, Morak M, Holzapfel S, Hüneburg R, Knebel Doeberitz MV, Loeffler M, Rahner N, Schackert HK, Steinke-Lange V, Schmiegel W, Vangala D, Pylvänäinen K, Renkonen-Sinisalo L, Hopper JL, Win AK, Haile RW, Lindor NM, Gallinger S, Le Marchand L, Newcomb PA, Figueiredo JC, Thibodeau SN, Wadt K, Therkildsen C, Okkels H, Ketabi Z, Moreira L, Sánchez A, Serra-Burriel M, Pineda M, Navarro M, Blanco I, Green K, Lalloo F, Crosbie EJ, Hill J, Denton OG, Frayling IM, Rødland EA, Vasen H, Mints M, Neffa F, Esperon P, Alvarez K, Kariv R, Rosner G, Pinero TA, Gonzalez ML, Kalfayan P, Tjandra D, Winship IM, Macrae F, Möslein G, Mecklin JP, Nielsen M, Møller P. Cancer risks by gene, age, and gender in 6350 carriers of pathogenic mismatch repair variants: findings from the Prospective Lynch Syndrome Database. *Genet Med* 2020; **22**: 15-25 [PMID: 31337882 DOI: 10.1038/s41436-019-0596-9]

69 **Lerner-Ellis J**, Mighton C, Lazaro C, Watkins N, Di Gioacchino V, Wong A, Chang MC, Charames GS. Multigene panel testing for hereditary breast and ovarian cancer in the province of Ontario. *J Cancer Res Clin Oncol* 2021; **147**: 871-879 [PMID: 32885271 DOI: 10.1007/s00432-020-03377-6]

70 **Shanbhogue KP**, Prasad AS, Ucisik-Keser FE, Katabathina VS, Morani AC. Hereditary ovarian tumour syndromes: current update on genetics and imaging. *Clin Radiol* 2021; **76**: 313.e15-313.e26 [PMID: 33353730 DOI: 10.1016/j.crad.2020.11.116]

71 **Zhu Q**, Zhang J, Chen Y, Hu Q, Shen H, Huang RY, Liu Q, Kaur J, Long M, Battaglia S, Eng KH, Lele SB, Zsiros E, Villella J, Lugade A, Yao S, Liu S, Moysich K, Odunsi KO. Whole-exome sequencing of ovarian cancer families uncovers putative predisposition genes. *Int J Cancer* 2020; **146**: 2147-2155 [PMID: 31265121 DOI: 10.1002/ijc.32545]

72 **Stradella A**, Del Valle J, Rofes P, Vargas-Parra G, Salinas M, González S, Montes E, López-Doriga A, Gómez C, de Cid R, Darder E, Teulé A, Solanes A, Munté E, Capellà G, Pineda M, Feliubadaló L, Brunet J, Lázaro C. ERCC3, a new ovarian cancer susceptibility gene? *Eur J Cancer* 2020; **141**: 1-8 [PMID: 33125943 DOI: 10.1016/j.ejca.2020.09.023]

73 **Lynch HT**, Krush AJ, Larsen AL. Heredity and multiple primary malignant neoplasms: six cancer families. *Am J Med Sci* 1967; **254**: 322-329 [PMID: 6054534 DOI: 10.1097/00000441-196709000-00007]

74 **Ligtenberg MJ**, Kuiper RP, Chan TL, Goossens M, Hebeda KM, Voorendt M, Lee TY, Bodmer D, Hoenselaar E, Hendriks-Cornelissen SJ, Tsui WY, Kong CK, Brunner HG, van Kessel AG, Yuen ST, van Krieken JH, Leung SY, Hoogerbrugge N. Heritable somatic methylation and inactivation of MSH2 in families with Lynch syndrome due to deletion of the 3' exons of TACSTD1. *Nat Genet* 2009; **41**: 112-117 [PMID: 19098912 DOI: 10.1038/ng.283]

75 **Yanus GA**, Belyaeva AV, Ivantsov AO, Kuligina ESh, Suspitsin EN, Mitiushkina NV, Aleksakhina SN, Iyevleva AG, Zaitseva OA, Yatsuk OS, Gorodnova TV, Strelkova TN, Efremova SA, Lepenchuk AY, Ochir-Garyaev AN, Paneyah MB, Matsko DE, Togo AV, Imyanitov EN. Pattern of clinically relevant mutations in consecutive series of Russian colorectal cancer patients. *Med Oncol* 2013; **30**: 686 [PMID: 23943423 DOI: 10.1007/s12032-013-0686-5]

76 **Valle L**, Vilar E, Tavtigian SV, Stoffel EM. Genetic predisposition to colorectal cancer: syndromes, genes, classification of genetic variants and implications for precision medicine. *J Pathol* 2019; **247**: 574-588 [PMID: 30584801 DOI: 10.1002/path.5229]

77 **Cohen SA**, Pritchard CC, Jarvik GP. Lynch Syndrome: From Screening to Diagnosis to Treatment in the Era of Modern Molecular Oncology. *Annu Rev Genomics Hum Genet* 2019; **20**: 293-307 [PMID: 30848956 DOI: 10.1146/annurev-genom-083118-015406]

78 **Clark SK**. Management of genetically determined colorectal cancer. *Surgeon* 2019; **17**: 165-171 [PMID: 30935877 DOI: 10.1016/j.surge.2019.03.003]

79 **Terradas M**, Capellá G, Valle L. Dominantly Inherited Hereditary Nonpolyposis Colorectal Cancer Not Caused by MMR Genes. *J Clin Med* 2020; **9** [PMID: 32585810 DOI: 10.3390/jcm9061954]

80 **Latham A**, Srinivasan P, Kemel Y, Shia J, Bandlamudi C, Mandelker D, Middha S, Hechtman J, Zehir A, Dubard-Gault M, Tran C, Stewart C, Sheehan M, Penson A, DeLair D, Yaeger R, Vijai J, Mukherjee S, Galle J, Dickson MA, Janjigian Y, O'Reilly EM, Segal N, Saltz LB, Reidy-Lagunes D, Varghese AM, Bajorin D, Carlo MI, Cadoo K, Walsh MF, Weiser M, Aguilar JG, Klimstra DS, Diaz LA Jr, Baselga J, Zhang L, Ladanyi M, Hyman DM, Solit DB, Robson ME, Taylor BS, Offit K, Berger MF, Stadler ZK. Microsatellite Instability Is Associated With the Presence of Lynch Syndrome Pan-Cancer. *J Clin Oncol* 2019; **37**: 286-295 [PMID: 30376427 DOI: 10.1200/JCO.18.00283]

81 **Vilar E**, Gruber SB. Microsatellite instability in colorectal cancer-the stable evidence. *Nat Rev Clin Oncol* 2010; **7**: 153-162 [PMID: 20142816 DOI: 10.1038/nrclinonc.2009.237]

82 **Cavazza A**, Radia C, Harlow C, Monahan KJ. Experience of the implementation and outcomes of universal testing for Lynch syndrome in the United Kingdom. *Colorectal Dis* 2019; **21**: 760-766 [PMID: 30815953 DOI: 10.1111/codi.14597]

83 **Palles C**, West HD, Chew E, Galavotti S, Flensburg C, Grolleman JE, Jansen EAM, Curley H, Chegwidden L, Arbe-Barnes EH, Lander N, Truscott R, Pagan J, Bajel A, Sherwood K, Martin L, Thomas H, Georgiou D, Fostira F, Goldberg Y, Adams DJ, van der Biezen SAM, Christie M, Clendenning M, Thomas LE, Deltas C, Dimovski AJ, Dymerska D, Lubinski J, Mahmood K, van der Post RS, Sanders M, Weitz J, Taylor JC, Turnbull C, Vreede L, van Wezel T, Whalley C, Arnedo-Pac C, Caravagna G, Cross W, Chubb D, Frangou A, Gruber AJ, Kinnersley B, Noyvert B, Church D, Graham T, Houlston R, Lopez-Bigas N, Sottoriva A, Wedge D; Genomics England Research Consortium; CORGI Consortium; WGS500 Consortium, Jenkins MA, Kuiper RP, Roberts AW, Cheadle JP, Ligtenberg MJL, Hoogerbrugge N, Koelzer VH, Rivas AD, Winship IM, Ponte CR, Buchanan DD, Power DG, Green A, Tomlinson IPM, Sampson JR, Majewski IJ, de Voer RM. Germline MBD4 deficiency causes a multi-tumor predisposition syndrome. *Am J Hum Genet* 2022; **109**: 953-960 [PMID: 35460607 DOI: 10.1016/j.ajhg.2022.03.018]

84 **Samadder NJ**, Baffy N, Giridhar KV, Couch FJ, Riegert-Johnson D. Hereditary Cancer Syndromes-A Primer on Diagnosis and Management, Part 2: Gastrointestinal Cancer Syndromes. *Mayo Clin Proc* 2019; **94**: 1099-1116 [PMID: 31171120 DOI: 10.1016/j.mayocp.2019.01.042]

85 **Daca Alvarez M**, Quintana I, Terradas M, Mur P, Balaguer F, Valle L. The Inherited and Familial Component of Early-Onset Colorectal Cancer. *Cells* 2021; **10** [PMID: 33806975 DOI: 10.3390/cells10030710]

86 **Yanus GA**, Akhapkina TA, Ivantsov AO, Preobrazhenskaya EV, Aleksakhina SN, Bizin IV, Sokolenko AP, Mitiushkina NV, Kuligina ES, Suspitsin EN, Venina AR, Holmatov MM, Zaitseva OA, Yatsuk OS, Pashkov DV, Belyaev AM, Togo AV, Imyanitov EN, Iyevleva AG. Spectrum of APC and MUTYH germ-line mutations in Russian patients with colorectal malignancies. *Clin Genet* 2018; **93**: 1015-1021 [PMID: 29406563 DOI: 10.1111/cge.13228]

87 **Zarkavelis G**, Boussios S, Papadaki A, Katsanos KH, Christodoulou DK, Pentheroudakis G. Current and future biomarkers in colorectal cancer. *Ann Gastroenterol* 2017; **30**: 613-621 [PMID: 29118555 DOI: 10.20524/aog.2017.0191]

88 **Smyth EC**, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. *Lancet* 2020; **396**: 635-648 [PMID: 32861308 DOI: 10.1016/S0140-6736(20)31288-5]

89 **Cosma LS**, Schlosser S, Tews HC, Müller M, Kandulski A. Hereditary Diffuse Gastric Cancer: Molecular Genetics, Biological Mechanisms and Current Therapeutic Approaches. *Int J Mol Sci* 2022; **23** [PMID: 35887173 DOI: 10.3390/ijms23147821]

90 **Guilford P**, Hopkins J, Harraway J, McLeod M, McLeod N, Harawira P, Taite H, Scoular R, Miller A, Reeve AE. E-cadherin germline mutations in familial gastric cancer. *Nature* 1998; **392**: 402-405 [PMID: 9537325 DOI: 10.1038/32918]

91 **Blair VR**, McLeod M, Carneiro F, Coit DG, D'Addario JL, van Dieren JM, Harris KL, Hoogerbrugge N, Oliveira C, van der Post RS, Arnold J, Benusiglio PR, Bisseling TM, Boussioutas A, Cats A, Charlton A, Schreiber KEC, Davis JL, Pietro MD, Fitzgerald RC, Ford JM, Gamet K, Gullo I, Hardwick RH, Huntsman DG, Kaurah P, Kupfer SS, Latchford A, Mansfield PF, Nakajima T, Parry S, Rossaak J, Sugimura H, Svrcek M, Tischkowitz M, Ushijima T, Yamada H, Yang HK, Claydon A, Figueiredo J, Paringatai K, Seruca R, Bougen-Zhukov N, Brew T, Busija S, Carneiro P, DeGregorio L, Fisher H, Gardner E, Godwin TD, Holm KN, Humar B, Lintott CJ, Monroe EC, Muller MD, Norero E, Nouri Y, Paredes J, Sanches JM, Schulpen E, Ribeiro AS, Sporle A, Whitworth J, Zhang L, Reeve AE, Guilford P. Hereditary diffuse gastric cancer: updated clinical practice guidelines. *Lancet Oncol* 2020; **21**: e386-e397 [PMID: 32758476 DOI: 10.1016/S1470-2045(20)30219-9]

92 **Adib E**, El Zarif T, Nassar AH, Akl EW, Abou Alaiwi S, Mouhieddine TH, Esplin ED, Hatchell K, Nielsen SM, Rana HQ, Choueiri TK, Kwiatkowski DJ, Sonpavde G. CDH1 germline variants are enriched in patients with colorectal cancer, gastric cancer, and breast cancer. *Br J Cancer* 2022; **126**: 797-803 [PMID: 34949788 DOI: 10.1038/s41416-021-01673-7]

93 **Sahasrabudhe R**, Lott P, Bohorquez M, Toal T, Estrada AP, Suarez JJ, Brea-Fernández A, Cameselle-Teijeiro J, Pinto C, Ramos I, Mantilla A, Prieto R, Corvalan A, Norero E, Alvarez C, Tapia T, Carvallo P, Gonzalez LM, Cock-Rada A, Solano A, Neffa F, Della Valle A, Yau C, Soares G, Borowsky A, Hu N, He LJ, Han XY; Latin American Gastric Cancer Genetics Collaborative Group, Taylor PR, Goldstein AM, Torres J, Echeverry M, Ruiz-Ponte C, Teixeira MR, Carvajal-Carmona LG. Germline Mutations in PALB2, BRCA1, and RAD51C, Which Regulate DNA Recombination Repair, in Patients With Gastric Cancer. *Gastroenterology* 2017; **152**: 983-986.e6 [PMID: 28024868 DOI: 10.1053/j.gastro.2016.12.010]

94 **Fewings E**, Larionov A, Redman J, Goldgraben MA, Scarth J, Richardson S, Brewer C, Davidson R, Ellis I, Evans DG, Halliday D, Izatt L, Marks P, McConnell V, Verbist L, Mayes R, Clark GR, Hadfield J, Chin SF, Teixeira MR, Giger OT, Hardwick R, di Pietro M, O'Donovan M, Pharoah P, Caldas C, Fitzgerald RC, Tischkowitz M. Germline pathogenic variants in PALB2 and other cancer-predisposing genes in families with hereditary diffuse gastric cancer without CDH1 mutation: a whole-exome sequencing study. *Lancet Gastroenterol Hepatol* 2018; **3**: 489-498 [PMID: 29706558 DOI: 10.1016/S2468-1253(18)30079-7]

95 **Yang X**, Leslie G, Doroszuk A, Schneider S, Allen J, Decker B, Dunning AM, Redman J, Scarth J, Plaskocinska I, Luccarini C, Shah M, Pooley K, Dorling L, Lee A, Adank MA, Adlard J, Aittomäki K, Andrulis IL, Ang P, Barwell J, Bernstein JL, Bobolis K, Borg Å, Blomqvist C, Claes KBM, Concannon P, Cuggia A, Culver JO, Damiola F, de Pauw A, Diez O, Dolinsky JS, Domchek SM, Engel C, Evans DG, Fostira F, Garber J, Golmard L, Goode EL, Gruber SB, Hahnen E, Hake C, Heikkinen T, Hurley JE, Janavicius R, Kleibl Z, Kleiblova P, Konstantopoulou I, Kvist A, Laduca H, Lee ASG, Lesueur F, Maher ER, Mannermaa A, Manoukian S, McFarland R, McKinnon W, Meindl A, Metcalfe K, Mohd Taib NA, Moilanen J, Nathanson KL, Neuhausen S, Ng PS, Nguyen-Dumont T, Nielsen SM, Obermair F, Offit K, Olopade OI, Ottini L, Penkert J, Pylkäs K, Radice P, Ramus SJ, Rudaitis V, Side L, Silva-Smith R, Silvestri V, Skytte AB, Slavin T, Soukupova J, Tondini C, Trainer AH, Unzeitig G, Usha L, van Overeem Hansen T, Whitworth J, Wood M, Yip CH, Yoon SY, Yussuf A, Zogopoulos G, Goldgar D, Hopper JL, Chenevix-Trench G, Pharoah P, George SHL, Balmaña J, Houdayer C, James P, El-Haffaf Z, Ehrencrona H, Janatova M, Peterlongo P, Nevanlinna H, Schmutzler R, Teo SH, Robson M, Pal T, Couch F, Weitzel JN, Elliott A, Southey M, Winqvist R, Easton DF, Foulkes WD, Antoniou AC, Tischkowitz M. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. *J Clin Oncol* 2020; **38**: 674-685 [PMID: 31841383 DOI: 10.1200/JCO.19.01907]

96 **Moiseyenko VM**, Volkov NM, Suspistin EN, Yanus GA, Iyevleva AG, Kuligina ESh, Togo AV, Kornilov AV, Ivantsov AO, Imyanitov EN. Evidence for predictive role of BRCA1 and bTUBIII in gastric cancer. *Med Oncol* 2013; **30**: 545 [PMID: 23532817 DOI: 10.1007/s12032-013-0545-4]

97 **Li S**, Silvestri V, Leslie G, Rebbeck TR, Neuhausen SL, Hopper JL, Nielsen HR, Lee A, Yang X, McGuffog L, Parsons MT, Andrulis IL, Arnold N, Belotti M, Borg Å, Buecher B, Buys SS, Caputo SM, Chung WK, Colas C, Colonna SV, Cook J, Daly MB, de la Hoya M, de Pauw A, Delhomelle H, Eason J, Engel C, Evans DG, Faust U, Fehm TN, Fostira F, Fountzilas G, Frone M, Garcia-Barberan V, Garre P, Gauthier-Villars M, Gehrig A, Glendon G, Goldgar DE, Golmard L, Greene MH, Hahnen E, Hamann U, Hanson H, Hassan T, Hentschel J, Horvath J, Izatt L, Janavicius R, Jiao Y, John EM, Karlan BY, Kim SW, Konstantopoulou I, Kwong A, Laugé A, Lee JW, Lesueur F, Mebirouk N, Meindl A, Mouret-Fourme E, Musgrave H, Ngeow Yuen Yie J, Niederacher D, Park SK, Pedersen IS, Ramser J, Ramus SJ, Rantala J, Rashid MU, Reichl F, Ritter J, Rump A, Santamariña M, Saule C, Schmidt G, Schmutzler RK, Senter L, Shariff S, Singer CF, Southey MC, Stoppa-Lyonnet D, Sutter C, Tan Y, Teo SH, Terry MB, Thomassen M, Tischkowitz M, Toland AE, Torres

D, Vega A, Wagner SA, Wang-Gohrke S, Wappenschmidt B, Weber BHF, Yannoukakos D, Spurdle AB, Easton DF, Chenevix-Trench G, Ottini L, Antoniou AC. Cancer Risks Associated With BRCA1 and BRCA2 Pathogenic Variants. *J Clin Oncol* 2022; **40**: 1529-1541 [PMID: 35077220 DOI: 10.1200/JCO.21.02112]

98 **Lerner BA**, Llor X. Genetic Gastric Cancer Risk Syndromes. *Curr Treat Options Gastroenterol* 2020; **18**: 604-615 [PMID: 33776403 DOI: 10.1007/s11938-020-00312-z]

99 **Hu C**, Hart SN, Polley EC, Gnanaolivu R, Shimelis H, Lee KY, Lilyquist J, Na J, Moore R, Antwi SO, Bamlet WR, Chaffee KG, DiCarlo J, Wu Z, Samara R, Kasi PM, McWilliams RR, Petersen GM, Couch FJ. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. *JAMA* 2018; **319**: 2401-2409 [PMID: 29922827 DOI: 10.1001/jama.2018.6228]

100 **Llach J**, Carballal S, Moreira L. Familial Pancreatic Cancer: Current Perspectives. *Cancer Manag Res* 2020; **12**: 743-758 [PMID: 32099470 DOI: 10.2147/CMAR.S172421]

101 **Abe K**, Kitago M, Kitagawa Y, Hirasawa A. Hereditary pancreatic cancer. *Int J Clin Oncol* 2021; **26**: 1784-1792 [PMID: 34476650 DOI: 10.1007/s10147-021-02015-6]

102 **Astiazaran-Symonds E**, Goldstein AM. A systematic review of the prevalence of germline pathogenic variants in patients with pancreatic cancer. *J Gastroenterol* 2021; **56**: 713-721 [PMID: 34255164 DOI: 10.1007/s00535-021-01806-y]

103 **Mersch J**, Jackson MA, Park M, Nebgen D, Peterson SK, Singletary C, Arun BK, Litton JK. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. *Cancer* 2015; **121**: 269-275 [PMID: 25224030 DOI: 10.1002/cncr.29041]

104 **Jones S**, Hruban RH, Kamiyama M, Borges M, Zhang X, Parsons DW, Lin JC, Palmisano E, Brune K, Jaffee EM, Iacobuzio-Donahue CA, Maitra A, Parmigiani G, Kern SE, Velculescu VE, Kinzler KW, Vogelstein B, Eshleman JR, Goggins M, Klein AP. Exomic sequencing identifies PALB2 as a pancreatic cancer susceptibility gene. *Science* 2009; **324**: 217 [PMID: 19264984 DOI: 10.1126/science.1171202]

105 **Roberts NJ**, Jiao Y, Yu J, Kopelovich L, Petersen GM, Bondy ML, Gallinger S, Schwartz AG, Syngal S, Cote ML, Axilbund J, Schulick R, Ali SZ, Eshleman JR, Velculescu VE, Goggins M, Vogelstein B, Papadopoulos N, Hruban RH, Kinzler KW, Klein AP. ATM mutations in patients with hereditary pancreatic cancer. *Cancer Discov* 2012; **2**: 41-46 [PMID: 22585167 DOI: 10.1158/2159-8290.CD-11-0194]

106 **Hsu FC**, Roberts NJ, Childs E, Porter N, Rabe KG, Borgida A, Ukaegbu C, Goggins MG, Hruban RH, Zogopoulos G, Syngal S, Gallinger S, Petersen GM, Klein AP. Risk of Pancreatic Cancer Among Individuals With Pathogenic Variants in the ATM Gene. *JAMA Oncol* 2021; **7**: 1664-1668 [PMID: 34529012 DOI: 10.1001/jamaoncol.2021.3701]

107 **Gardiner A**, Kidd J, Elias MC, Young K, Mabey B, Taherian N, Cummings S, Malafa M, Rosenthal E, Permuth JB. Pancreatic Ductal Carcinoma Risk Associated With Hereditary Cancer-Risk Genes. *J Natl Cancer Inst* 2022; **114**: 996-1002 [PMID: 35445726 DOI: 10.1093/jnci/djac069]

108 **Zeng C**, Bastarache LA, Tao R, Venner E, Hebbring S, Andujar JD, Bland ST, Crosslin DR, Pratap S, Cooley A, Pacheco JA, Christensen KD, Perez E, Zawatsky CLB, Witkowski L, Zouk H, Weng C, Leppig KA, Sleiman PMA, Hakonarson H, Williams MS, Luo Y, Jarvik GP, Green RC, Chung WK, Gharavi AG, Lennon NJ, Rehm HL, Gibbs RA, Peterson JF, Roden DM, Wiesner GL, Denny JC. Association of Pathogenic Variants in Hereditary Cancer Genes With Multiple Diseases. *JAMA Oncol* 2022; **8**: 835-844 [PMID: 35446370 DOI: 10.1001/jamaoncol.2022.0373]

109 **Chan SH**, Chiang J, Ngeow J. CDKN2A germline alterations and the relevance of genotype-phenotype associations in cancer predisposition. *Hered Cancer Clin Pract* 2021; **19**: 21 [PMID: 33766116 DOI: 10.1186/s13053-021-00178-x]

110 **Nissim S**, Leshchiner I, Mancias JD, Greenblatt MB, Maertens O, Cassa CA, Rosenfeld JA, Cox AG, Hedgepeth J, Wucherpfennig JI, Kim AJ, Henderson JE, Gonyo P, Brandt A, Lorimer E, Unger B, Prokop JW, Heidel JR, Wang XX, Ukaegbu CI, Jennings BC, Paulo JA, Gableske S, Fierke CA, Getz G, Sunyaev SR, Wade Harper J, Cichowski K, Kimmelman AC, Houvras Y, Syngal S, Williams C, Goessling W. Mutations in RABL3 alter KRAS prenylation and are associated with hereditary pancreatic cancer. *Nat Genet* 2019; **51**: 1308-1314 [PMID: 31406347 DOI: 10.1038/s41588-019-0475-y]

111 **Roberts NJ**, Grant RC, Gallinger S, Klein AP; Familial Pancreatic Cancer Genome Sequencing Project. Germline sequence analysis of RABL3 in a large series of pancreatic ductal adenocarcinoma patients reveals no evidence of deleterious variants. *Genes Chromosomes Cancer* 2021; **60**: 559-564 [PMID: 33724601 DOI: 10.1002/gcc.22947]

112 **Nicolosi P**, Ledet E, Yang S, Michalski S, Freschi B, O'Leary E, Esplin ED, Nussbaum RL, Sartor O. Prevalence of Germline Variants in Prostate Cancer and Implications for Current Genetic Testing Guidelines. *JAMA Oncol* 2019; **5**: 523-528 [PMID: 30730552 DOI: 10.1001/jamaoncol.2018.6760]

113 **Bree KK**, Hensley PJ, Pettaway CA. Germline Predisposition to Prostate Cancer in Diverse Populations. *Urol Clin North Am* 2021; **48**: 411-423 [PMID: 34210495 DOI: 10.1016/j.ucl.2021.03.008]

114 **Bhanji Y**, Isaacs WB, Xu J, Cooney KA. Prostate Cancer Predisposition. *Urol Clin North Am* 2021; **48**: 283-296 [PMID: 34210485 DOI: 10.1016/j.ucl.2021.03.001]

115 **Nyberg T**, Tischkowitz M, Antoniou AC. BRCA1 and BRCA2 pathogenic variants and prostate cancer risk: systematic review and meta-analysis. *Br J Cancer* 2022; **126**: 1067-1081 [PMID: 34963702 DOI: 10.1038/s41416-021-01675-5]

116 **Silvestri V**, Leslie G, Barnes DR; CIMBA Group, Agnarsson BA, Aittomäki K, Alducci E, Andrulis IL, Barkardottir RB, Barroso A, Barrowdale D, Benitez J, Bonanni B, Borg A, Buys SS, Caldés T, Caligo MA, Capalbo C, Campbell I, Chung WK, Claes KBM, Colonna SV, Cortesi L, Couch FJ, de la Hoya M, Diez O, Ding YC, Domchek S, Easton DF, Ejlertsen B, Engel C, Evans DG, Feliubadalò L, Foretova L, Fostira F, Géczi L, Gerdes AM, Glendon G, Godwin AK, Goldgar DE, Hahnen E, Hogervorst FBL, Hopper JL, Hulick PJ, Isaacs C, Izquierdo A, James PA, Janavicius R, Jensen UB, John EM, Joseph V, Konstantopoulou I, Kurian AW, Kwong A, Landucci E, Lesueur F, Loud JT, Machackova E, Mai PL, Majidzadeh-A K, Manoukian S, Montagna M, Moserle L, Mulligan AM, Nathanson KL, Nevanlinna H, Ngeow J, Nikitina-Zake L, Offit K, Olah E, Olopade OI, Osorio A, Papi L, Park SK, Pedersen IS, Perez-Segura P, Petersen AH, Pinto P, Porfirio B, Pujana MA, Radice P, Rantala J, Rashid MU, Rosenzweig B, Rossing M, Santamariña M, Schmutzler RK, Senter L, Simard J, Singer CF, Solano AR, Southey MC, Steele L, Steinsnyder Z, Stoppa-Lyonnet D, Tan YY, Teixeira MR, Teo SH, Terry MB, Thomassen M, Toland AE, Torres-Esquius S, Tung N, van Asperen CJ, Vega A, Viel A, Vierstraete J, Wappenschmidt B, Weitzel JN, Wieme G, Yoon SY, Zorn KK, McGuffog L, Parsons MT, Hamann U,

Greene MH, Kirk JA, Neuhausen SL, Rebbeck TR, Tischkowitz M, Chenevix-Trench G, Antoniou AC, Friedman E, Ottini L. Characterization of the Cancer Spectrum in Men With Germline BRCA1 and BRCA2 Pathogenic Variants: Results From the Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA). *JAMA Oncol* 2020; **6**: 1218-1230 [PMID: 32614418 DOI: 10.1001/jamaoncol.2020.2134]

117 **Momozawa Y**, Iwasaki Y, Hirata M, Liu X, Kamatani Y, Takahashi A, Sugano K, Yoshida T, Murakami Y, Matsuda K, Nakagawa H, Spurdle AB, Kubo M. Germline Pathogenic Variants in 7636 Japanese Patients With Prostate Cancer and 12 366 Controls. *J Natl Cancer Inst* 2020; **112**: 369-376 [PMID: 31214711 DOI: 10.1093/jnci/djz124]

118 **Bancroft EK**, Page EC, Brook MN, Thomas S, Taylor N, Pope J, McHugh J, Jones AB, Karlsson Q, Merson S, Ong KR, Hoffman J, Huber C, Maehle L, Grindedal EM, Stormorken A, Evans DG, Rothwell J, Lalloo F, Brady AF, Bartlett M, Snape K, Hanson H, James P, McKinley J, Mascarenhas L, Syngal S, Ukaegbu C, Side L, Thomas T, Barwell J, Teixeira MR, Izatt L, Suri M, Macrae FA, Poplawski N, Chen-Shtoyerman R, Ahmed M, Musgrave H, Nicolai N, Greenhalgh L, Brewer C, Pachter N, Spigelman AD, Azzabi A, Helfand BT, Halliday D, Buys S, Ramon Y Cajal T, Donaldson A, Cooney KA, Harris M, McGrath J, Davidson R, Taylor A, Cooke P, Myhill K, Hogben M, Aaronson NK, Ardern-Jones A, Bangma CH, Castro E, Dearnaley D, Dias A, Dudderidge T, Eccles DM, Green K, Eyfjord J, Falconer A, Foster CS, Gronberg H, Hamdy FC, Johannsson O, Khoo V, Lilja H, Lindeman GJ, Lubinski J, Axcrona K, Mikropoulos C, Mitra AV, Moynihan C, Ni Raghallaigh H, Rennert G, Collier R; IMPACT Study Collaborators, Offman J, Kote-Jarai Z, Eeles RA. A prospective prostate cancer screening programme for men with pathogenic variants in mismatch repair genes (IMPACT): initial results from an international prospective study. *Lancet Oncol* 2021; **22**: 1618-1631 [PMID: 34678156 DOI: 10.1016/S1470-2045(21)00522-2]

119 **Carlo MI**, Mukherjee S, Mandelker D, Vijai J, Kemel Y, Zhang L, Knezevic A, Patil S, Ceyhan-Birsoy O, Huang KC, Redzematovic A, Coskey DT, Stewart C, Pradhan N, Arnold AG, Hakimi AA, Chen YB, Coleman JA, Hyman DM, Ladanyi M, Cadoo KA, Walsh MF, Stadler ZK, Lee CH, Feldman DR, Voss MH, Robson M, Motzer RJ, Offit K. Prevalence of Germline Mutations in Cancer Susceptibility Genes in Patients With Advanced Renal Cell Carcinoma. *JAMA Oncol* 2018; **4**: 1228-1235 [PMID: 29978187 DOI: 10.1001/jamaoncol.2018.1986]

120 **Al-Shinnag M**, Marfan H, Susman R, Wakeling J, Gustafson S, Wood S, Mallett AJ. Birt-Hogg-Dubé Syndrome and Hereditary Leiomyomatosis and Renal Cell Carcinoma Syndrome: An Effective Multidisciplinary Approach to Hereditary Renal Cancer Predisposing Syndromes. *Front Oncol* 2021; **11**: 738822 [PMID: 34604083 DOI: 10.3389/fonc.2021.738822]

121 **Shuch B**, Zhang J. Genetic Predisposition to Renal Cell Carcinoma: Implications for Counseling, Testing, Screening, and Management. *J Clin Oncol* 2018; JCO2018792523 [PMID: 30372385 DOI: 10.1200/JCO.2018.79.2523]

122 **de Alencar VTL**, Formiga MN, de Lima VCC. Inherited lung cancer: a review. *Ecancermedicalscience* 2020; **14**: 1008 [PMID: 32104210 DOI: 10.3332/ecancer.2020.1008]

123 **Benusiglio PR**, Fallet V, Sanchis-Borja M, Coulet F, Cadranel J. Lung cancer is also a hereditary disease. *Eur Respir Rev* 2021; **30** [PMID: 34670806 DOI: 10.1183/16000617.0045-2021]

124 **Pao W**, Miller VA, Politi KA, Riely GJ, Somwar R, Zakowski MF, Kris MG, Varmus H. Acquired resistance of lung adenocarcinomas to gefitinib or erlotinib is associated with a second mutation in the EGFR kinase domain. *PLoS Med* 2005; **2**: e73 [PMID: 15737014 DOI: 10.1371/journal.pmed.0020073]

125 **Kobayashi S**, Boggon TJ, Dayaram T, Jänne PA, Kocher O, Meyerson M, Johnson BE, Eck MJ, Tenen DG, Halmos B. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med* 2005; **352**: 786-792 [PMID: 15728811 DOI: 10.1056/NEJMoa044238]

126 **Bell DW**, Gore I, Okimoto RA, Godin-Heymann N, Sordella R, Mulloy R, Sharma SV, Brannigan BW, Mohapatra G, Settleman J, Haber DA. Inherited susceptibility to lung cancer may be associated with the T790M drug resistance mutation in EGFR. *Nat Genet* 2005; **37**: 1315-1316 [PMID: 16258541 DOI: 10.1038/ng1671]

127 **Lavdovskaia ED**, Iyevleva AG, Sokolenko AP, Mitiushkina NV, Preobrazhenskaya EV, Tiurin VI, Ivantsov AO, Bizin IV, Stelmakh LV, Moiseyenko FV, Karaseva NA, Orlov SV, Moiseyenko VM, Korzhenevskaya MA, Zaitsev IA, Kozak AR, Chistyakov IV, Akopov AL, Volkov NM, Togo AV, Imyanitov EN. EGFR T790M Mutation in TKI-Naïve Clinical Samples: Frequency, Tissue Mosaicism, Predictive Value and Awareness on Artifacts. *Oncol Res Treat* 2018; **41**: 634-642 [PMID: 30145586 DOI: 10.1159/000491441]

128 **Lu S**, Yu Y, Li Z, Yu R, Wu X, Bao H, Ding Y, Shao YW, Jian H. EGFR and ERBB2 Germline Mutations in Chinese Lung Cancer Patients and Their Roles in Genetic Susceptibility to Cancer. *J Thorac Oncol* 2019; **14**: 732-736 [PMID: 30610926 DOI: 10.1016/j.jtho.2018.12.006]

129 **Mezquita L**, Jové M, Nadal E, Kfoury M, Morán T, Ricordel C, Dhooge M, Tlemsani C, Léna H, Teulé A, Álvarez JV, Raimbourg J, Hiret S, Lacroix L, Menéndez M, Saldaña J, Brunet J, Lianes P, Coupier I, Auclin E, Recondo G, Friboulet L, Adam J, Green E, Planchard D, Frébourg T, Capellà G, Rouleau E, Lázaro C, Caron O, Besse B. High Prevalence of Somatic Oncogenic Driver Alterations in Patients With NSCLC and Li-Fraumeni Syndrome. *J Thorac Oncol* 2020; **15**: 1232-1239 [PMID: 32179180 DOI: 10.1016/j.jtho.2020.03.005]

130 **Vasen HF**, Gruis NA, Frants RR, van Der Velden PA, Hille ET, Bergman W. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). *Int J Cancer* 2000; **87**: 809-811 [PMID: 10956390]

131 **Potjer TP**, van der Stoep N, Houwing-Duistermaat JJ, Konings IC, Aalfs CM, van den Akker PC, Ausems MG, Dommering CJ, van der Kolk LE, Maiburg MC, Spruijt L, Wagner A, Vasen HF, Hes FJ. Pancreatic cancer-associated gene polymorphisms in a nation-wide cohort of p16-Leiden germline mutation carriers; a case-control study. *BMC Res Notes* 2015; **8**: 264 [PMID: 26111702 DOI: 10.1186/s13104-015-1235-4]

132 **Revythis A**, Shah S, Kutka M, Moschetta M, Ozturk MA, Pappas-Gogos G, Ioannidou E, Sheriff M, Rassy E, Boussios S. Unraveling the Wide Spectrum of Melanoma Biomarkers. *Diagnostics (Basel)* 2021; **11** [PMID: 34441278 DOI: 10.3390/diagnostics11081341]

133 **Rossi M**, Pellegrini C, Cardelli L, Ciciarelli V, Di Nardo L, Fargnoli MC. Familial Melanoma: Diagnostic and Management Implications. *Dermatol Pract Concept* 2019; **9**: 10-16 [PMID: 30775140 DOI: 10.5826/dpc.0901a03]

134 **Al-Salameh A**, Cadiot G, Calender A, Goudet P, Chanson P. Clinical aspects of multiple endocrine neoplasia type 1. *Nat*

Rev Endocrinol 2021; **17**: 207-224 [PMID: 33564173 DOI: 10.1038/s41574-021-00468-3]
135 **Drilon A**, Hu ZI, Lai GGY, Tan DSW. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. *Nat Rev Clin Oncol* 2018; **15**: 150 [PMID: 29182164 DOI: 10.1038/nrclinonc.2017.188]
136 **Subbiah V**, Yang D, Velcheti V, Drilon A, Meric-Bernstam F. State-of-the-Art Strategies for Targeting RET-Dependent Cancers. *J Clin Oncol* 2020; **38**: 1209-1221 [PMID: 32083997 DOI: 10.1200/JCO.19.02551]
137 **Bouys L**, Bertherat J. MANAGEMENT OF ENDOCRINE DISEASE: Carney complex: clinical and genetic update 20 years after the identification of the CNC1 (PRKAR1A) gene. *Eur J Endocrinol* 2021; **184**: R99-R109 [PMID: 33444222 DOI: 10.1530/EJE-20-1120]
138 **Zhao Y**, Yu T, Sun J, Wang F, Cheng C, He S, Chen L, Xie D, Fu L, Guan X, Yan A, Li Y, Miao G, Zhu X. Germ-line mutations in WDR77 predispose to familial papillary thyroid cancer. *Proc Natl Acad Sci U S A* 2021; **118** [PMID: 34326253 DOI: 10.1073/pnas.2026327118]
139 **Muth A**, Crona J, Gimm O, Elmgren A, Filipsson K, Stenmark Askmalm M, Sandstedt J, Tengvar M, Tham E. Genetic testing and surveillance guidelines in hereditary pheochromocytoma and paraganglioma. *J Intern Med* 2019; **285**: 187-204 [PMID: 30536464 DOI: 10.1111/joim.12869]
140 **Cazabat L**, Bouligand J, Salenave S, Bernier M, Gaillard S, Parker F, Young J, Guiochon-Mantel A, Chanson P. Germline AIP mutations in apparently sporadic pituitary adenomas: prevalence in a prospective single-center cohort of 443 patients. *J Clin Endocrinol Metab* 2012; **97**: E663-E670 [PMID: 22319033 DOI: 10.1210/jc.2011-2291]
141 **Chang M**, Yang C, Bao X, Wang R. Genetic and Epigenetic Causes of Pituitary Adenomas. *Front Endocrinol (Lausanne)* 2020; **11**: 596554 [PMID: 33574795 DOI: 10.3389/fendo.2020.596554]
142 **Hahn EC**, Bittar CM, Vianna FSL, Netto CBO, Biazús JV, Cericatto R, Cavalheiro JA, de Melo MP, Menke CH, Rabin E, Leistner-Segal S, Ashton-Prolla P. TP53 p.Arg337His germline mutation prevalence in Southern Brazil: Further evidence for mutation testing in young breast cancer patients. *PLoS One* 2018; **13**: e0209934 [PMID: 30596752 DOI: 10.1371/journal.pone.0209934]
143 **Rocca V**, Blandino G, D'Antona L, Iuliano R, Di Agostino S. Li-Fraumeni Syndrome: Mutation of TP53 Is a Biomarker of Hereditary Predisposition to Tumor: New Insights and Advances in the Treatment. *Cancers (Basel)* 2022; **14** [PMID: 35954327 DOI: 10.3390/cancers14153664]
144 **Melhem-Bertrandt A**, Bojadzieva J, Ready KJ, Obeid E, Liu DD, Gutierrez-Barrera AM, Litton JK, Olopade OI, Hortobagyi GN, Strong LC, Arun BK. Early onset HER2-positive breast cancer is associated with germline TP53 mutations. *Cancer* 2012; **118**: 908-913 [PMID: 21761402 DOI: 10.1002/cncr.26377]
145 **Sokolova TN**, Breder VV, Shumskaya IS, Suspitsin EN, Aleksakhina SN, Yanus GA, Tiurin VI, Ivantsov AO, Vona B, Raskin GA, Gamajunov SV, Imyanitov EN. Revisiting multiple erroneous genetic testing results and clinical misinterpretations in a patient with Li-Fraumeni syndrome: lessons for translational medicine. *Hered Cancer Clin Pract* 2021; **19**: 2 [PMID: 33407806 DOI: 10.1186/s13053-020-00157-8]
146 **Kratz CP**, Achatz MI, Brugières L, Frebourg T, Garber JE, Greer MC, Hansford JR, Janeway KA, Kohlmann WK, McGee R, Mullighan CG, Onel K, Pajtler KW, Pfister SM, Savage SA, Schiffman JD, Schneider KA, Strong LC, Evans DGR, Wasserman JD, Villani A, Malkin D. Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome. *Clin Cancer Res* 2017; **23**: e38-e45 [PMID: 28572266 DOI: 10.1158/1078-0432.CCR-17-0408]
147 **Lin YH**, Jewell BE, Gingold J, Lu L, Zhao R, Wang LL, Lee DF. Osteosarcoma: Molecular Pathogenesis and iPSC Modeling. *Trends Mol Med* 2017; **23**: 737-755 [PMID: 28735817 DOI: 10.1016/j.molmed.2017.06.004]
148 **Evans DG**, Woodward ER, Bajalica-Lagercrantz S, Oliveira C, Frebourg T. Germline TP53 Testing in Breast Cancers: Why, When and How? *Cancers (Basel)* 2020; **12** [PMID: 33327514 DOI: 10.3390/cancers12123762]
149 **Mirabello L**, Zhu B, Koster R, Karlins E, Dean M, Yeager M, Gianferante M, Spector LG, Morton LM, Karyadi D, Robison LL, Armstrong GT, Bhatia S, Song L, Pankratz N, Pinheiro M, Gastier-Foster JM, Gorlick R, de Toledo SRC, Petrilli AS, Patino-Garcia A, Lecanda F, Gutierrez-Jimeno M, Serra M, Hattinger C, Picci P, Scotlandi K, Flanagan AM, Tirabosco R, Amary MF, Kurucu N, Ilhan IE, Ballinger ML, Thomas DM, Barkauskas DA, Mejia-Baltodano G, Valverde P, Hicks BD, Wang M, Hutchinson AA, Tucker M, Sampson J, Landi MT, Freedman ND, Gapstur S, Carter B, Hoover RN, Chanock SJ, Savage SA. Frequency of Pathogenic Germline Variants in Cancer-Susceptibility Genes in Patients With Osteosarcoma. *JAMA Oncol* 2020; **6**: 724-734 [PMID: 32191290 DOI: 10.1001/jamaoncol.2020.0197]
150 **Rogoża-Janiszewska E**, Malińska K, Górski B, Scott RJ, Cybulski C, Kluźniak W, Lener M, Jakubowska A, Gronwald J, Huzarski T, Lubiński J, Dębniak T. Prevalence of germline TP53 variants among early-onset breast cancer patients from Polish population. *Breast Cancer* 2021; **28**: 226-235 [PMID: 32888145 DOI: 10.1007/s12282-020-01151-7]
151 **Pilarski R**. PTEN Hamartoma Tumor Syndrome: A Clinical Overview. *Cancers (Basel)* 2019; **11** [PMID: 31216739 DOI: 10.3390/cancers11060844]
152 **Ngeow J**, Eng C. PTEN in Hereditary and Sporadic Cancer. *Cold Spring Harb Perspect Med* 2020; **10** [PMID: 31570378 DOI: 10.1101/cshperspect.a036087]
153 **Hendricks LAJ**, Hoogerbrugge N, Schuurs-Hoeijmakers JHM, Vos JR. A review on age-related cancer risks in PTEN hamartoma tumor syndrome. *Clin Genet* 2021; **99**: 219-225 [PMID: 33140411 DOI: 10.1111/cge.13875]
154 **Eissing M**, Ripken L, Schreibelt G, Westdorp H, Ligtenberg M, Netea-Maier R, Netea MG, de Vries IJM, Hoogerbrugge N. PTEN Hamartoma Tumor Syndrome and Immune Dysregulation. *Transl Oncol* 2019; **12**: 361-367 [PMID: 30504085 DOI: 10.1016/j.tranon.2018.11.003]
155 **Lee YR**, Yehia L, Kishikawa T, Ni Y, Leach B, Zhang J, Panch N, Liu J, Wei W, Eng C, Pandolfi PP. WWP1 Gain-of-Function Inactivation of PTEN in Cancer Predisposition. *N Engl J Med* 2020; **382**: 2103-2116 [PMID: 32459922 DOI: 10.1056/NEJMoa1914919]
156 **Klimkowski S**, Ibrahim M, Ibarra Rovira JJ, Elshikh M, Javadi S, Klekers AR, Abusaif AA, Moawad AW, Ali K, Elsayes KM. Peutz-Jeghers Syndrome and the Role of Imaging: Pathophysiology, Diagnosis, and Associated Cancers. *Cancers (Basel)* 2021; **13** [PMID: 34680270 DOI: 10.3390/cancers13205121]
157 **Meserve EE**, Nucci MR. Peutz-Jeghers Syndrome: Pathobiology, Pathologic Manifestations, and Suggestions for Recommending Genetic Testing in Pathology Reports. *Surg Pathol Clin* 2016; **9**: 243-268 [PMID: 27241107 DOI: 10.1016/j.path.2016.01.006]

158 **Daniell J**, Plazzer JP, Perera A, Macrae F. An exploration of genotype-phenotype link between Peutz-Jeghers syndrome and STK11: a review. *Fam Cancer* 2018; **17**: 421-427 [PMID: 28900777 DOI: 10.1007/s10689-017-0037-3]

159 **Onodera S**, Nakamura Y, Azuma T. Gorlin Syndrome: Recent Advances in Genetic Testing and Molecular and Cellular Biological Research. *Int J Mol Sci* 2020; **21** [PMID: 33066274 DOI: 10.3390/ijms21207559]

160 **Olafsdottir T**, Stacey SN, Sveinbjornsson G, Thorleifsson G, Norland K, Sigurgeirsson B, Thorisdottir K, Kristjansson AK, Tryggvadottir L, Sarin KY, Benediktsson R, Jonasson JG, Sigurdsson A, Jonasdottir A, Kristmundsdottir S, Jonsson H, Gylfason A, Oddsson A, Fridriksdottir R, Gudjonsson SA, Zink F, Lund SH, Rognvaldsson S, Melsted P, Steinthorsdottir V, Gudmundsson J, Mikaelsdottir E, Olason PI, Stefansdottir L, Eggertsson HP, Halldorsson BV, Thorsteinsdottir U, Agustsson TT, Olafsson K, Olafsson JH, Sulem P, Rafnar T, Gudbjartsson DF, Stefansson K. Loss-of-Function Variants in the Tumor-Suppressor Gene PTPN14 Confer Increased Cancer Risk. *Cancer Res* 2021; **81**: 1954-1964 [PMID: 33602785 DOI: 10.1158/0008-5472.CAN-20-3065]

161 **Zhang J**, Walsh MF, Wu G, Edmonson MN, Gruber TA, Easton J, Hedges D, Ma X, Zhou X, Yergeau DA, Wilkinson MR, Vadodaria B, Chen X, McGee RB, Hines-Dowell S, Nuccio R, Quinn E, Shurtleff SA, Rusch M, Patel A, Becksfort JB, Wang S, Weaver MS, Ding L, Mardis ER, Wilson RK, Gajjar A, Ellison DW, Pappo AS, Pui CH, Nichols KE, Downing JR. Germline Mutations in Predisposition Genes in Pediatric Cancer. *N Engl J Med* 2015; **373**: 2336-2346 [PMID: 26580448 DOI: 10.1056/NEJMoa1508054]

162 **Newman S**, Nakitandwe J, Kesserwan CA, Azzato EM, Wheeler DA, Rusch M, Shurtleff S, Hedges DJ, Hamilton KV, Foy SG, Edmonson MN, Thrasher A, Bahrami A, Orr BA, Klco JM, Gu J, Harrison LW, Wang L, Clay MR, Ouma A, Silkov A, Liu Y, Zhang Z, Brady SW, Zhou X, Chang TC, Pande M, Davis E, Becksfort J, Patel A, Wilkinson MR, Rahbarinia D, Kubal M, Maciaszek JL, Pastor V, Knight J, Gout AM, Wang J, Gu Z, Mullighan CG, McGee RB, Quinn EA, Nuccio R, Mostafavi R, Gerhardt EL, Taylor LM, Valdez JM, Hines-Dowell SJ, Pappo AS, Robinson G, Johnson LM, Pui CH, Ellison DW, Downing JR, Zhang J, Nichols KE. Genomes for Kids: The Scope of Pathogenic Mutations in Pediatric Cancer Revealed by Comprehensive DNA and RNA Sequencing. *Cancer Discov* 2021; **11**: 3008-3027 [PMID: 34301788 DOI: 10.1158/2159-8290.CD-20-1631]

163 **Kratz CP**, Jongmans MC, Cavé H, Wimmer K, Behjati S, Guerrini-Rousseau L, Milde T, Pajtler KW, Golmard L, Gauthier-Villars M, Jewell R, Duncan C, Maher ER, Brugieres L, Pritchard-Jones K, Bourdeaut F. Predisposition to cancer in children and adolescents. *Lancet Child Adolesc Health* 2021; **5**: 142-154 [PMID: 33484663 DOI: 10.1016/S2352-4642(20)30275-3]

164 **Fabius AWM**, van Hoefen Wijsard M, van Leeuwen FE, Moll AC. Subsequent Malignant Neoplasms in Retinoblastoma Survivors. *Cancers (Basel)* 2021; **13** [PMID: 33801943 DOI: 10.3390/cancers13061200]

165 **Tu J**, Huo Z, Yu Y, Zhu D, Xu A, Huang MF, Hu R, Wang R, Gingold JA, Chen YH, Tsai KL, Forcioli-Conti NR, Huang SXL, Webb TR, Su J, Bazer DA, Jia P, Yustein JT, Wang LL, Hung MC, Zhao Z, Huff CD, Shen J, Zhao R, Lee DF. Hereditary retinoblastoma iPSC model reveals aberrant spliceosome function driving bone malignancies. *Proc Natl Acad Sci U S A* 2022; **119**: e2117857119 [PMID: 35412907 DOI: 10.1073/pnas.2117857119]

166 **Maciaszek JL**, Oak N, Nichols KE. Recent advances in Wilms' tumor predisposition. *Hum Mol Genet* 2020; **29**: R138-R149 [PMID: 32412586 DOI: 10.1093/hmg/ddaa091]

167 **Sur ML**, Armat I, Sur G, Pop DC, Samasca G, Lupan I, Timis TL, Florian IA, Sur D. Neurofibromatosis in Children: Actually and Perspectives. *Children (Basel)* 2022; **9** [PMID: 35053664 DOI: 10.3390/children9010040]

168 **Hill DA**, Ivanovich J, Priest JR, Gurnett CA, Dehner LP, Desruisseau D, Jarzembowski JA, Wikenheiser-Brokamp KA, Suarez BK, Whelan AJ, Williams G, Bracamontes D, Messinger Y, Goodfellow PJ. DICER1 mutations in familial pleuropulmonary blastoma. *Science* 2009; **325**: 965 [PMID: 19556464 DOI: 10.1126/science.1174334]

169 **Guillerman RP**, Foulkes WD, Priest JR. Imaging of DICER1 syndrome. *Pediatr Radiol* 2019; **49**: 1488-1505 [PMID: 31620849 DOI: 10.1007/s00247-019-04429-x]

170 **Stewart DR**, Best AF, Williams GM, Harney LA, Carr AG, Harris AK, Kratz CP, Dehner LP, Messinger YH, Rosenberg PS, Hill DA, Schultz KAP. Neoplasm Risk Among Individuals With a Pathogenic Germline Variant in DICER1. *J Clin Oncol* 2019; **37**: 668-676 [PMID: 30715996 DOI: 10.1200/JCO.2018.78.4678]

171 **Plon SE**, Lupo PJ. Genetic Predisposition to Childhood Cancer in the Genomic Era. *Annu Rev Genomics Hum Genet* 2019; **20**: 241-263 [PMID: 31082280 DOI: 10.1146/annurev-genom-083118-015415]

172 **Sestini R**, Bacci C, Provenzano A, Genuardi M, Papi L. Evidence of a four-hit mechanism involving SMARCB1 and NF2 in schwannomatosis-associated schwannomas. *Hum Mutat* 2008; **29**: 227-231 [PMID: 18072270 DOI: 10.1002/humu.20679]

173 **Tabori U**, Hansford JR, Achatz MI, Kratz CP, Plon SE, Frebourg T, Brugières L. Clinical Management and Tumor Surveillance Recommendations of Inherited Mismatch Repair Deficiency in Childhood. *Clin Cancer Res* 2017; **23**: e32-e37 [PMID: 28572265 DOI: 10.1158/1078-0432.CCR-17-0574]

174 **Mangaonkar AA**, Patnaik MM. Hereditary Predisposition to Hematopoietic Neoplasms: When Bloodline Matters for Blood Cancers. *Mayo Clin Proc* 2020; **95**: 1482-1498 [PMID: 32571604 DOI: 10.1016/j.mayocp.2019.12.013]

175 **Klco JM**, Mullighan CG. Advances in germline predisposition to acute leukaemias and myeloid neoplasms. *Nat Rev Cancer* 2021; **21**: 122-137 [PMID: 33328584 DOI: 10.1038/s41568-020-00315-z]

176 **Szmyd B**, Mlynarski W, Pastorczak A. Genetic predisposition to lymphomas: Overview of rare syndromes and inherited familial variants. *Mutat Res Rev Mutat Res* 2021; **788**: 108386 [PMID: 34893151 DOI: 10.1016/j.mrrev.2021.108386]

177 **Samadder NJ**, Giridhar KV, Baffy N, Riegert-Johnson D, Couch FJ. Hereditary Cancer Syndromes-A Primer on Diagnosis and Management: Part 1: Breast-Ovarian Cancer Syndromes. *Mayo Clin Proc* 2019; **94**: 1084-1098 [PMID: 31171119 DOI: 10.1016/j.mayocp.2019.02.017]

178 **Marmolejo DH**, Wong MYZ, Bajalica-Lagercrantz S, Tischkowitz M, Balmaña J; extended ERN-GENTURIS Thematic Group 3. Overview of hereditary breast and ovarian cancer (HBOC) guidelines across Europe. *Eur J Med Genet* 2021; **64**: 104350 [PMID: 34606975 DOI: 10.1016/j.ejmg.2021.104350]

179 **Piombino C**, Cortesi L, Lambertini M, Punie K, Grandi G, Toss A. Secondary Prevention in Hereditary Breast and/or Ovarian Cancer Syndromes Other Than BRCA. *J Oncol* 2020; **2020**: 6384190 [PMID: 32733558 DOI: 10.1155/2020/6384190]

180 **Pouptsis A**, Swafe L, Patwardhan M, Stavraka C. Surgical and Systemic Treatment of Hereditary Breast Cancer: A Mini-Review With a Focus on BRCA1 and BRCA2 Mutations. *Front Oncol* 2020; **10**: 553080 [PMID: 33194613 DOI: 10.3389/fonc.2020.553080]

181 **Al-Sarhani H**, Gottumukkala RV, Grasparil ADS 2nd, Tung EL, Gee MS, Greer MC. Screening of cancer predisposition syndromes. *Pediatr Radiol* 2022; **52**: 401-417 [PMID: 33791839 DOI: 10.1007/s00247-021-05023-w]

182 **Møller P**, Stormorken A, Jonsrud C, Holmen MM, Hagen AI, Clark N, Vabø A, Sun P, Narod SA, Mæhle L. Survival of patients with BRCA1-associated breast cancer diagnosed in an MRI-based surveillance program. *Breast Cancer Res Treat* 2013; **139**: 155-161 [PMID: 23615785 DOI: 10.1007/s10549-013-2540-z]

183 **Jacobson M**, Coakley N, Bernardini M, Branco KA, Elit L, Ferguson S, Kim R. Risk reduction strategies for BRCA1/2 hereditary ovarian cancer syndromes: a clinical practice guideline. *Hered Cancer Clin Pract* 2021; **19**: 39 [PMID: 34565426 DOI: 10.1186/s13053-021-00196-9]

184 **Machens A**, Dralle H. Long-term outcome after DNA-based prophylactic neck surgery in children at risk of hereditary medullary thyroid cancer. *Best Pract Res Clin Endocrinol Metab* 2019; **33**: 101274 [PMID: 31043326 DOI: 10.1016/j.beem.2019.04.008]

185 **Mathiesen JS**, Effraimidis G, Rossing M, Rasmussen ÅK, Hoejberg L, Bastholt L, Godballe C, Oturai P, Feldt-Rasmussen U. Multiple endocrine neoplasia type 2: A review. *Semin Cancer Biol* 2022; **79**: 163-179 [PMID: 33812987 DOI: 10.1016/j.semcancer.2021.03.035]

186 **Eleje GU**, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, Okonkwo OO. Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations. *Cochrane Database Syst Rev* 2018; **8**: CD012464 [PMID: 30141832 DOI: 10.1002/14651858.CD012464.pub2]

187 **Heemskerk-Gerritsen BAM**, Jager A, Koppert LB, Obdeijn AI, Collée M, Meijers-Heijboer HEJ, Jenner DJ, Oldenburg HSA, van Engelen K, de Vries J, van Asperen CJ, Devilee P, Blok MJ, Kets CM, Ausems MGEM, Seynaeve C, Rookus MA, Hooning MJ. Survival after bilateral risk-reducing mastectomy in healthy BRCA1 and BRCA2 mutation carriers. *Breast Cancer Res Treat* 2019; **177**: 723-733 [PMID: 31302855 DOI: 10.1007/s10549-019-05345-2]

188 **Iyevleva AG**, Imyanitov EN. Cytotoxic and targeted therapy for hereditary cancers. *Hered Cancer Clin Pract* 2016; **14**: 17 [PMID: 27555886 DOI: 10.1186/s13053-016-0057-2]

189 **Thavaneswaran S**, Rath E, Tucker K, Joshua AM, Hess D, Pinese M, Ballinger ML, Thomas DM. Therapeutic implications of germline genetic findings in cancer. *Nat Rev Clin Oncol* 2019; **16**: 386-396 [PMID: 30783251 DOI: 10.1038/s41571-019-0179-3]

190 **Byrski T**, Gronwald J, Huzarski T, Grzybowska E, Budryk M, Stawicka M, Mierzwa T, Szwiec M, Wisniowski R, Siolek M, Dent R, Lubinski J, Narod S. Pathologic complete response rates in young women with BRCA1-positive breast cancers after neoadjuvant chemotherapy. *J Clin Oncol* 2010; **28**: 375-379 [PMID: 20008645 DOI: 10.1200/JCO.2008.20.7019]

191 **Tutt A**, Tovey H, Cheang MCU, Kernaghan S, Kilburn L, Gazinska P, Owen J, Abraham J, Barrett S, Barrett-Lee P, Brown R, Chan S, Dowsett M, Flanagan JM, Fox L, Grigoriadis A, Gutin A, Harper-Wynne C, Hatton MQ, Hoadley KA, Parikh J, Parker P, Perou CM, Roylance R, Shah V, Shaw A, Smith IE, Timms KM, Wardley AM, Wilson G, Gillett C, Lanchbury JS, Ashworth A, Rahman N, Harries M, Ellis P, Pinder SE, Bliss JM. Carboplatin in BRCA1/2-mutated and triple-negative breast cancer BRCAness subgroups: the TNT Trial. *Nat Med* 2018; **24**: 628-637 [PMID: 29713086 DOI: 10.1038/s41591-018-0009-7]

192 **Imyanitov EN**. Cytotoxic and targeted therapy for BRCA1/2-driven cancers. *Hered Cancer Clin Pract* 2021; **19**: 36 [PMID: 34454564 DOI: 10.1186/s13053-021-00193-y]

193 **Gorodnova TV**, Kotiv KB, Ivantsov AO, Mikheyeva ON, Mikhailiuk GI, Lisyanskaya AS, Mikaya NA, Guseynov KD, Bondarev NE, Matveyeva NS, Nekrasova EA, Sidoruk AA, Roman LD, Manikhas GM, Belyaev AM, Sokolenko AP, Berlev IV, Imyanitov EN. Efficacy of Neoadjuvant Therapy With Cisplatin Plus Mitomycin C in BRCA1-Mutated Ovarian Cancer. *Int J Gynecol Cancer* 2018; **28**: 1498-1506 [PMID: 30247247 DOI: 10.1097/IGC.0000000000001352]

194 **Gorodnova TV**, Sokolenko AP, Kondratiev SV, Kotiv KB, Belyaev AM, Berlev IV, Imyanitov EN. Mitomycin C plus cisplatin for systemic treatment of recurrent BRCA1-associated ovarian cancer. *Invest New Drugs* 2020; **38**: 1872-1878 [PMID: 32591974 DOI: 10.1007/s10637-020-00965-8]

195 **Chan CY**, Tan KV, Cornelissen B. PARP Inhibitors in Cancer Diagnosis and Therapy. *Clin Cancer Res* 2021; **27**: 1585-1594 [PMID: 33082213 DOI: 10.1158/1078-0432.CCR-20-2766]

196 **Póti Á**, Gyergyák H, Németh E, Rusz O, Tóth S, Kovácsházi C, Chen D, Szikriszt B, Spisák S, Takeda S, Szakács G, Szallasi Z, Richardson AL, Szüts D. Correlation of homologous recombination deficiency induced mutational signatures with sensitivity to PARP inhibitors and cytotoxic agents. *Genome Biol* 2019; **20**: 240 [PMID: 31727117 DOI: 10.1186/s13059-019-1867-0]

197 **Stopsack KH**. Efficacy of PARP Inhibition in Metastatic Castration-resistant Prostate Cancer is Very Different with Non-BRCA DNA Repair Alterations: Reconstructing Prespecified Endpoints for Cohort B from the Phase 3 PROfound Trial of Olaparib. *Eur Urol* 2021; **79**: 442-445 [PMID: 33012578 DOI: 10.1016/j.eururo.2020.09.024]

198 **Westphalen CB**, Fine AD, André F, Ganesan S, Heinemann V, Rouleau E, Turnbull C, Garcia Palacios L, Lopez JA, Sokol ES, Mateo J. Pan-cancer Analysis of Homologous Recombination Repair-associated Gene Alterations and Genome-wide Loss-of-Heterozygosity Score. *Clin Cancer Res* 2022; **28**: 1412-1421 [PMID: 34740923 DOI: 10.1158/1078-0432.CCR-21-2096]

199 **André T**, Shiu KK, Kim TW, Jensen BV, Jensen LH, Punt C, Smith D, Garcia-Carbonero R, Benavides M, Gibbs P, de la Fouchardiere C, Rivera F, Elez E, Bendell J, Le DT, Yoshino T, Van Cutsem E, Yang P, Farooqui MZH, Marinello P, Diaz LA Jr; KEYNOTE-177 Investigators. Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. *N Engl J Med* 2020; **383**: 2207-2218 [PMID: 33264544 DOI: 10.1056/NEJMoa2017699]

200 **Le DT**, Durham JN, Smith KN, Wang H, Bartlett BR, Aulakh LK, Lu S, Kemberling H, Wilt C, Luber BS, Wong F, Azad NS, Rucki AA, Laheru D, Donehower R, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Greten TF, Duffy AG, Ciombor KK, Eyring AD, Lam BH, Joe A, Kang SP, Holdhoff M, Danilova L, Cope L, Meyer C, Zhou S, Goldberg RM, Armstrong DK, Bever KM, Fader AN, Taube J, Housseau F, Spetzler D, Xiao N, Pardoll DM, Papadopoulos N, Kinzler KW, Eshleman JR, Vogelstein B, Anders RA, Diaz LA Jr. Mismatch repair deficiency predicts response of solid tumors to PD-

1 blockade. *Science* 2017; **357**: 409-413 [PMID: 28596308 DOI: 10.1126/science.aan6733]

201 **Bellone S**, Roque DM, Siegel ER, Buza N, Hui P, Bonazzoli E, Guglielmi A, Zammataro L, Nagarkatti N, Zaidi S, Lee J, Silasi DA, Huang GS, Andikyan V, Damast S, Clark M, Azodi M, Schwartz PE, Tymon-Rosario JR, Harold JA, Mauricio D, Zeybek B, Menderes G, Altwerger G, Ratner E, Alexandrov LB, Iwasaki A, Kong Y, Song E, Dong W, Elvin JA, Choi J, Santin AD. A phase 2 evaluation of pembrolizumab for recurrent Lynch-like versus sporadic endometrial cancers with microsatellite instability. *Cancer* 2022; **128**: 1206-1218 [PMID: 34875107 DOI: 10.1002/cncr.34025]

202 **Lenz HJ**, Van Cutsem E, Luisa Limon M, Wong KYM, Hendlisz A, Aglietta M, García-Alfonso P, Neyns B, Luppi G, Cardin DB, Dragovich T, Shah U, Abdullaev S, Gricar J, Ledeine JM, Overman MJ, Lonardi S. First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study. *J Clin Oncol* 2022; **40**: 161-170 [PMID: 34637336 DOI: 10.1200/JCO.21.01015]

203 **Johanns TM**, Miller CA, Dorward IG, Tsien C, Chang E, Perry A, Uppaluri R, Ferguson C, Schmidt RE, Dahiya S, Ansstas G, Mardis ER, Dunn GP. Immunogenomics of Hypermutated Glioblastoma: A Patient with Germline POLE Deficiency Treated with Checkpoint Blockade Immunotherapy. *Cancer Discov* 2016; **6**: 1230-1236 [PMID: 27683556 DOI: 10.1158/2159-8290.CD-16-0575]

204 **Volkov NM**, Yanus GA, Ivantsov AO, Moiseenko FV, Matorina OG, Bizin IV, Moiseyenko VM, Imyanitov EN. Efficacy of immune checkpoint blockade in MUTYH-associated hereditary colorectal cancer. *Invest New Drugs* 2020; **38**: 894-898 [PMID: 31377904 DOI: 10.1007/s10637-019-00842-z]

205 **AlHarbi M**, Ali Mobark N, AlMubarak L, Aljelaify R, AlSaeed M, Almutairi A, Alqubaishi F, Hussain ME, Balbaid AAO, Said Marie A, AlSubaie L, AlShieban S, alTassan N, Ramkissoon SH, Abedalthagafi M. Durable Response to Nivolumab in a Pediatric Patient with Refractory Glioblastoma and Constitutional Biallelic Mismatch Repair Deficiency. *Oncologist* 2018; **23**: 1401-1406 [PMID: 30104292 DOI: 10.1634/theoncologist.2018-0163]

206 **Pavelka Z**, Zitterbart K, Nosková H, Bajčiová V, Slabý O, Štěrba J. Effective Immunotherapy of Glioblastoma in an Adolescent with Constitutional Mismatch Repair-Deficiency Syndrome. *Klin Onkol* 2019; **32**: 70-74 [PMID: 30764633 DOI: 10.14735/amko201970]

207 **Fox E**, Widemann BC, Chuk MK, Marcus L, Aikin A, Whitcomb PO, Merino MJ, Lodish M, Dombi E, Steinberg SM, Wells SA, Balis FM. Vandetanib in children and adolescents with multiple endocrine neoplasia type 2B associated medullary thyroid carcinoma. *Clin Cancer Res* 2013; **19**: 4239-4248 [PMID: 23766359 DOI: 10.1158/1078-0432.CCR-13-0071]

208 **Wirth LJ**, Sherman E, Robinson B, Solomon B, Kang H, Lorch J, Worden F, Brose M, Patel J, Leboulleux S, Godbert Y, Barlesi F, Morris JC, Owonikoko TK, Tan DSW, Gautschi O, Weiss J, de la Fouchardière C, Burkard ME, Laskin J, Taylor MH, Kroiss M, Medioni J, Goldman JW, Bauer TM, Levy B, Zhu VW, Lakhani N, Moreno V, Ebata K, Nguyen M, Heirich D, Zhu EY, Huang X, Yang L, Kherani J, Rothenberg SM, Drilon A, Subbiah V, Shah MH, Cabanillas ME. Efficacy of Selpercatinib in RET-Altered Thyroid Cancers. *N Engl J Med* 2020; **383**: 825-835 [PMID: 32846061 DOI: 10.1056/NEJMoa2005651]

209 **Zheng X**, Ji Q, Sun Y, Ge M, Zhang B, Cheng Y, Lei S, Shi F, Guo Y, Li L, Chen L, Shao J, Zhang W, Gao M. Efficacy and safety of selpercatinib in Chinese patients with advanced RET-altered thyroid cancers: results from the phase II LIBRETTO-321 study. *Ther Adv Med Oncol* 2022; **14**: 17588359221119318 [PMID: 36062046 DOI: 10.1177/17588359221119318]

210 **Fangusaro J**, Onar-Thomas A, Young Poussaint T, Wu S, Ligon AH, Lindeman N, Banerjee A, Packer RJ, Kilburn LB, Goldman S, Pollack IF, Qaddoumi I, Jakacki RI, Fisher PG, Dhall G, Baxter P, Kreissman SG, Stewart CF, Jones DTW, Pfister SM, Vezina G, Stern JS, Panigrahy A, Patay Z, Tamrazi B, Jones JY, Haque SS, Enterline DS, Cha S, Fisher MJ, Doyle LA, Smith M, Dunkel IJ, Fouladi M. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. *Lancet Oncol* 2019; **20**: 1011-1022 [PMID: 31151904 DOI: 10.1016/S1470-2045(19)30277-3]

211 **Gross AM**, Wolters PL, Dombi E, Baldwin A, Whitcomb P, Fisher MJ, Weiss B, Kim A, Bornhorst M, Shah AC, Martin S, Roderick MC, Pichard DC, Carbonell A, Paul SM, Therrien J, Kapustina O, Heisey K, Clapp DW, Zhang C, Peer CJ, Figg WD, Smith M, Glod J, Blakeley JO, Steinberg SM, Venzon DJ, Doyle LA, Widemann BC. Selumetinib in Children with Inoperable Plexiform Neurofibromas. *N Engl J Med* 2020; **382**: 1430-1442 [PMID: 32187457 DOI: 10.1056/NEJMoa1912735]

212 **Campbell BB**, Galati MA, Stone SC, Riemenschneider AN, Edwards M, Sudhaman S, Siddaway R, Komosa M, Nunes NM, Nobre L, Morrissy AS, Zatzman M, Zapotocky M, Joksimovic L, Kalimuthu SN, Samuel D, Mason G, Bouffet E, Morgenstern DA, Aronson M, Durno C, Malkin D, Maris JM, Taylor MD, Shlien A, Pugh TJ, Ohashi PS, Hawkins CE, Tabori U. Mutations in the RAS/MAPK Pathway Drive Replication Repair-Deficient Hypermutated Tumors and Confer Sensitivity to MEK Inhibition. *Cancer Discov* 2021; **11**: 1454-1467 [PMID: 33563663 DOI: 10.1158/2159-8290.CD-20-1050]

213 **Tang JY**, Ally MS, Chanana AM, Mackay-Wiggan JM, Aszterbaum M, Lindgren JA, Ulerio G, Rezaee MR, Gildengorin G, Marji J, Clark C, Bickers DR, Epstein EH Jr. Inhibition of the hedgehog pathway in patients with basal-cell nevus syndrome: final results from the multicentre, randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Oncol* 2016; **17**: 1720-1731 [PMID: 27838224 DOI: 10.1016/S1470-2045(16)30566-6]

214 **Franz DN**, Belousova E, Sparagana S, Bebin EM, Frost M, Kuperman R, Witt O, Kohrman MH, Flamini JR, Wu JY, Curatolo P, de Vries PJ, Berkowitz N, Anak O, Niolat J, Jozwiak S. Everolimus for subependymal giant cell astrocytoma in patients with tuberous sclerosis complex: 2-year open-label extension of the randomised EXIST-1 study. *Lancet Oncol* 2014; **15**: 1513-1520 [PMID: 25456370 DOI: 10.1016/S1470-2045(14)70489-9]

215 **Geynisman DM**, Kadow BT, Shuch BM, Boorjian SA, Matin SF, Rampersaud E, Milestone BN, Plimack ER, Zibelman MR, Kutikov A, Smaldone MC, Chen DY, Viterbo R, Joshi S, Greenberg RE, Malizzia L, McGowan T, Ross EA, Uzzo RG. Sporadic Angiomyolipomas Growth Kinetics While on Everolimus: Results of a Phase II Trial. *J Urol* 2020; **204**: 531-537 [PMID: 32250730 DOI: 10.1097/JU.0000000000001065]

216 **Jonasch E**, Donskov F, Iliopoulos O, Rathmell WK, Narayan VK, Maughan BL, Oudard S, Else T, Maranchie JK, Welsh SJ, Thamake S, Park EK, Perini RF, Linehan WM, Srinivasan R; MK-6482-004 Investigators. Belzutifan for Renal Cell

Carcinoma in von Hippel-Lindau Disease. *N Engl J Med* 2021; **385**: 2036-2046 [PMID: 34818478 DOI: 10.1056/NEJMoa2103425]

217 **Carril-Ajuria L**, Colomba E, Cerbone L, Romero-Ferreiro C, Crouzet L, Laguerre B, Thibault C, Vicier C, de Velasco G, Fléchon A, Saldana C, Benusiglio PR, Bressac-de Paillerets B, Guillaud-Bataille M, Gaignard P, Scoazec JY, Richard S, Caron O, Escudier B, Albiges L. Response to systemic therapy in fumarate hydratase-deficient renal cell carcinoma. *Eur J Cancer* 2021; **151**: 106-114 [PMID: 33975058 DOI: 10.1016/j.ejca.2021.04.009]

218 **Gleeson JP**, Nikolovski I, Dinatale R, Zucker M, Knezevic A, Patil S, Ged Y, Kotecha RR, Shapnik N, Murray S, Russo P, Coleman J, Lee CH, Stadler ZK, Hakimi AA, Feldman DR, Motzer RJ, Reznik E, Voss MH, Chen YB, Carlo MI. Comprehensive Molecular Characterization and Response to Therapy in Fumarate Hydratase-Deficient Renal Cell Carcinoma. *Clin Cancer Res* 2021; **27**: 2910-2919 [PMID: 33658299 DOI: 10.1158/1078-0432.CCR-20-4367]

219 **Telli ML**, Timms KM, Reid J, Hennessy B, Mills GB, Jensen KC, Szallasi Z, Barry WT, Winer EP, Tung NM, Isakoff SJ, Ryan PD, Greene-Colozzi A, Gutin A, Sangale Z, Iliev D, Neff C, Abkevich V, Jones JT, Lanchbury JS, Hartman AR, Garber JE, Ford JM, Silver DP, Richardson AL. Homologous Recombination Deficiency (HRD) Score Predicts Response to Platinum-Containing Neoadjuvant Chemotherapy in Patients with Triple-Negative Breast Cancer. *Clin Cancer Res* 2016; **22**: 3764-3773 [PMID: 26957554 DOI: 10.1158/1078-0432.CCR-15-2477]

220 **Sokolenko AP**, Gorodnova TV, Bizin IV, Kuligina ES, Kotiv KB, Romanko AA, Ermachenkova TI, Ivantsov AO, Preobrazhenskaya EV, Sokolova TN, Broyde RV, Imyanitov EN. Molecular predictors of the outcome of paclitaxel plus carboplatin neoadjuvant therapy in high-grade serous ovarian cancer patients. *Cancer Chemother Pharmacol* 2021; **88**: 439-450 [PMID: 34080040 DOI: 10.1007/s00280-021-04301-6]

221 **Mighton C**, Lerner-Ellis JP. Principles of molecular testing for hereditary cancer. *Genes Chromosomes Cancer* 2022; **61**: 356-381 [PMID: 35436018 DOI: 10.1002/gcc.23048]

222 **Kuligina ESh**, Sokolenko AP, Mitiushkina NV, Abysheva SN, Preobrazhenskaya EV, Gorodnova TV, Yanus GA, Togo AV, Cherdyntseva NV, Bekhtereva SA, Dixon JM, Larionov AA, Kuznetsov SG, Imyanitov EN. Value of bilateral breast cancer for identification of rare recessive at-risk alleles: evidence for the role of homozygous GEN1 c.2515_2519delAAGTT mutation. *Fam Cancer* 2013; **12**: 129-132 [PMID: 23104382 DOI: 10.1007/s10689-012-9575-x]

223 **Kurian AW**. BRCA1 and BRCA2 mutations across race and ethnicity: distribution and clinical implications. *Curr Opin Obstet Gynecol* 2010; **22**: 72-78 [PMID: 19841585 DOI: 10.1097/GCO.0b013e328332dca3]

224 **AlHarthi FS**, Qari A, Edress A, Abedalthagafi M. Familial/inherited cancer syndrome: a focus on the highly consanguineous Arab population. *NPJ Genom Med* 2020; **5**: 3 [PMID: 32025336 DOI: 10.1038/s41525-019-0110-y]

225 **Palmer JR**, Polley EC, Hu C, John EM, Haiman C, Hart SN, Gaudet M, Pal T, Anton-Culver H, Trentham-Dietz A, Bernstein L, Ambrosone CB, Bandera EV, Bertrand KA, Bethea TN, Gao C, Gnanaolivu RD, Huang H, Lee KY, LeMarchand L, Na J, Sandler DP, Shah PD, Yadav S, Yang W, Weitzel JN, Domchek SM, Goldgar DE, Nathanson KL, Kraft P, Yao S, Couch FJ. Contribution of Germline Predisposition Gene Mutations to Breast Cancer Risk in African American Women. *J Natl Cancer Inst* 2020; **112**: 1213-1221 [PMID: 32427313 DOI: 10.1093/jnci/djaa040]

226 **Yadav S**, LaDuca H, Polley EC, Hu C, Niguidula N, Shimelis H, Lilyquist J, Na J, Lee KY, Gutierrez S, Yussuf A, Hart SN, Davis BT, Chao EC, Pesaran T, Goldgar DE, Dolinsky JS, Couch FJ. Racial and Ethnic Differences in Multigene Hereditary Cancer Panel Test Results for Women With Breast Cancer. *J Natl Cancer Inst* 2021; **113**: 1429-1433 [PMID: 33146377 DOI: 10.1093/jnci/djaa167]

227 **Monteiro AN**, Bouwman P, Kousholt AN, Eccles DM, Millot GA, Masson JY, Schmidt MK, Sharan SK, Scully R, Wiesmüller L, Couch F, Vreeswijk MPG. Variants of uncertain clinical significance in hereditary breast and ovarian cancer genes: best practices in functional analysis for clinical annotation. *J Med Genet* 2020; **57**: 509-518 [PMID: 32152249 DOI: 10.1136/jmedgenet-2019-106368]

228 **Boonen RACM**, Wiegant WW, Celosse N, Vroling B, Heijl S, Kote-Jarai Z, Mijuskovic M, Cristea S, Solleveld-Westerink N, van Wezel T, Beerenwinkel N, Eeles R, Devilee P, Vreeswijk MPG, Marra G, van Attikum H. Functional Analysis Identifies Damaging CHEK2 Missense Variants Associated with Increased Cancer Risk. *Cancer Res* 2022; **82**: 615-631 [PMID: 34903604 DOI: 10.1158/0008-5472.CAN-21-1845]

229 **Evans DGR**, van Veen EM, Byers HJ, Wallace AJ, Ellingford JM, Beaman G, Santoyo-Lopez J, Aitman TJ, Eccles DM, Lalloo FI, Smith MJ, Newman WG. A Dominantly Inherited 5' UTR Variant Causing Methylation-Associated Silencing of BRCA1 as a Cause of Breast and Ovarian Cancer. *Am J Hum Genet* 2018; **103**: 213-220 [PMID: 30075112 DOI: 10.1016/j.ajhg.2018.07.002]

230 **Hansen TV**, Ejlertsen B, Albrechtsen A, Bergsten E, Bjerregaard P, Hansen T, Myrhøj T, Nielsen PB, Timmermans-Wielenga V, Andersen MK, Jønson L, Nielsen FC. A common Greenlandic Inuit BRCA1 RING domain founder mutation. *Breast Cancer Res Treat* 2009; **115**: 69-76 [PMID: 18500671 DOI: 10.1007/s10549-008-0060-z]

231 **Harboe TL**, Eiberg H, Kern P, Ejlertsen B, Nedergaard L, Timmermans-Wielenga V, Nielsen IM, Bisgaard ML. A high frequent BRCA1 founder mutation identified in the Greenlandic population. *Fam Cancer* 2009; **8**: 413-419 [PMID: 19504351 DOI: 10.1007/s10689-009-9257-5]

232 **Marchetti C**, De Leo R, Musella A, D'Indinosante M, Capoluongo E, Minucci A, Benedetti Panici P, Scambia G, Fagotti A. BRCA Mutation Status to Personalize Management of Recurrent Ovarian Cancer: A Multicenter Study. *Ann Surg Oncol* 2018; **25**: 3701-3708 [PMID: 30128899 DOI: 10.1245/s10434-018-6700-6]

233 **Morgan RD**, Burghel GJ, Flaum N, Bulman M, Clamp AR, Hasan J, Mitchell CL, Schlecht H, Woodward ER, Lallo FI, Crosbie EJ, Edmondson RJ, Wallace AJ, Jayson GC, Evans DGR. Prevalence of germline pathogenic BRCA1/2 variants in sequential epithelial ovarian cancer cases. *J Med Genet* 2019; **56**: 301-307 [PMID: 30683677 DOI: 10.1136/jmedgenet-2018-105792]

234 **AlDubayan SH**, Pyle LC, Gamulin M, Kulis T, Moore ND, Taylor-Weiner A, Hamid AA, Reardon B, Wubbenhorst B, Godse R, Vaughn DJ, Jacobs LA, Meien S, Grgic M, Kastelan Z, Markt SC, Damrauer SM, Rader DJ, Kember RL, Loud JT, Kanetsky PA, Greene MH, Sweeney CJ, Kubisch C, Nathanson KL, Van Allen EM, Stewart DR, Lessel D; Regeneron Genetics Center (RGC) Research Team. Association of Inherited Pathogenic Variants in Checkpoint Kinase 2 (CHEK2) With Susceptibility to Testicular Germ Cell Tumors. *JAMA Oncol* 2019; **5**: 514-522 [PMID: 30676620 DOI: 10.1001/jamaoncol.2018.6477]

235 **Ni VI**, Ivantsov AO, Kotkova MA, Baskina SV, Ponomareva EV, Orlova RV, Topuzov EE, Kryukov KK, Shelekhova KV, Aleksakhina SN, Sokolenko AP, Imyanitov EN. Small fraction of testicular cancer cases may be causatively related to CHEK2 inactivating germ-line mutations: evidence for somatic loss of the remaining CHEK2 allele in the tumor tissue. *Fam Cancer* 2021; **20**: 49-53 [PMID: 32451744 DOI: 10.1007/s10689-020-00190-5]

236 **Ring KL**, Bruegl AS, Allen BA, Elkin EP, Singh N, Hartman AR, Daniels MS, Broaddus RR. Germline multi-gene hereditary cancer panel testing in an unselected endometrial cancer cohort. *Mod Pathol* 2016; **29**: 1381-1389 [PMID: 27443514 DOI: 10.1038/modpathol.2016.135]

237 **Cameron A**, Chiarella-Redfern H, Chu P, Perrier R, Duggan MA. Universal Testing to Identify Lynch Syndrome Among Women With Newly Diagnosed Endometrial Carcinoma. *J Obstet Gynaecol Can* 2020; **42**: 137-143 [PMID: 31679916 DOI: 10.1016/j.jogc.2019.06.018]

238 **Pearlman R**, Frankel WL, Swanson BJ, Jones D, Zhao W, Yilmaz A, Miller K, Bacher J, Bigley C, Nelsen L, Goodfellow PJ, Goldberg RM, Paskett E, Shields PG, Freudenheim JL, Stanich PP, Lattimer I, Arnold M, Prior TW, Haut M, Kalady MF, Heald B, Paquette I, Draper DJ, Brell JM, Mahesh S, Weeman K, Bastola S, Zangmeister J, Gowda A, Kencana F, Malcolm A, Liu Y, Cole S, Bane C, Li C, Rehmus E, Pritchard CC, Shirts BH, Jacobson A, Cummings SA, de la Chapelle A, Hampel H. Prospective Statewide Study of Universal Screening for Hereditary Colorectal Cancer: The Ohio Colorectal Cancer Prevention Initiative. *JCO Precis Oncol* 2021; **5** [PMID: 34250417 DOI: 10.1200/PO.20.00525]

239 **Bakhuizen JJ**, Hogervorst FB, Velthuizen ME, Ruijs MW, van Engelen K, van Os TA, Gille JJ, Collée M, van den Ouweland AM, van Asperen CJ, Kets CM, Mensenkamp AR, Leter EM, Blok MJ, de Jong MM, Ausems MG. TP53 germline mutation testing in early-onset breast cancer: findings from a nationwide cohort. *Fam Cancer* 2019; **18**: 273-280 [PMID: 30607672 DOI: 10.1007/s10689-018-00118-0]

240 **Evans DG**, van Veen EM, Byers HJ, Evans SJ, Burghel GJ, Woodward ER, Harkness EF, Eccles DM, Greville-Haygate SL, Ellingford JM, Bowers NL, Pereira M, Wallace AJ, Howell SJ, Howell A, Lalloo F, Newman WG, Smith MJ. High likelihood of actionable pathogenic variant detection in breast cancer genes in women with very early onset breast cancer. *J Med Genet* 2022; **59**: 115-121 [PMID: 33758026 DOI: 10.1136/jmedgenet-2020-107347]

241 **Beebe-Dimmer JL**, Hathcock M, Yee C, Okoth LA, Ewing CM, Isaacs WB, Cooney KA, Thibodeau SN. The HOXB13 G84E Mutation Is Associated with an Increased Risk for Prostate Cancer and Other Malignancies. *Cancer Epidemiol Biomarkers Prev* 2015; **24**: 1366-1372 [PMID: 26108461 DOI: 10.1158/1055-9965.EPI-15-0247]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2023 February 24; 14(2): 69-80

DOI: 10.5306/wjco.v14.i2.69

ISSN 2218-4333 (online)

REVIEW

Significance of music therapy in treating depression and anxiety disorders among people with cancer

Chiedu Eseadi, Millicent O Ngwu

Specialty type: Behavioral sciences

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Liu Z, China; Lu H, China

Received: December 29, 2022
Peer-review started: December 29, 2022
First decision: January 9, 2023
Revised: January 16, 2023
Accepted: February 7, 2023
Article in press: February 7, 2023
Published online: February 24, 2023

Chiedu Eseadi, Department of Educational Psychology, University of Johannesburg, Gauteng 2006, South Africa

Millicent O Ngwu, Department of Sociology and Anthropology, University of Nigeria, Nsukka 41001, Enugu, Nigeria

Corresponding author: Chiedu Eseadi, PhD, Senior Postdoctoral Fellow, Department of Educational Psychology, University of Johannesburg, Gauteng 2006, South Africa. chiedu.eseadi@unn.edu.ng

Abstract

Globally, cancer cases and mortality have recently escalated and have attracted global concern. The clinical diagnosis and manifestation of cancer can result in significant mental health issues like depression and anxiety disorders. The tendency of people with cancer to suffer from psychological disorders such as anxiety and depression is usually high. A significant number of deaths related to cancer may likely not be from the killer disease but from psychological disorders associated with the illness. The utilization of music as a remedial approach to healing mental disorders cannot be overstated. Thus, identifying the impacts of music therapy in dealing with depression and anxiety disorders among people with cancer is relevant, as the majority of methods used in treating cancer have some side effects which may trigger psychological disorders in cancer patients. Ultimately, this study explored the significance of music therapy in treating depression and anxiety disorders among people with cancer. To achieve the aim of this study, the authors employed a narrative literature review to investigate the significance of music therapy in addressing depression and anxiety disorders among people with cancer. The type of literature review employed in this study is to provide an understanding of the selected research papers. The review found that music therapy significantly reduces depression and anxiety disorders among breast cancer, lung cancer, prostate cancer, and colorectal cancer patients. It is needful for healthcare providers to incorporate music therapy interventions while treating people with cancer. This will help reduce cancer deaths resulting from psychological disorders rather than the killer disease, cancer. However, the standardized procedures and evaluation criteria for applying music-based intervention strategies in oncology medicine still need to be further established and improved.

Key Words: Anxiety disorders; Breast cancer; Cancer; Cancer patients; Colorectal cancer;

Depression; Lung cancer; Music therapy; Prostate cancer

Core Tip: People diagnosed with cancer and receiving treatment experience anxiety and depression, which may influence their healing process. Most cancer patients may die from depression, anxiety, and other psychological disorders. The mental health of cancer patients is important as their physical health. Therefore, addressing the psychological needs of people with cancer is necessary to improve their health status. In this review, we demonstrate music therapy as a significant treatment approach for reducing depression and anxiety disorders among patients with breast cancer, lung cancer, prostate cancer, and colorectal cancer.

Citation: Eseadi C, Ngwu MO. Significance of music therapy in treating depression and anxiety disorders among people with cancer. *World J Clin Oncol* 2023; 14(2): 69-80
URL: https://www.wjgnet.com/2218-4333/full/v14/i2/69.htm
DOI: https://dx.doi.org/10.5306/wjco.v14.i2.69

INTRODUCTION

A health condition known as cancer occurs when a small percentage of the cells in the body develop abnormally and disseminate to other bodily regions. Cancer can develop from any body part that accommodates trillions of cells[1]. The dissemination of cancerous cells to other parts of the body system is known as metastasizing, which mainly results in death from cancer. Whereas the 21st century has witnessed an improved performance of public nutrition, social behavior, and personal hygiene, as well as the methods adopted in preventing, controlling, and treating infectious diseases, which have all contributed to the current rise in the average lifespan of people, there is still an upsurge of cancer-related cases and deaths[2]. Globally, cancer has had a remarkable impact on the physical and psychological well-being and finances of individuals, family relations, communities, and the healthcare sector. Most of the healthcare system in resource-limited areas is poorly equipped. Thus, many cancer patients in these locations lack access to prompt, effective detection and subsequent medical therapy. The availability of early detection, effective therapy, and post-treatment care in nations with robust health systems have improved the survival rates of many different malignancies[3,4]. However, cancer prevalence and its common occurrence in emerging economies have continued to vary globally. Thus, in 1975, limited-resource areas accounted for over half (51%) of all cancer cases globally. By 2007, this number had risen to 55%, it has been predicted to rise to 61% by 2050[5,6]. Lung, breast, colorectal, and prostate cancers primarily associated with advanced economics have become a global concern. Diagnosing cancer induces mental stress, which may result in depression, fear, and anxiety[7,8].

Approximately 50% to 85% of cancer patients experiencing late-stage treatment report anxiety and depression[7]. Depression and anxiety negatively influence all aspects of cancer malignancy and its development, the efficacy of given therapy, and the patient's quality of life[9]. The practice of using music to aid recovery and improve the quality of life by medical and music experts is known as music therapy. Music therapy can have several advantages when used in conjunction with traditional cancer treatment[10]. Music therapy is referred to as the most widely used supportive and creative method of treating psychosocial-related impacts of cancer disease[11]. Music therapy is further defined as a systematic method of using music as a therapeutic means of rejuvenating, maintaining, and improving individuals' psychological and physical well-being[12]. Music therapy aims to reduce or eliminate psychological discomfort and improve the health status of individuals suffering from cancer-related health issues. Studies on people living with chronic cancer cases and those in palliative care have revealed that music therapy has drawn massive attention in research and medical treatment[13,14].

Further, the utilization of music as a remedial approach to healing mental disorders dates back to the olden days. Music is referred to as a healer as it aids in the reduction of anxiety and improves relaxation in patients suffering from chronic illness[15]. In the same vein, the realization of music as a contemporary psychotherapeutic approach in medical practice started after the second world war in the 20th century, which witnessed the introduction of courses and training sections and the establishment of national bodies around the globe[16]. The primary objective of this study is to examine depression and anxiety disorders' reports in cancer patients, give a narrative review of related studies and assess the significance of music interventions or music therapy in addressing depression and anxiety disorders among people suffering from the most common types of cancer diseases such as cancer of the breast, lung, prostate, and colorectal cancer[17]. In other words, the study focuses on the need to address the mental health of cancer patients using music therapy. Furthermore, the study aimed to enhance

awareness among medical practitioners providing oncological support and care regarding the significance of music therapy in treating the psychiatric conditions that may emanate from cancer diagnosis.

METHODOLOGY

This study employed a narrative literature review of studies to ascertain the significance of music therapy in treating depression and anxiety disorders among people with cancer. Since the study is a narrative literature review, ethical approval and informed consent are not required. Through a literature search on electronic databases, the authors could access published reviews and research articles, which were analysed using narrative syntheses. A narrative literature review provides informative educational materials as it draws ideas from a variety of papers and transforms these ideas into a readable resource. Thus, a narrative review provides a broader perspective on the topic of discussion. The authors conducted an extensive literature search and were able to find papers on depression and anxiety disorders in relation to people with various cancer malignancies, music therapy in caring for patients with cancer, and the effects of music therapy in treating depression and other psychosocial disorders from varieties of electronic databases such as Google Scholar, Lens, DOAJ, Scilit, Reference Citation Analysis, Dimensions, Scopus, PubMed Central, and SciElo. Also, searches through the references of the articles retrieved for the study were conducted to access more resources, peer-reviewed papers, and authoritative texts. The literature search terms were limited to depression and anxiety disorders, music therapy, people with cancer or cancer patients, music intervention, colorectal cancer, breast cancer, lung cancer, prostate cancer, psychological disorders, and cancer treatment. This study included relevant qualitative and quantitative research and review papers published in English.

DISCUSSION

Depression and anxiety disorders among people with cancer

Recently, cancer has been considered the primary cause of death, resulting in about a 10 million mortality rate in 2020, accounting for 1 in 6 deaths globally. The most prevalent cancer affecting the human race include breast cancer which accounts for 2.26 million cancer manifestations. This is followed by lung cancer with about 2.21 million recorded victims, colon and rectum with 1.93 million, and prostate with about 1.20 million cases. Lung cancer led to about 1.80 million deaths, while colorectal and breast cancer accounted for 916000 and 685000, respectively, in 2020[5]. Hence, the mortality rate from chronic diseases such as cancer has recently increased. The most significant psychological disorders affecting people with this chronic disease are depression and anxiety disorders. Depression is characterized by sadness, emptiness, or irritating moods, along with mental and physical abnormalities that negatively impact an individual's functioning, which may be attributed to environmental factors [18]. Anxiety disorder is an emotional state associated with excessive fear of uncertainty, lack of concentration, insomnia, and restlessness[19]. Globally, about 154 million people are affected by this disorder, and it is ranked as the most common cause of the severe impact of the disease. Depression is predicted to surpass all other causes by 2030[20]. According to estimates, the likelihood of early death will be higher for 40% to 60% of those with this condition than for the general population[21]. According to a research finding, about 75% of cancer patients are reported to develop depression and anxiety disorders. At the same time, 50% and 85% of cancer patients suffer acute depression and anxiety simultaneously[7, 22]. Depression and anxiety disorders are common psychiatric conditions that are often disregarded. These neglected psychiatric conditions are some of the impacts of cancer that affect the physical and mental well-being, adherence to therapy, the rate of surviving cancer, and cost of care among people with cancer[23].

Depression and anxiety disorders resulting from an individual being diagnosed with cancer at the initial stage is further exacerbated during therapeutic cancer management, which may have an unfavourable impact on the cancer patient. Studies revealed that a significant number of people living with cancer and receiving treatment have suffered from psychological distress, such as depression and anxiety disorders; between 15% and 54% of cancer patients experience these psychological conditions [24-27]. There are perhaps some variables that may be attributed to having caused depression and anxiety among cancer patients. Some of the variables that may lead to depression and anxiety at the individual level include demographic variables like age, sex, location, gender, and religion. Also, social and economic barriers like the inability to secure paid employment, low-level educational attainment, and inadequate social support are contributing factors[27]. The interaction between two or more of these factors often results in some mental health conditions among people with cancer[26].

Cancer management has a significant financial burden on patients. Thus, a psychological disorder affecting people with cancer can be linked to structural-level indicators such as availability, access, and utilization of healthcare services for the treatment of cancer, as well as the provision of welfare packages

for people with cancer[28,29]. This is because of the potential financial consequences of cancer. Psychological factors such as distinctiveness of the severe mental illness have been identified as one of the variables. Studies have also revealed that people with a high tendency to mental illness occurrence and subsequently diagnosed with cancer constitute the more significant percentage of cancer deaths. This can also be due to the severity of the cancer disease, late clinical diagnosis, poor therapeutic procedures, and a substantial decline in good healthcare-seeking behavior[30,31]. Also, people with cancer tend to suffer from depression and anxiety disorders due to factors such as a lack of adequate coping skills and neuroticism[32]. Another risk associated with cancer patients is suicide. People with cancer have a high probability of committing suicide when compared to the general population. Individuals who had suicidal thoughts in the past are more vulnerable, especially in the first six months of being diagnosed with such malignancy[33,34]. Another factor worthy of mention is how people with cancer deal with a cancer diagnosis using psychological coping strategies. An individual diagnosed with cancer may be susceptible to grief which could, in turn, affect how well the individual accepts their condition, especially if the diagnosis was delayed and the cancer cells have developed to a large extent[35].

However, despair, helplessness, and uncertainty about survival and death may also have detrimental effects on the mental health of people diagnosed with cancer. In addition, the distress associated with receiving a positive cancer diagnosis can interfere with sleep, which reduces the ability to concentrate, thereby increasing the risk of depression and anxiety[36]. People living with cancer may suffer from feelings of guilt and shame which often results from the stigma associated with being mentally ill and having some cancers, such as lung cancer. Depression and anxiety may be triggered by this event[35]. For example, women who develop cervical cancer due to promiscuity may blame themselves for their health condition and tend to feel isolated if they remember the activity that led to the manifestation of cervical cancer.

Additionally, during cancer management, the development of depression and anxiety disorders can also be attributed to the following variables-type of cancer an individual is diagnosed with, the stage of cancer, and the future outcome of the malignancy. The inability to recognize depression and anxiety among individuals with cancer can also potentially impair their quality of life. The treatment of cancers using chemotherapy, corticosteroids, and immunotherapy can also cause depression and anxiety among people with cancers as it involves biochemical procedures which result in inflammatory cytokines. Further, most of the medication used during chemotherapeutic procedures causes nausea, affecting dopamine receptors' neurotransmitter process. This action gives rise to depressive feelings among people with cancer[37]. Research has demonstrated that steroid treatment and androgen deprivation therapy is associated with depression and an increased risk of anxiety disorders in patients with cancer [38,39]. Among people with prostate cancer, depression may also be exacerbated by the clinical manifestations of some malignancies, such as leakage and erectile problems linked to prostate cancer [40]. Research on the psychological condition of people with cancer and the stages or survival rate has recently become a significant and expanding clinical research focus. Research has shown that many variables, including the kind and stage of the cancer malignancy, contribute to the declining mental health of people with cancer. In comparison with the general population, cancer patients are more likely to suffer from anxiety and depression[26].

Treatment of depression and anxiety disorders among people with cancer using music therapy

Music has psychological and physiological impacts and, as such, provides support in improving the mental and physical health of people with depression and anxiety disorders[21]. Musical stimuli are associated with the large production of endorphins and hormones secreted in the brain and nervous system. This hormone has many psychological functions. It activates enthusiasm, vital energy, excitement, and confidence in individuals. Therefore, the endorphins produced during musical display aid in lessening pain perception, stress, depression, and anxiety and increasing well-being[41]. Furthermore, music therapy (MT) is a significant contributor to the psychological well-being of cancer patients at all stages of their treatment[12].

Music therapy research indicates that people with cancer have benefitted from music expression and experience[42]. Music therapy is a simple, affordable, effective, and convenient method of treating depression and anxiety disorders[22,43]. As such, music therapy is highly recommended to be incorporated into healthcare services for people with cancer. The use of music therapy among cancer patients is helpful and supportive in ameliorating the depressive symptoms and anxiety exhibited by people with cancer[44].

Depression and anxiety disorders are often linked to non-compliance with proper treatment and poor cancer survival and health outcome among people with cancer. It is pertinent to note that cancer patients have an elevated risk of committing suicide[45,46]. Thus, adequate attention is required to address the resulting psychological disorders among cancer patients. Treating depression and anxiety disorders using music therapy involves qualified music therapists employing music as a supplementary or holistic therapeutic solution to help cancer patients cope with their sickness and reduce symptoms related to their condition or treatment procedures[47]. There is growing evidence that supports the use of MT in cancer patients. According to studies, music therapy aids in reducing anxiety levels in cancer patients undergoing major surgery[48,49]. Also, MT reduces depression, as revealed by studies[22,50]. Thus, cancer patients who undergo music therapy have been shown to benefit from its treatment of

depression and anxiety disorders.

The result of a meta-analysis on the effectiveness of music therapy for addressing psychological disorders among cancer patients shows that, compared to other conventional treatments, music therapy is more efficient in addressing depression and anxiety disorders[51]. The study found that music therapy can significantly improve the mental health of patients suffering from depression and anxiety disorders. Cancer patients are recommended to receive music therapy sessions for 1-2 mo to improve their quality of life[51]. Chen *et al*[52] stated that cancer treatment using music therapy reduces depressed mood, neuroticism, despair, and hopelessness. The therapeutic use of music therapy in managing depression and anxiety disorders and treatments carried out in surgery departments, and medical oncology should be encouraged among healthcare professionals[53]. Literature indicate that in addition to music interventions, it is also crucial for patients to receive social support, exercise, and relaxation interventions to minimize the mental health problems associated with a cancer diagnosis and the financial and emotional consequences of the disease[54-69].

Significance of music therapy in managing depression and anxiety disorders in people with various kinds of cancer

This section is dedicated to reviewing papers that examined the significant results of applying music therapy in treating mental health issue in patients with breast cancer, lung cancer, prostate cancer, and colorectal cancer (see also Table 1).

Breast cancer

Women are more likely to develop breast cancer than any other cancer malignancy. There are approximately 685000 cancer deaths in women worldwide caused by this type of cancer[54], resulting in the largest share of all cancer deaths in women[3,54]. Globally, about 2261419 new breast cancer occurrences were recorded in 2020, constituting 12.5% of all cancer recorded in 2020[55]. Despite the medical advancement in cancer treatment and prevention, which has resulted in an increased survival rate, breast cancer has a long-term negative mental and physical impacts[56]. Breast cancer patients often express a worse quality of life, experience cancer-related tiredness, and struggle to manage their condition and therapeutic tasks[57-59].

Women diagnosed with breast cancer may experience severe psychological and physical trauma, including altered body views, sleeplessness, exhaustion, discomfort, sadness, and other distressful feelings[60]. Depression and anxiety disorders are regarded to be most prevalent at the acute stage of cancer therapy[61]. The decision of people with cancer to receive cancer treatment may be influenced by depressive symptoms, including feelings of helplessness. It is estimated that approximately half (50%) of all breast cancer patients suffer from depression or anxiety. There is a possibility of experiencing severe depression during conventional chemotherapy, particularly with taxane-based chemotherapies. This condition may last for as long as 18 mo following the conclusion of the chemotherapy treatment[62,63].

Improving the depression and anxiety conditions of women diagnosed with breast cancer involves many interventions ranging from muscle relaxation training, music therapy, exercise, and laughter therapy[64-67]. Research has shown that they might also have unforeseen consequences and adverse implications that could affect breast cancer patients' mental health conditions[68]. Also, the chemotherapeutic session has been reported to be stressful and may negatively impact the mental state of breast cancer patients. Integrating music therapy and emotional expression could help reduce the negative psychological consequences of the treatment[69]. Music therapy is a distraction tool aimed at managing emotions and diverting an individual's attention from an unpleasant condition to a more pleasant and happy moment thereby reducing the risk of mental stress associated with an unpleasant or life-threatening health condition like breast cancer. This distraction method involves the breast cancer patient listening to music regulated by the music therapist[70,71].

Additionally, adopting music therapy in the treatment of depression and anxiety disorders among female patients with breast cancer fosters the reduction of the psychiatric consequences of cancer during and after an oncology treatment session[72]. Kievisiene *et al*[73] stated that music therapy helps reduce adverse psychological effects resulting from the clinical manifestation and treatment of breast cancer. Similarly, music therapy intervention could assist people with breast cancer to ease the cardiotoxicity pain resulting from chemotherapy treatment consisting of anthracycline[74]. Thus, music therapy is efficient and recommended for the treatment of psychological disorders like depression and anxiety as well in people with breast cancer.

Lung cancer

Lung cancer is among the most prevalent type of cancer affecting people, with an estimated 1.8 million recorded cases as of 2012 and 2.21 million new cases, according to recent reports[3,75]. Patients with severe lung cancer experience excruciating pain. About 75% and 80% of these patients reported that pain management is inefficient in reducing the painful consequence of lung cancer[76]. Lung cancer is majorly treated using a chemotherapeutic approach which also has side effects. About 25% of 50% of people with small cell lung cancer were reported to experience psychological distress after chemotherapy[77]. The physical pains and psychological trauma associated with post-surgery and

Table 1 Results on the significance of music therapy on people with the most common types of cancer

Ref.	Objective of the study	Research designs/Methods	Findings/Results
Romito *et al* [69]	To measure the effects of music therapy and emotional expression on the reduction of negative emotions in patients undergoing chemotherapy for breast cancer	62 breast cancer patients were randomly recruited into the experimental and control group	The combination of music therapy and emotional expression was identified to help reduce anger and depression that impacts the mental health of women with breast cancer
Zhou *et al* [72]	To examine the effects of music therapy and muscle relaxation training on depression and anxiety, as well as the length of hospitalization	An intervention group of 170 patients was randomly selected and assigned to the study; a randomized controlled trial was conducted	Depression and anxiety level reduction using music therapy
Kievisiene *et al*[73]	To explore the available reports on the effects of music therapy and art therapy interventions among breast cancer patients	A systematic literature search was conducted in PubMed, EBSCO, and the Cochrane Central database. A total of 20 randomized controlled trials were systematically reviewed	Music therapy is commonly used for anxiety reduction during and after oncological treatment sessions
Wang *et al* [83]	To examine the effect on hemodynamics and analgesia of postoperative intravenous sufentanil combined with music therapy in patients with lung cancer in comparison to sufentanil alone	60 lung cancer patients were randomly distributed to a music therapy group and a control group	After lung cancer surgery, patients in the music therapy group were reported to have significantly low anxiety rate, heart rate, blood pressure *etc.* which would have resulted in a psychological disorder
Mou *et al* [84]	To examine the effects of passive music therapy on patients with lung cancer during the initial peripherally implanted central catheter implantation operation on their anxiety levels and vital signs	304 lung cancer patients participated in the randomized controlled trial	Blood pressure, heart rate, and anxiety decreased significantly among lung cancer patients in the experimental group. The findings indicate that music therapy is beneficial for lung cancer patients when they are undergoing central catheter insertion
Tang *et al* [86]	To determine if six-step music therapy is effective in reducing pain and anxiety in patients with lung cancer receiving platinum-based chemotherapy and whether it improves sleep	Two groups-music treatment and a control group-each consisting of 100 patients with small cell lung cancer, were chosen at random	Patients with lung cancer who receive music therapy report less discomfort, less worry, and better sleep
Mishra *et al* [93]	To explore how music therapy affects patients having a RALP after surgery	18 yr and older men (40 patients) undergoing RALP were randomly assigned to music and control group	Music facilitates the comfort and reduction of narcotic usage among prostate cancer patients
Yung *et al* [94]	To ascertain how music therapy affects Chinese males having transurethral prostate resections in terms of pre-operative anxiety	A quasi-experimental design involving 30 patients with TURP	Music intervention is associated with a significant reduction in anxiety levels
Smolen *et al* [99]	To investigate the impact of music therapy on physiological and self-reported indicators of anxiety	32 adult patients scheduled for ambulatory colonoscopy were involved in the study	Patients who are having colonoscopies benefit from music therapy as it reduces the level of anxiety
Tanriverdi *et al*[100]	To determine how music therapy affects patients with early-stage colorectal cancer in terms of anxiety and chemotherapy-related nausea	A randomized controlled trial involving 62 patients	Music therapy was identified to be associated with a decrease in anxiety levels
Li *et al*[101]	To investigate the effects of music therapy on patients suffering from breast cancer in terms of their mental and physical state	25 to 65 years old female patients with breast cancer and receiving mastectomy were grouped into intervention and control groups	Music therapy was found to be useful and significant in improving the mental and physical health of women with breast cancer
Chirico *et al* [102]	To access the efficacy of virtual reality and compare its effects with music therapy	30 breast cancer patients were recruited into VR and MT groups respectively and 34 who were receiving standard chemotherapeutic care were assigned to a control group	Music intervention was discovered to be useful in addressing anxiety and facilitating the mental well-being of breast cancer patients

RALP: Robotically assisted laparoscopic prostatectomy; TURP: Transurethral resection of the prostate.

chemotherapy often harm the physical and psychosocial well-being of the lung cancer patient. While it is pertinent to provide adequate pain relief therapy for patients with lung cancer after surgery[78,79], the analgesia known as opioids which are commonly used to provide relief, has adverse side effects[80].

Music therapy is employed as an alternative intervention in managing pains associated with lung cancer that could lead to psychological distress, such as depression and anxiety disorders[81,82]. The aim is to enhance the patient's quality of life, promote longevity, and maintain the patient's mental health. The combination of music therapy with other care given to lung cancer patients after surgery helps reduce blood pressure, stress, anxiety disorder, and other psychological problems associated with lung cancer pain and trauma[83] and improves the general well-being of people living with lung cancer.

Music therapy is highly suggested for lung cancer patients undergoing any invasive clinical surgery[84] as it aids in improving the psychological issues resulting from both preoperative and postoperative surgery interventions. Studies have revealed that music therapy efficiently reduces adverse physical and psychological effects associated with terminal illnesses like cancer[77,85,86]. Music therapy, according to Tang *et al*[86], helps treat anxiety among patients with lung cancer. It is an efficient form of cancer care support that can be employed as a therapeutic means of improving lung cancer patients' psychological well-being[86] during chemotherapy or other treatment procedures.

Prostate cancer

Prostate cancer is the leading cause of death for men in 48 countries and the most common cancer affecting men in 112 countries[55]. Similarly, prostate cancer is among men's most prevalent diagnosed cancer in 2022, accounting for 27% of diagnosed cases[17]. Death resulting from this type of cancer malignancy accounts for 37.5 per 100000 and 11.3 per 100000 in higher and lower Human Development Index countries, respectively[87]. Prostate cancer is treated using radical prostatectomy[88]. Although the use of robotic-assisted laparoscopic prostatectomy has contributed to the reduction of postoperative pain among prostate cancer patients, there is a need for further advancement in managing pain and other psychological issues associated with prostate cancer[89]. During the perioperative stage, anxiety and pain are commonly associated with cancer patients. According to Kühlmann *et al*[90], about 75% of surgery patients experience anxiety, increasing postoperative pain. Prostate cancer patients often develop severe anxiety due to concern over the diagnosed cancer and its impact on their sexual life[91, 92]. Music therapy has been identified as a helpful approach in supporting prostate cancer patients and reducing anxiety[93]. Also, for prostate cancer patients undergoing transurethral resection of the prostate (that is, a surgical procedure aimed at treating an enlarged prostate-related urinary issues), music therapy intervention efficiently reduces preoperative anxiety during surgery[94]. Therefore, research evidence has revealed that music therapy can be used to treat psychological problems such as anxiety disorder and depression associated with prostate cancer diagnosis and should be introduced during preoperative and postoperative care.

Colorectal cancer

Men are highly susceptible to colorectal cancer, one of the leading causes of cancer death. In 2020, about 1.9 million people had colorectal cancer, and 935000 deaths were predicted to occur. Thus, accounting for one-tenth of all cancer cases and mortalities[55]. Colorectal cancer ranks second for death and third for incidence in men and accounts for 29 per 100000 on the higher Human Development Index (that is, an indicator of a country's performance in three of the major aspects of human development, namely health, education, and standard of living)[87,95,96]. Music therapy is used in addressing the psychological problems of colorectal cancer patients. A review of related research shows that a colorectal cancer patient listening to preferred music while having a sigmoidoscopy significantly lowers anxiety and increases comfort during surgery[97,98]. When music therapy was used, according to Palakanis *et al* [98], the patient's preferred music led to a decrease in the level of anxiety during sigmoidoscopy operations. Music therapy can potentially reduce anxiety and other indicators of psychological disorders among colorectal cancer patients undergoing colonoscopy[99]. Music therapy also reduces anxiety levels among patients with colorectal cancer during chemotherapy sessions[100]. Thus, music therapy intervention is efficient in supporting patients with colorectal cancer to adjust to psychological issues like depression and anxiety associated with a cancer diagnosis. Conversely, research on the effectiveness of using music as a kind of therapy to help people with colorectal cancer cope better with procedures like sigmoidoscopy or colonoscopy and to lessen their anxiety has been fragmentary.

RESEARCH IMPLICATIONS AND RECOMMENDATIONS

Music therapy improves the mental and physical state of people with cancer[101,102]. While cancer diagnosis and treatment procedures are linked to substantial financial costs[103], music therapy's cheap costs, absence of side effects, and significant benefits in reducing stress are crucial for the prevention and treatment of psychological issues caused by cancer and its diagnosis[104]. People with various kinds of cancer tend to suffer from psychological disorders like depression and anxiety, as stated earlier in this paper. Most cancer patients, as well as their families, music therapists, and medical experts feel optimistic about the remedies provided by music therapy[105]. Because the use of music therapy significantly lessens anxiety and depressive symptoms associated with cancer[106], it is vital for practitioners to continue to examine the significance of music therapy in addressing these psychiatric disorders among patients with various types of cancer malignancy.

A large percentage of cancer mortality could be attributed to depression and anxiety disorders resulting from cancer diagnosis and treatment. However, accessing the psychological state of people with cancer before and after clinical diagnosis and treatment is essential to reducing cancer death. The findings of this review are essential to medical practice and policy concerning oncological disease and treatment procedures. It is, therefore, pertinent to investigate and address the psychological disorders

observed in people with cancer. Because music therapy has been found to be significant in treating depression and anxiety in people with cancer, music therapists should be among the medical team treating cancer patients.

Medical practitioners who provide medical care to people with cancer should endeavor to examine the psychological health of cancer patients under their care. Given the significance of music therapy in reducing anxiety levels and treating depression in people with breast cancer, lung cancer, prostate cancer and colorectal cancer, it is therefore pertinent for the oncologist collaborate with qualified music professionals in order employ music therapy during the treatment of cancer patients. Music therapy should also be incorporated into medical, radiation, and surgical oncology curriculum. A further empirical study should be conducted to obtain more research on this issue.

CONCLUSION

Identifying the symptoms of mental illness in cancer patients is essential for managing their mental health. Cancer deaths may occur due to the inability to address the psychological disorders associated with cancer diagnosis among people with any of the most common cancer types. Music therapy has been identified to be significant in treating psychological issues like depression and anxiety that many cancer patients experience. It is needful for healthcare providers to incorporate music therapy interventions while treating people with cancer. This will help reduce cancer deaths resulting from psychological disorders rather than the killer disease, cancer. However, the standardized procedures and evaluation criteria for applying music-based intervention strategies in oncology medicine still need to be further established and improved.

FOOTNOTES

Author contributions: Eseadi C and Ngwu MO conceived the study; Eseadi C and Ngwu MO designed the study, conducted the literature review and were all responsible for the analysis, drafting, editing, and approval of the final version of this manuscript.

Conflict-of-interest statement: All the author declare no conflict of interests for this article.

Country/Territory of origin: South Africa

ORCID number: Chiedu Eseadi 0000-0003-1711-7558; Millicent O Ngwu 0000-0002-9125-1037.

S-Editor: Liu JH
L-Editor: A
P-Editor: Liu JH

REFERENCES

1 **National Cancer Institute**. Understanding Cancer. What is cancer ? 2021. Available from: https://www.cancer.gov/about-cancer/understanding/what-is-cancer
2 **Rahmani A**, Ferguson C, Jabarzadeh F, Mohammadpoorasl A, Moradi N, Pakpour V. Supportive care needs of Iranian cancer patients. *Indian J Palliat Care* 2014; **20**: 224-228 [PMID: 25191012 DOI: 10.4103/0973-1075.138400]
3 **World Health Organization [WHO]**. Cancer Reports. Heal. Top. 2022. Available from: https://www.who.int/news-room/fact-sheets/detail/cancer#:~:text=The problem-, Cancer is a leading cause of death worldwide%2C accounting for,lung (2.21 million cases)%3B
4 **Shah SC**, Kayamba V, Peek RM Jr, Heimburger D. Cancer Control in Low- and Middle-Income Countries: Is It Time to Consider Screening? *J Glob Oncol* 2019; **5**: 1-8 [PMID: 30908147 DOI: 10.1200/JGO.18.00200]
5 **Ferlay J**, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. *Int J Cancer* 2021 [PMID: 33818764 DOI: 10.1002/ijc.33588]
6 **Bray F**, Møller B. Predicting the future burden of cancer. *Nat Rev Cancer* 2006; **6**: 63-74 [PMID: 16372017 DOI: 10.1038/nrc1781]
7 **Zabora J**, BrintzenhofeSzoc K, Curbow B, Hooker C, Piantadosi S. The prevalence of psychological distress by cancer site. *Psychooncology* 2001; **10**: 19-28 [PMID: 11180574 DOI:

10.1002/1099-1611(200101/02)10:1<19::AID-PON501>3.0.CO;2-6]
8 **Zaza C**, Sellick SM, Hillier LM. Coping with cancer: what do patients do. *J Psychosoc Oncol* 2005; **23**: 55-73 [PMID: 16492644 DOI: 10.1300/J077v23n01_04]
9 **Priscilla D**, Hamidin A, Azhar MZ, Noorjan KO, Salmiah MS, Bahariah K. Assessment of depression and anxiety in haematological cancer patients and their relationship with quality of life. *East Asian Arch Psychiatry* 2011; **21**: 108-114 [PMID: 21921304]
10 **O'Callaghan CC**, McDermott F, Reid P, Michael N, Hudson P, Zalcberg JR, Edwards J. Music's Relevance for People Affected by Cancer: A Meta-Ethnography and Implications for Music Therapists. *J Music Ther* 2016; **53**: 398-429 [PMID: 27980035 DOI: 10.1093/jmt/thw013]
11 **Bro ML**, Jespersen KV, Hansen JB, Vuust P, Abildgaard N, Gram J, Johansen C. Kind of blue: A systematic review and meta-analysis of music interventions in cancer treatment. *Psychooncology* 2018; **27**: 386-400 [PMID: 28626867 DOI: 10.1002/pon.4470]
12 **Köhler F**, Martin ZS, Hertrampf RS, Gäbel C, Kessler J, Ditzen B, Warth M. Music Therapy in the Psychosocial Treatment of Adult Cancer Patients: A Systematic Review and Meta-Analysis. *Front Psychol* 2020; **11**: 651 [PMID: 32373019 DOI: 10.3389/fpsyg.2020.00651]
13 **Warth M**, Kessler J, Koehler F, Aguilar-Raab C, Bardenheuer HJ, Ditzen B. Brief psychosocial interventions improve quality of life of patients receiving palliative care: A systematic review and meta-analysis. *Palliat Med* 2019; **33**: 332-345 [PMID: 30648926 DOI: 10.1177/0269216318818011]
14 **Yang T**, Wang S, Wang R, Wei Y, Kang Y, Liu Y, Zhang C. Effectiveness of five-element music therapy in cancer patients: A systematic review and meta-analysis. *Complement Ther Clin Pract* 2021; **44**: 101416. [PMID: 34020291 DOI: 10.1016/j.ctcp.2021.101416]
15 **Umbrello M**, Sorrenti T, Mistraletti G, Formenti P, Chiumello D, Terzoni S. Music therapy reduces stress and anxiety in critically ill patients: a systematic review of randomized clinical trials. *Minerva Anestesiol* 2019; **85**: 886-898 [PMID: 30947484 DOI: 10.23736/S0375-9393.19.13526-2]
16 **Edwards J**. The Use of Music in Healthcare Contexts: A Select Review of Writings From the 1890s to the 1940s. *Voices A World Forum Music Ther* 2008; **8** [DOI: 10.15845/voices.v8i2.428]
17 **Siegel RL**, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* 2022; **72**: 7-33 [PMID: 35020204 DOI: 10.3322/caac.21708]
18 **Spitzer RL**, Gibbon ME, Skodol AE, Williams JB, First MB. DSM-IV-TR Casebook: A Learning Companion to the Diagnostic and Statistical Manual of Mental Disorders. *APA* [DOI: 10.1176/appi.books.9781585622665]
19 **American Psychiatric Association**. Diagnostic and statistical manual of mental disorders, 4th edn. Washington DC: American Psychiatric Publishing Inc, 1994. Available from: https://psycnet.apa.org/record/1994-97698-000
20 **Malhi GS,** Mann JJ. Depression. *Lancet* 2018; **392**: 2299-2312 [PMID: 30396512 DOI: 10.1016/S0140-6736(18)31948-2]
21 **Antonio E**, Marchant E, Angeles M, Amparo M. Effects of music therapy in depression and anxiety disorder. *Life Res* 2019; **2**: 64 [DOI: 10.53388/life2019-0425-003]
22 **Jasemi M**, Aazami S, Zabihi RE. The Effects of Music Therapy on Anxiety and Depression of Cancer Patients. *Indian J Palliat Care* 2016; **22**: 455-458 [PMID: 27803568 DOI: 10.4103/0973-1075.191823]
23 **Hage MP**, Azar ST. The Link between Thyroid Function and Depression. *J Thyroid Res* 2012; **2012**: 590648 [PMID: 22220285 DOI: 10.1155/2012/590648]
24 **Soqia J**, Al-Shafie M, Agha LY, Alameer MB, Alhomsi D, Saadoun R, Saifo M. Depression, anxiety and related factors among Syrian breast cancer patients: a cross-sectional study. *BMC Psychiatry* 2022; **22**: 796 [PMID: 36528568 DOI: 10.1186/s12888-022-04469-y]
25 **Lin MF**, Hsieh YJ, Hsu YY, Fetzer S, Hsu MC. A randomised controlled trial of the effect of music therapy and verbal relaxation on chemotherapy-induced anxiety. *J Clin Nurs* 2011; **20**: 988-999 [PMID: 21385249 DOI: 10.1111/j.1365-2702.2010.03525.x]
26 **Niedzwiedz CL**, Knifton L, Robb KA, Katikireddi SV, Smith DJ. Depression and anxiety among people living with and beyond cancer: a growing clinical and research priority. *BMC Cancer* 2019; **19**: 943 [PMID: 31604468 DOI: 10.1186/s12885-019-6181-4]
27 **Wen S**, Xiao H, Yang Y. The risk factors for depression in cancer patients undergoing chemotherapy: a systematic review. *Support Care Cancer* 2019; **27**: 57-67 [PMID: 30225571 DOI: 10.1007/s00520-018-4466-9]
28 **Gilligan AM**, Alberts DS, Roe DJ, Skrepnek GH. Death or Debt? *Am J Med* 2018; **131**: 1187-1199.e5 [PMID: 29906429 DOI: 10.1016/j.amjmed.2018.05.020]
29 **Lu L**, O'Sullivan E, Sharp L. Cancer-related financial hardship among head and neck cancer survivors: Risk factors and associations with health-related quality of life. *Psychooncology* 2019; **28**: 863-871 [PMID: 30779397 DOI: 10.1002/pon.5034]
30 **Klaassen Z**, Wallis CJD, Goldberg H, Chandrasekar T, Sayyid RK, Williams SB, Moses KA, Terris MK, Nam RK, Urbach D, Austin PC, Kurdyak P, Kulkarni GS. The impact of psychiatric utilisation prior to cancer diagnosis on survival of solid organ malignancies. *Br J Cancer* 2019; **120**: 840-847 [PMID: 30837680 DOI: 10.1038/s41416-019-0390-0]
31 **Musuuza JS**, Sherman ME, Knudsen KJ, Sweeney HA, Tyler CV, Koroukian SM. Analyzing excess mortality from cancer among individuals with mental illness. *Cancer* 2013; **119**: 2469-2476 [PMID: 23585241 DOI: 10.1002/cncr.28091]
32 **Cook SA**, Salmon P, Hayes G, Byrne A, Fisher PL. Predictors of emotional distress a year or more after diagnosis of cancer: A systematic review of the literature. *Psychooncology* 2018; **27**: 791-801 [PMID: 29318702 DOI: 10.1002/pon.4601]
33 **Henson KE**, Brock R, Charnock J, Wickramasinghe B, Will O, Pitman A. Risk of Suicide After Cancer Diagnosis in England. *JAMA Psychiatry* 2019; **76**: 51-60 [PMID: 30476945 DOI: 10.1001/jamapsychiatry.2018.3181]
34 **Wang SM**, Chang JC, Weng SC, Yeh MK, Lee CS. Risk of suicide within 1 year of cancer diagnosis. *Int J Cancer* 2018; **142**: 1986-1993 [PMID: 29250783 DOI: 10.1002/ijc.31224]
35 **Ball H**, Moore S, Leary A. A systematic literature review comparing the psychological care needs of patients with

mesothelioma and advanced lung cancer. *Eur J Oncol Nurs* 2016; **25**: 62-67 [PMID: 27865254 DOI: 10.1016/j.ejon.2016.09.007]

36 **Howell D**, Oliver TK, Keller-Olaman S, Davidson JR, Garland S, Samuels C, Savard J, Harris C, Aubin M, Olson K, Sussman J, MacFarlane J, Taylor C. Sleep disturbance in adults with cancer: a systematic review of evidence for best practices in assessment and management for clinical practice. *Ann Oncol* 2014; **25**: 791-800 [PMID: 24287882 DOI: 10.1093/annonc/mdt506]

37 **Smith HR**. Depression in cancer patients: Pathogenesis, implications and treatment (Review). *Oncol Lett* 2015; **9**: 1509-1514 [PMID: 25788991 DOI: 10.3892/ol.2015.2944]

38 **Ismail MF**, Lavelle C, Cassidy EM. Steroid-induced mental disorders in cancer patients: a systematic review. *Future Oncol* 2017; **13**: 2719-2731 [PMID: 29186986 DOI: 10.2217/fon-2017-0306]

39 **Nead KT**, Sinha S, Yang DD, Nguyen PL. Association of androgen deprivation therapy and depression in the treatment of prostate cancer: A systematic review and meta-analysis. *Urol Oncol* 2017; **35**: 664.e1-664.e9 [PMID: 28803700 DOI: 10.1016/j.urolonc.2017.07.016]

40 **De Sousa A**, Sonavane S, Mehta J. Psychological aspects of prostate cancer: a clinical review. *Prostate Cancer Prostatic Dis* 2012; **15**: 120-127 [PMID: 22212706 DOI: 10.1038/pcan.2011.66]

41 **Schulkin J**, Raglan GB. The evolution of music and human social capability. *Front Neurosci* 2014; **8**: 292 [DOI: 10.3389/fnins.2014.00292]

42 **Stanczyk MM**. Music therapy in supportive cancer care. *Rep Pract Oncol Radiother* 2011; **16**: 170-172 [PMID: 24376975 DOI: 10.1016/j.rpor.2011.04.005]

43 **Jiménez-Jiménez M**, García-Escalona A, Martín-López A, De Vera-Vera R, De Haro J. Intraoperative stress and anxiety reduction with music therapy: a controlled randomized clinical trial of efficacy and safety. *J Vasc Nurs* 2013; **31**: 101-106 [PMID: 23953858 DOI: 10.1016/j.jvn.2012.10.002]

44 **Bradt J**, Potvin N, Kesslick A, Shim M, Radl D, Schriver E, Gracely EJ, Komarnicky-Kocher LT. The impact of music therapy versus music medicine on psychological outcomes and pain in cancer patients: a mixed methods study. *Support Care Cancer* 2015; **23**: 1261-1271 [PMID: 25322972 DOI: 10.1007/s00520-014-2478-7]

45 **DiMatteo MR**, Haskard-Zolnierek KB. Impact of depression on treatment adherence and survival from cancer. Depression and cancer. Depress Cancer 2011; 101–124 [DOI: 10.1002/9780470972533.ch5]

46 **Robson A**, Scrutton F, Wilkinson L, MacLeod F. The risk of suicide in cancer patients: a review of the literature. *Psychooncology* 2010; **19**: 1250-1258 [PMID: 20213857 DOI: 10.1002/pon.1717]

47 **Kruse J**. Music Therapy in United States Cancer Settings: Recent Trends in Practice. *Ther Perspect* 2003; **21**: 89-98 [DOI: 10.1093/mtp/21.2.89]

48 **Clements-Cortés A**. Singing and Vocal Interventions in Palliative and Cancer Care: Music Therapists' Perceptions of Usage. *J Music Ther* 2017; **54**: 336-361 [PMID: 28992349 DOI: 10.1093/jmt/thx010]

49 **Mirbagher M**, Aghajani N. Comparing the Effect of Holy Quran Recitation and Music on Patient Anxiety and Vital Signs before Abdominal Surgeries. *Islam Lifestyle Cent Heal* 2012; **1:** 66–84. Available from: http://islamiclifej.com/browse.php?a_id=105&sid=1&slc_lang=fa

50 **Zhou KN**, Li XM, Yan H, Dang SN, Wang DL. Effects of music therapy on depression and duration of hospital stay of breast cancer patients after radical mastectomy. *Chin Med J (Engl)* 2011; **124**: 2321-2327 [PMID: 21933563 DOI: 10.3760/cma.j.issn.0366-6999.2011.15.014]

51 **Li Y**, Xing X, Shi X, Yan P, Chen Y, Li M, Zhang W, Li X, Yang K. The effectiveness of music therapy for patients with cancer: A systematic review and meta-analysis. *J Adv Nurs* 2020; **76**: 1111-1123 [PMID: 32017183 DOI: 10.1111/jan.14313]

52 **Chen SC**, Chou CC, Chang HJ, Lin MF. Comparison of group vs self-directed music interventions to reduce chemotherapy-related distress and cognitive appraisal: an exploratory study. *Support Care Cancer* 2018; **26**: 461-469 [PMID: 28799076 DOI: 10.1007/s00520-017-3850-1]

53 **Gramaglia C**, Gambaro E, Vecchi C, Licandro D, Raina G, Pisani C, Burgio V, Farruggio S, Rolla R, Deantonio L, Grossini E, Krengli M, Zeppegno P. Outcomes of music therapy interventions in cancer patients-A review of the literature. *Crit Rev Oncol Hematol* 2019; **138**: 241-254 [PMID: 31121392 DOI: 10.1016/j.critrevonc.2019.04.004]

54 **Kaye EC**, Snaman JM, Johnson L, Levine D, Powell B, Love A, Smith J, Ehrentraut JH, Lyman J, Cunningham M, Baker JN. Communication with children with cancer and their families throughout the illness journey and at the end of life. In: Wolfe J, Jones BL, Kreicbergs U, Jankovic M, editor. Pediatric Oncology. 2018: 55–93. [DOI: 10.1007/978-3-319-61391-8_4]

55 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

56 **Bodai BI**, Tuso P. Breast cancer survivorship: a comprehensive review of long-term medical issues and lifestyle recommendations. *Perm J* 2015; **19**: 48-79 [PMID: 25902343 DOI: 10.7812/TPP/14-241]

57 **Triberti S**, Savioni L, Sebri V, Pravettoni G. eHealth for improving quality of life in breast cancer patients: A systematic review. *Cancer Treat Rev* 2019; **74**: 1-14 [PMID: 30658289 DOI: 10.1016/j.ctrv.2019.01.003]

58 **Berger AM**, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, Cleeland C, Dotan E, Eisenberger MA, Escalante CP, Jacobsen PB, Jankowski C, LeBlanc T, Ligibel JA, Loggers ET, Mandrell B, Murphy BA, Palesh O, Pirl WF, Plaxe SC, Riba MB, Rugo HS, Salvador C, Wagner LI, Wagner-Johnston ND, Zachariah FJ, Bergman MA, Smith C; National comprehensive cancer network. Cancer-Related Fatigue, Version 2.2015. *J Natl Compr Canc Netw* 2015; **13**: 1012-1039 [PMID: 26285247 DOI: 10.6004/jnccn.2015.0122]

59 **Abrahams HJG**, Gielissen MFM, Verhagen CAHHVM, Knoop H. The relationship of fatigue in breast cancer survivors with quality of life and factors to address in psychological interventions: A systematic review. *Clin Psychol Rev* 2018; **63**: 1-11 [PMID: 29852324 DOI: 10.1016/j.cpr.2018.05.004]

60 **Shinden Y**, Kijima Y, Hirata M, Nakajo A, Tanoue K, Arigami T, Kurahara H, Maemura K, Natsugoe S. Clinical characteristics of breast cancer patients with mental disorders. *Breast* 2017; **36**: 39-43 [PMID: 28942099 DOI:

10.1016/j.breast.2017.08.010]
61 **Krebber AM**, Buffart LM, Kleijn G, Riepma IC, de Bree R, Leemans CR, Becker A, Brug J, van Straten A, Cuijpers P, Verdonck-de Leeuw IM. Prevalence of depression in cancer patients: a meta-analysis of diagnostic interviews and self-report instruments. *Psychooncology* 2014; **23**: 121-130 [PMID: 24105788 DOI: 10.1002/pon.3409]
62 **Burgess C**, Cornelius V, Love S, Graham J, Richards M, Ramirez A. Depression and anxiety in women with early breast cancer: five year observational cohort study. *BMJ* 2005; **330**: 702 [PMID: 15695497 DOI: 10.1136/bmj.38343.670868.D3]
63 **Thornton LM**, Carson WE 3rd, Shapiro CL, Farrar WB, Andersen BL. Delayed emotional recovery after taxane-based chemotherapy. *Cancer* 2008; **113**: 638-647 [PMID: 18521922 DOI: 10.1002/cncr.23589]
64 **Li XM**, Zhou KN, Yan H, Wang DL, Zhang YP. Effects of music therapy on anxiety of patients with breast cancer after radical mastectomy: a randomized clinical trial. *J Adv Nurs* 2012; **68**: 1145-1155 [PMID: 21978087 DOI: 10.1111/j.1365-2648.2011.05824.x]
65 **Kashani F**, Babaee S, Bahrami M, Valiani M. The effects of relaxation on reducing depression, anxiety and stress in women who underwent mastectomy for breast cancer. *Iran J Nurs Midwifery Res* 2012; **17**: 30-33 [PMID: 23493112]
66 **Ergun M**, Eyigor S, Karaca B, Kisim A, Uslu R. Effects of exercise on angiogenesis and apoptosis-related molecules, quality of life, fatigue and depression in breast cancer patients. *Eur J Cancer Care (Engl)* 2013; **22**: 626-637 [PMID: 23731173 DOI: 10.1111/ecc.12068]
67 **Cho EA**, Oh HE. [Effects of laughter therapy on depression, quality of life, resilience and immune responses in breast cancer survivors]. *J Korean Acad Nurs* 2011; **41**: 285-293 [PMID: 21804337 DOI: 10.4040/jkan.2011.41.3.285]
68 **Stanton AL**, Bower JE. Psychological Adjustment in Breast Cancer Survivors. *Adv Exp Med Biol* 2015; **862**: 231-242 [PMID: 26059939 DOI: 10.1007/978-3-319-16366-6_15]
69 **Romito F**, Lagattolla F, Costanzo C, Giotta F, Mattioli V. Music therapy and emotional expression during chemotherapy. How do breast cancer patients feel? Eur J Integr Med 2013; 5: 438–442 [DOI: 10.1016/j.eujim.2013.04.001]
70 **Atiwannapat P**, Thaipisuttikul P, Poopityastaporn P, Katekaew W. Active versus receptive group music therapy for major depressive disorder-A pilot study. *Complement Ther Med* 2016; **26**: 141-145 [PMID: 27261995 DOI: 10.1016/j.ctim.2016.03.015]
71 **Bruscia KE**. A working definition of Music Therapy (3rd Edition, 2014). 3rd ed. Available from: https://www.researchgate.net/publication/325204109_A_working_definition_of_Music_Therapy_3rd_Edition_2014
72 **Zhou K**, Li X, Li J, Liu M, Dang S, Wang D, Xin X. A clinical randomized controlled trial of music therapy and progressive muscle relaxation training in female breast cancer patients after radical mastectomy: results on depression, anxiety and length of hospital stay. *Eur J Oncol Nurs* 2015; **19**: 54-59 [PMID: 25181938 DOI: 10.1016/j.ejon.2014.07.010]
73 **Kievisiene J**, Jautakyte R, Rauckiene-Michaelsson A, Fatkulina N, Agostinis-Sobrinho C. The Effect of Art Therapy and Music Therapy on Breast Cancer Patients: What We Know and What We Need to Find out - A Systematic Review. *Evidence-based Complement Altern Med* 2020; **2020**: 1-14 [DOI: 10.1155/2020/7390321]
74 **Chuang CY**, Han WR, Li PC, Song MY, Young ST. Effect of long-term music therapy intervention on autonomic function in anthracycline-treated breast cancer patients. *Integr Cancer Ther* 2011; **10**: 312-316 [PMID: 21382955 DOI: 10.1177/1534735411400311]
75 **Torre LA**, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; **65**: 87-108 [PMID: 25651787 DOI: 10.3322/caac.21262]
76 **Tagányi K**. [Management of lung cancer-related pain]. *Orv Hetil* 2011; **152**: 1184-1191 [PMID: 21733791 DOI: 10.1556/OH.2011.29136]
77 **Wintner LM**, Giesinger JM, Zabernigg A, Sztankay M, Meraner V, Pall G, Hilbe W, Holzner B. Quality of life during chemotherapy in lung cancer patients: results across different treatment lines. *Br J Cancer* 2013; **109**: 2301-2308 [PMID: 24091620 DOI: 10.1038/bjc.2013.585]
78 **Magill L**. The use of music therapy to address the suffering in advanced cancer pain. *J Palliat Care* 2001; **17**: 167-172 [PMID: 11816757]
79 **Wu CL**, Raja SN. Treatment of acute postoperative pain. *Lancet* 2011; **377**: 2215-2225 [PMID: 21704871 DOI: 10.1016/S0140-6736(11)60245-6]
80 **Raehal KM**, Schmid CL, Groer CE, Bohn LM. Functional selectivity at the μ-opioid receptor: implications for understanding opioid analgesia and tolerance. *Pharmacol Rev* 2011; **63**: 1001-1019 [PMID: 21873412 DOI: 10.1124/pr.111.004598]
81 **Li XM**, Yan H, Zhou KN, Dang SN, Wang DL, Zhang YP. Effects of music therapy on pain among female breast cancer patients after radical mastectomy: results from a randomized controlled trial. *Breast Cancer Res Treat* 2011; **128**: 411-419 [PMID: 21537935 DOI: 10.1007/s10549-011-1533-z]
82 **Archie P**, Bruera E, Cohen L. Music-based interventions in palliative cancer care: a review of quantitative studies and neurobiological literature. *Support Care Cancer* 2013; **21**: 2609-2624 [PMID: 23715815 DOI: 10.1007/s00520-013-1841-4]
83 **Wang Y**, Tang H, Guo Q, Liu J, Liu X, Luo J, Yang W. Effects of Intravenous Patient-Controlled Sufentanil Analgesia and Music Therapy on Pain and Hemodynamics After Surgery for Lung Cancer: A Randomized Parallel Study. *J Altern Complement Med* 2015; **21**: 667-672 [PMID: 26331434 DOI: 10.1089/acm.2014.0310]
84 **Mou Q**, Wang X, Xu H, Liu X, Li J. Effects of passive music therapy on anxiety and vital signs in lung cancer patients undergoing peripherally inserted central catheter placement procedure. *J Vasc Access* 2020; **21**: 875-882 [PMID: 32141365 DOI: 10.1177/1129729820908088]
85 **Samakouri M**, Bouhos G, Kadoglou M, Giantzelidou A, Tsolaki K, Livaditis M. [Standardization of the Greek version of Zung's Self-rating Anxiety Scale (SAS)]. *Psychiatriki* 2012; **23**: 212-220 [PMID: 23073544]
86 **Tang H**, Chen L, Wang Y, Zhang Y, Yang N. The efficacy of music therapy to relieve pain, anxiety, and promote sleep quality, in patients with small cell lung cancer receiving platinum-based chemotherapy. *Support Care Cancer* 2021; **29**:

7299-7306 [PMID: 34041615 DOI: 10.1007/s00520-021-06152-6]
87 **Arnold M**, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut* 2017; **66**: 683-691 [PMID: 26818619 DOI: 10.1136/gutjnl-2015-310912]
88 **Lowrance WT**, Eastham JA, Savage C, Maschino AC, Laudone VP, Dechet CB, Stephenson RA, Scardino PT, Sandhu JS. Contemporary open and robotic radical prostatectomy practice patterns among urologists in the United States. *J Urol* 2012; **187**: 2087-2092 [PMID: 22498227 DOI: 10.1016/j.juro.2012.01.061]
89 **Batley SE**, Prasad V, Vasdev N, Mohan-S G. Post-Operative Pain Management in Patients Undergoing Robotic Urological Surgery. *Curr Urol* 2016; **9**: 5-11 [PMID: 26989364 DOI: 10.1159/000442843]
90 **Kühlmann AYR**, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. Meta-analysis evaluating music interventions for anxiety and pain in surgery. *Br J Surg* 2018; **105**: 773-783 [PMID: 29665028 DOI: 10.1002/bjs.10853]
91 **Arslan S**, Özer N, Özyurt F. Effect of music on preoperative anxiety in men undergoing urogenital surgery. *Aust J Adv Nursing* 2008; **26:** 46–54. Available from: https://www.ajan.com.au/archive/Vol26/26-2_Ozer.pdf
92 **Yadav N**, Singhal S, Bharti D. Effect of music on preoperative anxiety in patients undergoing laparoscopic cholecystectomy. *Bali J Anesthesiol* 2020; **4**: 90-94 [DOI: 10.4103/BJOA.BJOA_19_20]
93 **Mishra K**, Jesse E, Bukavina L, Sopko E, Arojo I, Fernstrum A, Ray A 3rd, Mahran A, Calaway A, Block S, Ponsky L. Impact of Music on Postoperative Pain, Anxiety, and Narcotic Use After Robotic Prostatectomy: A Randomized Controlled Trial. *J Adv Pract Oncol* 2022; **13**: 121-126 [PMID: 35369398 DOI: 10.6004/jadpro.2022.13.2.3]
94 **Yung PM**, Chui-Kam S, French P, Chan TM. A controlled trial of music and pre-operative anxiety in Chinese men undergoing transurethral resection of the prostate. *J Adv Nurs* 2002; **39**: 352-359 [PMID: 12139647 DOI: 10.1046/j.1365-2648.2002.02296.x]
95 **Bray F**. Transitions in human development and the global cancer burden. *World cancer Rep* 2014; **4:** 54-68. Available from: http://scholar.google.com.sci-hub.io/scholar?q=Transitions in human development and the global cancer burden In Wild CP Stewart B Eds World Cancer Report#0
96 **Fidler MM**, Soerjomataram I, Bray F. A global view on cancer incidence and national levels of the human development index. *Int J Cancer* 2016; **139**: 2436-2446 [PMID: 27522007 DOI: 10.1002/ijc.30382]
97 **Bampton P**, Draper B. Effect of relaxation music on patient tolerance of gastrointestinal endoscopic procedures. *J Clin Gastroenterol* 1997; **25**: 343-345 [PMID: 9412917 DOI: 10.1097/00004836-199707000-00010]
98 **Palakanis KC**, DeNobile JW, Sweeney WB, Blankenship CL. Effect of music therapy on state anxiety in patients undergoing flexible sigmoidoscopy. *Dis Colon Rectum* 1994; **37**: 478-481 [PMID: 8181411 DOI: 10.1007/BF02076195]
99 **Smolen D**, Topp R, Singer L. The effect of self-selected music during colonoscopy on anxiety, heart rate, and blood pressure. *Appl Nurs Res* 2002; **15**: 126-136 [PMID: 12173164 DOI: 10.1053/apnr.2002.34140]
100 **Tanriverdi O**, Karaoglu T, Aydemir NF. 1855P Music therapy can reduce both anxiety and chemotherapy-related nausea and vomiting in patients with early stage colorectal cancer treated with adjuvant infusion chemotherapy: A controlled, randomized study (PEGASUS study). *Ann Oncol* 2020; **31**: S1061-S1062 [DOI: 10.1016/j.annonc.2020.08.1502]
101 **Li X**, Du G, Liu W, Wang F. Music intervention improves the physical and mental status for patients with breast cancer: A protocol of randomized controlled trial. *Medicine (Baltimore)* 2020; **99**: e23461 [PMID: 33285746 DOI: 10.1097/MD.0000000000023461]
102 **Chirico A**, Maiorano P, Indovina P, Milanese C, Giordano GG, Alivernini F, Iodice G, Gallo L, De Pietro G, Lucidi F, Botti G, De Laurentiis M, Giordano A. Virtual reality and music therapy as distraction interventions to alleviate anxiety and improve mood states in breast cancer patients during chemotherapy. *J Cell Physiol* 2020; **235**: 5353-5362 [PMID: 31957873 DOI: 10.1002/jcp.29422]
103 **Carrera PM**, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: Understanding and stepping-up action on the financial toxicity of cancer treatment. *Cancer J Clin* 2018; **68**: 153-165 [PMID: 29338071 DOI: 10.3322/caac.21443]
104 **de Witte M**, Pinho ADS, Stams GJ, Moonen X, Bos AER, van Hooren S. Music therapy for stress reduction: a systematic review and meta-analysis. *Health Psychol Rev* 2022; **16**: 134-159 [PMID: 33176590 DOI: 10.1080/17437199.2020.1846580]
105 **Rodríguez-Rodríguez RC**, Noreña-Peña A, Chafer-Bixquert T, Lorenzo Vásquez A, González de Dios J, Solano Ruiz C. The relevance of music therapy in paediatric and adolescent cancer patients: a scoping review. *Glob Health Action* 2022; **15**: 2116774 [PMID: 36174131 DOI: 10.1080/16549716.2022.2116774]
106 **Zang L**, Cheng C, Zhou Y, Liu X. Music therapy effect on anxiety reduction among patients with cancer: A meta-analysis. *Front Psychol* 2022; **13**: 1028934 [PMID: 36687940 DOI: 10.3389/fpsyg.2022.1028934]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2023 February 24; 14(2): 81-88

DOI: 10.5306/wjco.v14.i2.81

ISSN 2218-4333 (online)

MINIREVIEWS

Therapeutic challenge for immunotherapy targeting cold colorectal cancer: A narrative review

Shi-Xun Ma, Li Li, Hui Cai, Tian-Kang Guo, Lei-Sheng Zhang

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Cabezuelo AS, Spain; Govindarajan KK, India; Jeong KY, South Korea

Received: September 20, 2022
Peer-review started: September 20, 2022
First decision: November 28, 2022
Revised: December 13, 2022
Accepted: February 7, 2023
Article in press: February 7, 2023
Published online: February 24, 2023

Shi-Xun Ma, Hui Cai, Tian-Kang Guo, Lei-Sheng Zhang, Department of General Surgery, Gansu Provincial Hospital, Lanzhou 73000, Gansu Province, China

Li Li, Scientific Research Division, Gansu Provincial Hospital, Lanzhou 730000, Gansu Province, China

Lei-Sheng Zhang, Key Laboratory of Radiation Technology and Biophysics, Hefei Institute of Physical Science, Chinese Academy of Sciences, Hefei 230031, Anhui Province, China

Corresponding author: Lei-Sheng Zhang, PhD, Professor, Department of General Surgery, Gansu Provincial Hospital, No. 204 West Donggang RD, Lanzhou 730000, Gansu Province, China. leisheng_zhang@163.com

Abstract

Cold colorectal tumors are not likely to trigger a robust immune response and tend to suppress the immune response. There may be three reasons. First, the complex tumor microenvironment of cold colorectal cancer (CRC) leads to tolerance and clearance of immunotherapy. Second, the modification and concealment of tumor-specific targets in cold CRC cause immune escape and immune response interruption. Finally, the difference in number and function of immune cell subsets in patients with cold CRC makes them respond poorly to immunotherapy. Therefore, we can only overcome the challenges in immunotherapy of cold CRC through in-depth research and understanding the changes and mechanisms in the above three aspects of cold CRC.

Key Words: Cold colorectal cancer; Immunotherapy; Tumor microenvironment; Immune targets; Immune cells

Core Tip: Advanced colorectal tumors are poorly treated, and immunotherapy has improved these patients' outcomes. However, cold colorectal tumors are less likely to trigger a robust immune response and tend to suppress it. To address this phenomenon, we discuss the role of the tumor microenvironment, immune targets, and immune cells in the treatment of cold colorectal tumors.

Citation: Ma SX, Li L, Cai H, Guo TK, Zhang LS. Therapeutic challenge for immunotherapy targeting cold colorectal cancer: A narrative review. *World J Clin Oncol* 2023; 14(2): 81-88
URL: https://www.wjgnet.com/2218-4333/full/v14/i2/81.htm
DOI: https://dx.doi.org/10.5306/wjco.v14.i2.81

INTRODUCTION

Colorectal cancer (CRC) has the third highest incidence and fourth mortality (after lung cancer, hepatic carcinoma, and stomach cancer) worldwide, which also serves as a biological and genetic paradigm for dissecting the evolutionary paths of solid tumors[1]. The risk factors of CRC are advanced age, dietary habits, obesity, lack of physical activity, constipation, chronic enteritis, intestinal polyps, alcohol consumption, and smoking[2]. With the robust advancement of fundamental research and medical technology, the treatment options for CRC have gradually formed a personalized and comprehensive treatment schedule led by surgery (*e.g.*, manual surgery, robotic surgery)[3]. Current treatment options include local endoscopic resection, radical surgical resection, local radiotherapy, systemic chemotherapy, palliative surgery, radiofrequency ablation of metastases, targeted therapy, and immunotherapy[4]. Of note, the survival benefit of patients with various tumors has increased significantly due to the rapid development of immunotherapy and the combined utilization with surgery, chemotherapy, radiotherapy, and targeted therapy. Generally, cancer immunotherapy can be divided into monoclonal antibodies, cytokines, immune checkpoint inhibitors (ICIs), tumor vaccines, and immune cells (*e.g.*, natural killer cells, tumor-infiltrating cells, T lymphocytes)[5]. Despite the increase in overall survival of patients with advanced CRC, new challenges have continuously emerged in treating "cold" CRC due to the current strategies in triggering a robust immune response and suppressing cancer[6].

To manage this phenomenon, we discuss the role of the tumor microenvironment (TME), immune targets, and immune cells in treating colorectal tumors.

LITERATURE SEARCH AND REVIEW

For the purpose, we primarily searched the literature on CRC immunotherapy published in the last 5 years through PubMed and Google Scholar databases. After importing them into the literature management software EndNote and de-duplicating them, we double-checked their titles, abstracts, and texts one-by-one to screen out the literature related to cold CRC treatment. The article was written according to a pre-planned framework, and the references were added by selecting the National Library of Medicine mode.

IMMUNOLOGICAL SIGNATURE-BASED CRC CLASSIFICATION

Accurate monomolecular typing is essential to screen CRC patients who may benefit from immunotherapy and whose TME needs reprogramming for beneficial immune-mediated responses[5]. Based on the degree of immune infiltration, tumors can be classified as "hot tumors" with high infiltration, "variable tumors" with rejection and immunosuppression, and "cold tumors" without infiltration[7]. Overall, the subsets of the aforementioned cancers have variations in pathological features, genetic mutations, immune cell composition, immune phenotypes, cytokines, clinical outcomes, and responses to immunotherapy[5]. CRC patients with a resistant "cold" phenotype are extremely challenging to treat with immunotherapy due to the low tumor mutation rate and lack of immune cell infiltration[5]. Approximately 80%-85% of CRC patients are considered to have "cold" tumors with microsatellite stability (MSS) or low microsatellite instability (MSI-L) (referred to as MSS/MSI-L CRC), which lack response to ICIs[8-10]. Immunosubtype classification can identify altered immune microenvironments in CRC patients. In addition, immune subtyping can guide personalized CRC immunotherapy and tumor prognosis[11-15].

RELATED STUDIES BASED ON THE TME

CRC is a highly heterogeneous disease, and mutant gene polymorphisms create a diversity of tumor subtypes and their corresponding TME. Sobral *et al*[16] demonstrated, in a study of genetic and microenvironmental intra-tumor heterogeneity affecting the evolution and metastatic development of CRC, that the diversity of CRC is caused by asynchronous forms of molecular alterations in which

mutations and chromosomal instability collectively contribute to the genetic and microenvironmental intra-tumor heterogeneity. Studies have shown that the greater the genetic mutation and TME differences, the lower the ability of tumors to metastasize. By contrast, advanced tumor gene mutations exploit tumor proliferation and metastasis. Wang *et al*[17] employed methionine enkephalin to inhibit colorectal carcinogenesis by reshaping the immune status of the TME. It has been shown that methionine enkephalin promotes antitumor immune responses, remodels the immune state of the tumor immune microenvironment in CRC, inhibits tumor development, and is a potential therapeutic agent for CRC, especially useful for improving the efficacy of immunotherapy. Chen *et al*[18] further proposed that metabolic changes in the TME were closely related to the development of CRC. In details, tumor cells secrete carriers beneficially utilized by surrounding cells in the TME to induce metabolic changes and cancer transformation. At the same time, tumor cells secrete pages that provide energy for their proliferation, metastasis, and drug resistance.

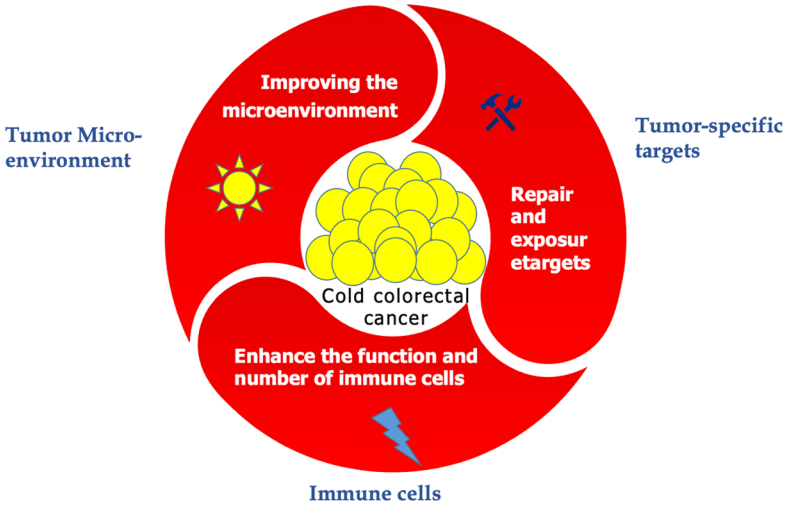
The tumor immune microenvironment is highly variable and extremely complex, and many immunosuppressive pathways have been identified in microsatellite-stabilized CRC[19]. Regorafenib, a tyrosine kinase inhibitor, is one of two drugs approved for treating MSS CRC[20]. The REGONIVO study showed a 36% response rate for regorafenib in metastatic MSS CRC[23]. Cabozantinib is another drug being investigated for the treatment of MSS CRC. Toll-like receptor (TLR) modulators are a new class of immunomodulatory drugs[24]. REVEAL is a phase 2 trial investigating TLR7/8 agonists in combination with nivolumab against tumors. Keynote-559 is a phase 1/2 trial investigating C-X-C motif chemokine ligand 12 (CXCL12) antagonists in combination with pembrolizumab for mCRC and metastatic pancreatic cancer. The chemokine CXCL12 promotes tumor proliferation, metastasis and angiogenesis by inducing signals, which can recruit B cells, plasma cells, and regulatory T cells to induce an immunosuppressive environment[25]. Investigators are devoted to developing multidisciplinary approaches to increase immune-mediated responses, improve the TME, and convert "cold" tumors into "hot" tumors to promote immunotherapy[15].

RELATED STUDIES BASED ON IMMUNE TARGETS

ICIs typically respond to CRCs with defective mismatch repair (dMMR) or high MSI (MSI-H). Approximately 85% of CRCs do not respond to immunotherapy or eventually become resistant due to MMR resistance or MSS[10]. MMR/MSS CRCs typically have low tumor mutational load, low chemotherapy response rates, low tumor-infiltrating lymphocytes, and poor prognosis compared to dMMR/MSI CRCs. Ros *et al*[26] verified that inhibition of transforming growth factor beta (TGF-β) could play a vital role in the development and metastasis of CRC by enhancing T-cell action. He *et al*[27] used *in situ*-forming albumin corpuscles to target liposomes and reshape the "cold" tumor immune microenvironment through epigenetic-based therapy. It was found that *in situ*-forming albumin corpuscles further enhanced tumor-targeted delivery, and that targeted liposome treatment effectively inhibited the effects between tumor metabolism and immune evasion by inhibiting glycolysis and immune normalization. Janssen *et al*[28] explained the available evidence for the potential impact of RAS mutations on the microenvironment of CRC in a study of mutated RAS and TME as dual therapeutic targets in advanced CRC[29]. Takahashi *et al*[30] showed that the combination of stromal programmed death ligand 1 (PD-L1)+ immune cells and nuclear β-catenin$^+$ tumor budding might contribute to tumor progression in CRC and resistance to neoadjuvant chemotherapy in locally advanced rectal cancer. Dmitrieva-Posocco *et al*[31] found that the ketogenic diet exhibited strong tumor suppressive effects. The ketone body β-hydroxybutyric acid reduced colonic crypt cells proliferation and effectively inhibited intestinal tumor growth. It is suggested that oral or systemic interventions using a single metabolite could complement current CRC prevention and treatment strategies. High PD-L1 expression in tumors is a sign of poor prognosis, which also shows good responsiveness to ICIs and immunomodulatory drugs such as C-X-C motif chemokine receptor 4, poly (ADP-ribose) polymerase or TGF-β inhibitors in combination[6]. Li *et al*[32] investigated the relationship between genetic changes in CRC and intercellular transformation in cancer cell biology and TME. Key advances in the development of effective therapeutic approaches for this cancer were analyzed from immunological and single-cell perspectives[33]. Long-noncoding RNAs (lncRNAs) are important regulators of microRNA expression in CRC and might be promising biomarkers and potential therapeutic targets in CRC research. For example, Lv *et al*[34] provided insights into the pathogenesis, diagnosis, and development of therapeutic strategies for CRC by studying lncRNAs.

RELATED STUDIES BASED ON IMMUNE CELLS

The current therapeutic strategies have limited efficacy in CRC[35-38]. Approximately one-quarter of CRC patients are diagnosed with a combination of distant metastases[39-41], and of these, another one-quarter recurs or metastasizes within 5 years. The 5-year survival rate for CRC patients with combined metastases is approximately 15%[42-44]. Therefore, there is an urgent need for new approaches to treat



DOI: 10.5306/wjco.v14.i2.81

Figure 1 Pattern of immunotherapy strategies for cold colorectal cancer.

CRC using immunotherapy[28,45]. The current cancer classification is based on the American Joint Committee on Cancer/Union for International Cancer Control - Tumor Node Metastasis (TNM) system, and the prediction of the effect of immunotherapy cannot be assessed[35]. Relevant evidence suggests that the prognosis of CRC patients correlates with the type, density, and function of immune cells within the tumor[46]. Galon *et al*[35] developed an immunohistochemical and digital pathology-based assay named Immunoscore, which quantified two tumor regions (core and invasive margin of the tumor) in two T-cell subsets (cluster of differentiation 3 [CD3] and [CD8]). Immunoscore is an immune function-based scoring system that is more valuable than the traditional TNM score in determining the predictive value of patients with CRC[47-50]. Relative studies have also demonstrated the predictive value of Immunoscore for the prognosis of patients with colon cancer[51-53], which is conducive to classify tumors and guide clinical decisions[54-58]. Tumor lysis virus is a novel antitumor agent that both lyses tumor cells and modulates the TME, which can convert "cold" tumors into "hot" tumors and thus allows ICIs to work. For example, Ren *et al*[36] recently investigated the status of tumor lysing viruses and ICIs for treating CRC. The feasibility of combining tumor lysis virus with ICIs for treating CRC will be discussed in terms of the mechanism of action of tumor lysis virus for tumor treatment.

FUTURE DIRECTIONS

For cold CRC, immunotherapy strategies focus on converting "cold" tumors to "hot" tumors through various approaches[6,59-62]. Various immunotherapies or chemotherapy can be used to modulate the patient's immune status[63-66]. Regulation of the number and function of *Escherichia coli* in the patient's intestine can improve the role of the patient's immune microenvironment[67-69]. Therapies that enhance the operation and number of immune cells may also improve treatment outcomes[70-72]. Further functional and mechanistic studies of mutated genes could identify new targets for cold CRC therapy [73-75].

CONCLUSION

In summary, the fundamental reasons for the challenge of immunotherapy for cold CRC are the low tumor mutational load and lack of immune cell infiltration. To conquer this phenomenon, we should conduct comprehensive research on the TME, immune targets and immune cells to warm up CRC (Figure 1). Meanwhile, we should also combine the aforementioned cancer immunotherapy with traditional tumor treatment remedies such as surgery, radiotherapy, and chemotherapy. Only personalized, comprehensive treatment plans for CRC, and a good prognosis for patients are the ultimate goals we pursue.

FOOTNOTES

Author contributions: Ma SX, and Li L wrote the paper; Zhang LS, Cai H, and Guo TK performed the data collection; All authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors have no conflicts of interest to declare.

Country/Territory of origin: China

ORCID number: Shi-Xun Ma 0000-0002-4208-9248; Hui Cai 0000-0001-5857-1744; Tian-Kang Guo https://orcid.org/0000-0003-1035-7348; Lei-Sheng Zhang 0000-0001-6540-0943.

S-Editor: Liu GL
L-Editor: Filipodia
P-Editor: Liu GL

REFERENCES

1 **Baidoun F**, Elshiwy K, Elkeraie Y, Merjaneh Z, Khoudari G, Sarmini MT, Gad M, Al-Husseini M, Saad A. Colorectal Cancer Epidemiology: Recent Trends and Impact on Outcomes. *Curr Drug Targets* 2021; **22**: 998-1009 [PMID: 33208072 DOI: 10.2174/1389450121999201117115717]
2 **Dekker E**, Tanis PJ, Vleugels JLA, Kasi PM, Wallace MB. Colorectal cancer. *Lancet* 2019; **394**: 1467-1480 [PMID: 31631858 DOI: 10.1016/S0140-6736(19)32319-0]
3 **Fleming-de-Moraes CD**, Rocha MR, Tessmann JW, de Araujo WM, Morgado-Diaz JA. Crosstalk between PI3K/Akt and Wnt/β-catenin pathways promote colorectal cancer progression regardless of mutational status. *Cancer Biol Ther* 2022; **23**: 1-13 [PMID: 35944058 DOI: 10.1080/15384047.2022.2108690]
4 **Paty PB**, Garcia-Aguilar J. Colorectal cancer. *J Surg Oncol* 2022; **126**: 881-887 [PMID: 36087081 DOI: 10.1002/jso.27079]
5 **Xu M**, Chang J, Wang W, Wang X, Weng W, Tan C, Zhang M, Ni S, Wang L, Huang Z, Deng Z, Li W, Huang D, Sheng W. Classification of colon adenocarcinoma based on immunological characterizations: Implications for prognosis and immunotherapy. *Front Immunol* 2022; **13**: 934083 [PMID: 35967414 DOI: 10.3389/fimmu.2022.934083]
6 **Majidpoor J**, Mortezaee K. The efficacy of PD-1/PD-L1 blockade in cold cancers and future perspectives. *Clin Immunol* 2021; **226**: 108707 [PMID: 33662590 DOI: 10.1016/j.clim.2021.108707]
7 **Galon J**, Bruni D. Approaches to treat immune hot, altered and cold tumours with combination immunotherapies. *Nat Rev Drug Discov* 2019; **18**: 197-218 [PMID: 30610226 DOI: 10.1038/s41573-018-0007-y]
8 **Le DT**, Uram JN, Wang H, Bartlett BR, Kemberling H, Eyring AD, Skora AD, Luber BS, Azad NS, Laheru D, Biedrzycki B, Donehower RC, Zaheer A, Fisher GA, Crocenzi TS, Lee JJ, Duffy SM, Goldberg RM, de la Chapelle A, Koshiji M, Bhaijee F, Huebner T, Hruban RH, Wood LD, Cuka N, Pardoll DM, Papadopoulos N, Kinzler KW, Zhou S, Cornish TC, Taube JM, Anders RA, Eshleman JR, Vogelstein B, Diaz LA Jr. PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. *N Engl J Med* 2015; **372**: 2509-2520 [PMID: 26028255 DOI: 10.1056/NEJMoa1500596]
9 **Chen DS**, Mellman I. Elements of cancer immunity and the cancer-immune set point. *Nature* 2017; **541**: 321-330 [PMID: 28102259 DOI: 10.1038/nature21349]
10 **Lizardo DY**, Kuang C, Hao S, Yu J, Huang Y, Zhang L. Immunotherapy efficacy on mismatch repair-deficient colorectal cancer: From bench to bedside. *Biochim Biophys Acta Rev Cancer* 2020; **1874**: 188447 [PMID: 33035640 DOI: 10.1016/j.bbcan.2020.188447]
11 **Goodman AM**, Kato S, Bazhenova L, Patel SP, Frampton GM, Miller V, Stephens PJ, Daniels GA, Kurzrock R. Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers. *Mol Cancer Ther* 2017; **16**: 2598-2608 [PMID: 28835386 DOI: 10.1158/1535-7163.MCT-17-0386]
12 **Goodman AM**, Sokol ES, Frampton GM, Lippman SM, Kurzrock R. Microsatellite-Stable Tumors with High Mutational Burden Benefit from Immunotherapy. *Cancer Immunol Res* 2019; **7**: 1570-1573 [PMID: 31405947 DOI: 10.1158/2326-6066.CIR-19-0149]
13 **Wang W**, Green M, Choi JE, Gijón M, Kennedy PD, Johnson JK, Liao P, Lang X, Kryczek I, Sell A, Xia H, Zhou J, Li G, Li J, Li W, Wei S, Vatan L, Zhang H, Szeliga W, Gu W, Liu R, Lawrence TS, Lamb C, Tanno Y, Cieslik M, Stone E, Georgiou G, Chan TA, Chinnaiyan A, Zou W. CD8(+) T cells regulate tumour ferroptosis during cancer immunotherapy. *Nature* 2019; **569**: 270-274 [PMID: 31043744 DOI: 10.1038/s41586-019-1170-y]
14 **Golstein P**, Griffiths GM. An early history of T cell-mediated cytotoxicity. *Nat Rev Immunol* 2018; **18**: 527-535 [PMID: 29662120 DOI: 10.1038/s41577-018-0009-3]
15 **Newman JH**, Chesson CB, Herzog NL, Bommareddy PK, Aspromonte SM, Pepe R, Estupinian R, Aboelatta MM, Buddhadev S, Tarabichi S, Lee M, Li S, Medina DJ, Giurini EF, Gupta KH, Guevara-Aleman G, Rossi M, Nowicki C, Abed A, Goldufsky JW, Broucek JR, Redondo RE, Rotter D, Jhawar SR, Wang SJ, Kohlhapp FJ, Kaufman HL, Thomas

PG, Gupta V, Kuzel TM, Reiser J, Paras J, Kane MP, Singer EA, Malhotra J, Denzin LK, Sant'Angelo DB, Rabson AB, Lee LY, Lasfar A, Langenfeld J, Schenkel JM, Fidler MJ, Ruiz ES, Marzo AL, Rudra JS, Silk AW, Zloza A. Intratumoral injection of the seasonal flu shot converts immunologically cold tumors to hot and serves as an immunotherapy for cancer. *Proc Natl Acad Sci U S A* 2020; **117**: 1119-1128 [PMID: 31888983 DOI: 10.1073/pnas.1904022116]

16 **Sobral D**, Martins M, Kaplan S, Golkaram M, Salmans M, Khan N, Vijayaraghavan R, Casimiro S, Fernandes A, Borralho P, Ferreira C, Pinto R, Abreu C, Costa AL, Zhang S, Pawlowski T, Godsey J, Mansinho A, Macedo D, Lobo-Martins S, Filipe P, Esteves R, Coutinho J, Costa PM, Ramires A, Aldeia F, Quintela A, So A, Liu L, Grosso AR, Costa L. Genetic and microenvironmental intra-tumor heterogeneity impacts colorectal cancer evolution and metastatic development. *Commun Biol* 2022; **5**: 937 [PMID: 36085309 DOI: 10.1038/s42003-022-03884-x]

17 **Wang X**, Li S, Yan S, Shan Y, Wang X, Jingbo Z, Wang Y, Shan F, Griffin N, Sun X. Methionine enkephalin inhibits colorectal cancer by remodeling the immune status of the tumor microenvironment. *Int Immunopharmacol* 2022; **111**: 109125 [PMID: 35988519 DOI: 10.1016/j.intimp.2022.109125]

18 **Chen J**, Zhu H, Yin Y, Jia S, Luo X. Colorectal cancer: Metabolic interactions reshape the tumor microenvironment. *Biochim Biophys Acta Rev Cancer* 2022; **1877**: 188797 [PMID: 36100193 DOI: 10.1016/j.bbcan.2022.188797]

19 **Lazarus J**, Maj T, Smith JJ, Perusina Lanfranca M, Rao A, D'Angelica MI, Delrosario L, Girgis A, Schukow C, Shia J, Kryczek I, Shi J, Wasserman I, Crawford H, Nathan H, Pasca Di Magliano M, Zou W, Frankel TL. Spatial and phenotypic immune profiling of metastatic colon cancer. *JCI Insight* 2018; **3** [PMID: 30429368 DOI: 10.1172/jci.insight.121932]

20 **Grothey A**, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D; CORRECT Study Group. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 2013; **381**: 303-312 [PMID: 23177514 DOI: 10.1016/S0140-6736(12)61900-X]

21 **Fondevila F**, Méndez-Blanco C, Fernández-Palanca P, González-Gallego J, Mauriz JL. Anti-tumoral activity of single and combined regorafenib treatments in preclinical models of liver and gastrointestinal cancers. *Exp Mol Med* 2019; **51**: 1-15 [PMID: 31551425 DOI: 10.1038/s12276-019-0308-1]

22 **Abou-Elkacem L**, Arns S, Brix G, Gremse F, Zopf D, Kiessling F, Lederle W. Regorafenib inhibits growth, angiogenesis, and metastasis in a highly aggressive, orthotopic colon cancer model. *Mol Cancer Ther* 2013; **12**: 1322-1331 [PMID: 23619301 DOI: 10.1158/1535-7163.MCT-12-1162]

23 **Fukuoka S**, Hara H, Takahashi N, Kojima T, Kawazoe A, Asayama M, Yoshii T, Kotani D, Tamura H, Mikamoto Y, Hirano N, Wakabayashi M, Nomura S, Sato A, Kuwata T, Togashi Y, Nishikawa H, Shitara K. Regorafenib Plus Nivolumab in Patients With Advanced Gastric or Colorectal Cancer: An Open-Label, Dose-Escalation, and Dose-Expansion Phase Ib Trial (REGONIVO, EPOC1603). *J Clin Oncol* 2020; **38**: 2053-2061 [PMID: 32343640 DOI: 10.1200/JCO.19.03296]

24 **Urban-Wojciuk Z**, Khan MM, Oyler BL, Fåhraeus R, Marek-Trzonkowska N, Nita-Lazar A, Hupp TR, Goodlett DR. The Role of TLRs in Anti-cancer Immunity and Tumor Rejection. *Front Immunol* 2019; **10**: 2388 [PMID: 31695691 DOI: 10.3389/fimmu.2019.02388]

25 **Nagarsheth N**, Wicha MS, Zou W. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. *Nat Rev Immunol* 2017; **17**: 559-572 [PMID: 28555670 DOI: 10.1038/nri.2017.49]

26 **Ros XR**, Vermeulen L. Turning Cold Tumors Hot by Blocking TGF-β. *Trends Cancer* 2018; **4**: 335-337 [PMID: 29709256 DOI: 10.1016/j.trecan.2018.03.005]

27 **He Y**, Fang Y, Zhang M, Zhao Y, Tu B, Shi M, Muhitdinov B, Asrorov A, Xu Q, Huang Y. Remodeling "cold" tumor immune microenvironment *via* epigenetic-based therapy using targeted liposomes with in situ formed albumin corona. *Acta Pharm Sin B* 2022; **12**: 2057-2073 [PMID: 35847495 DOI: 10.1016/j.apsb.2021.09.022]

28 **Janssen JBE**, Medema JP, Gootjes EC, Tauriello DVF, Verheul HMW. Mutant RAS and the tumor microenvironment as dual therapeutic targets for advanced colorectal cancer. *Cancer Treat Rev* 2022; **109**: 102433 [PMID: 35905558 DOI: 10.1016/j.ctrv.2022.102433]

29 **Sun Y**, Li Z, Wang W, Zhang X, Li W, Du G, Yin J, Xiao W, Yang H. Identification and verification of YBX3 and its regulatory gene HEIH as an oncogenic system: A multidimensional analysis in colon cancer. *Front Immunol* 2022; **13**: 957865 [PMID: 36059530 DOI: 10.3389/fimmu.2022.957865]

30 **Takahashi H**, Watanabe H, Hashimura M, Matsumoto T, Yokoi A, Nakagawa M, Ishibashi Y, Ito T, Ohhigata K, Saegusa M. A combination of stromal PD-L1 and tumoral nuclear β-catenin expression as an indicator of colorectal carcinoma progression and resistance to chemoradiotherapy in locally advanced rectal carcinoma. *J Pathol Clin Res* 2022; **8**: 458-469 [PMID: 35762092 DOI: 10.1002/cjp2.285]

31 **Dmitrieva-Posocco O**, Wong AC, Lundgren P, Golos AM, Descamps HC, Dohnalová L, Cramer Z, Tian Y, Yueh B, Eskiocak O, Egervari G, Lan Y, Liu J, Fan J, Kim J, Madhu B, Schneider KM, Khoziainova S, Andreeva N, Wang Q, Li N, Furth EE, Bailis W, Kelsen JR, Hamilton KE, Kaestner KH, Berger SL, Epstein JA, Jain R, Li M, Beyaz S, Lengner CJ, Katona BW, Grivennikov SI, Thaiss CA, Levy M. β-Hydroxybutyrate suppresses colorectal cancer. *Nature* 2022; **605**: 160-165 [PMID: 35477756 DOI: 10.1038/s41586-022-04649-6]

32 **Li J**, Ma X, Chakravarti D, Shalapour S, DePinho RA. Genetic and biological hallmarks of colorectal cancer. *Genes Dev* 2021; **35**: 787-820 [PMID: 34074695 DOI: 10.1101/gad.348226.120]

33 **Zhao EY**, Jones M, Jones SJM. Whole-Genome Sequencing in Cancer. *Cold Spring Harb Perspect Med* 2019; **9** [PMID: 29844223 DOI: 10.1101/cshperspect.a034579]

34 **Lv Y**, Wang Y, Zhang Z, Bao J, Su H. Potentials of long non-coding RNAs as biomarkers of colorectal cancer. *Clin Transl Oncol* 2022; **24**: 1715-1731 [PMID: 35581419 DOI: 10.1007/s12094-022-02834-7]

35 **Galon J**, Lanzi A. Immunoscore and its introduction in clinical practice. *Q J Nucl Med Mol Imaging* 2020; **64**: 152-161 [PMID: 32107902 DOI: 10.23736/S1824-4785.20.03249-5]

36 **Ren Y**, Miao JM, Wang YY, Fan Z, Kong XB, Yang L, Cheng G. Oncolytic viruses combined with immune checkpoint therapy for colorectal cancer is a promising treatment option. *Front Immunol* 2022; **13**: 961796 [PMID: 35911673 DOI: 10.3389/fimmu.2022.961796]

37 **Lian W**, Wang Z, Ma Y, Tong Y, Zhang X, Jin H, Zhao S, Yu R, Ju S, Guo X, Huang T, Ding X, Peng M. FABP6 Expression Correlates with Immune Infiltration and Immunogenicity in Colorectal Cancer Cells. *J Immunol Res* 2022; **2022**: 3129765 [PMID: 36033394 DOI: 10.1155/2022/3129765]

38 **Bolzacchini E**, Libera L, Church SE, Sahnane N, Bombelli R, Digiacomo N, Giordano M, Petracco G, Sessa F, Capella C, Furlan D. Tumor Antigenicity and a Pre-Existing Adaptive Immune Response in Advanced BRAF Mutant Colorectal Cancers. *Cancers (Basel)* 2022; **14** [PMID: 36010943 DOI: 10.3390/cancers14163951]

39 **Collienne M**, Loghmani H, Heineman TC, Arnold D. GOBLET: a phase I/II study of pelareorep and atezolizumab +/- chemo in advanced or metastatic gastrointestinal cancers. *Future Oncol* 2022; **18**: 2871-2878 [PMID: 35796248 DOI: 10.2217/fon-2022-0453]

40 **Wu JY**, Song QY, Huang CZ, Shao Y, Wang ZL, Zhang HQ, Fu Z. N7-methylguanosine-related lncRNAs: Predicting the prognosis and diagnosis of colorectal cancer in the cold and hot tumors. *Front Genet* 2022; **13**: 952836 [PMID: 35937987 DOI: 10.3389/fgene.2022.952836]

41 **Li S**, Na R, Li X, Zhang Y, Zheng T. Targeting interleukin-17 enhances tumor response to immune checkpoint inhibitors in colorectal cancer. *Biochim Biophys Acta Rev Cancer* 2022; **1877**: 188758 [PMID: 35809762 DOI: 10.1016/j.bbcan.2022.188758]

42 **Hubbard JM**, Tőke ER, Moretto R, Graham RP, Youssoufian H, Lőrincz O, Molnár L, Csiszovszki Z, Mitchell JL, Wessling J, Tóth J, Cremolini C. Safety and Activity of PolyPEPI1018 Combined with Maintenance Therapy in Metastatic Colorectal Cancer: an Open-Label, Multicenter, Phase Ib Study. *Clin Cancer Res* 2022; **28**: 2818-2829 [PMID: 35472243 DOI: 10.1158/1078-0432.CCR-22-0112]

43 **Li C**, Li T, Niu K, Xiao Z, Huang J, Pan X, Sun Y, Wang Y, Ma D, Xie P, Shuai X, Meng X. Mild phototherapy mediated by manganese dioxide-loaded mesoporous polydopamine enhances immunotherapy against colorectal cancer. *Biomater Sci* 2022; **10**: 3647-3656 [PMID: 35670464 DOI: 10.1039/d2bm00505k]

44 **Yu G**, Wang W, He X, Xu J, Xu R, Wan T, Wu Y. Synergistic Therapeutic Effects of Low Dose Decitabine and NY-ESO-1 Specific TCR-T Cells for the Colorectal Cancer With Microsatellite Stability. *Front Oncol* 2022; **12**: 895103 [PMID: 35774131 DOI: 10.3389/fonc.2022.895103]

45 **Gatenbee CD**, Baker AM, Schenck RO, Strobl M, West J, Neves MP, Hasan SY, Lakatos E, Martinez P, Cross WCH, Jansen M, Rodriguez-Justo M, Whelan CJ, Sottoriva A, Leedham S, Robertson-Tessi M, Graham TA, Anderson ARA. Immunosuppressive niche engineering at the onset of human colorectal cancer. *Nat Commun* 2022; **13**: 1798 [PMID: 35379804 DOI: 10.1038/s41467-022-29027-8]

46 **Qiao G**, Kone LB, Phillips EH, Lee SS, Brown GE, Khetani SR, Thakur A, Lum LG, Prabhakar BS, Maker AV. LIGHT enhanced bispecific antibody armed T-cells to treat immunotherapy resistant colon cancer. *Oncogene* 2022; **41**: 2054-2068 [PMID: 35177811 DOI: 10.1038/s41388-022-02209-w]

47 **Wen H**, Li F, Bukhari I, Mi Y, Guo C, Liu B, Zheng P, Liu S. Comprehensive Analysis of Colorectal Cancer Immunity and Identification of Immune-Related Prognostic Targets. *Dis Markers* 2022; **2022**: 7932655 [PMID: 35401882 DOI: 10.1155/2022/7932655]

48 **Zheng Y**, Fu Y, Wang PP, Ding ZY. Neoantigen: A Promising Target for the Immunotherapy of Colorectal Cancer. *Dis Markers* 2022; **2022**: 8270305 [PMID: 35211210 DOI: 10.1155/2022/8270305]

49 **Di Guida R**, Casillo A, Stellavato A, Kawai S, Ogawa T, Di Meo C, Kawamoto J, Kurihara T, Schiraldi C, Corsaro MM. Capsular polysaccharide from a fish-gut bacterium induces/promotes apoptosis of colon cancer cells *in vitro* through Caspases' pathway activation. *Carbohydr Polym* 2022; **278**: 118908 [PMID: 34973729 DOI: 10.1016/j.carbpol.2021.118908]

50 **Wang Z**, Moresco P, Yan R, Li J, Gao Y, Biasci D, Yao M, Pearson J, Hechtman JF, Janowitz T, Zaidi RM, Weiss MJ, Fearon DT. Carcinomas assemble a filamentous CXCL12-keratin-19 coating that suppresses T cell-mediated immune attack. *Proc Natl Acad Sci U S A* 2022; **119** [PMID: 35046049 DOI: 10.1073/pnas.2119463119]

51 **Kristensen LK**, Christensen C, Alfsen MZ, Cold S, Nielsen CH, Kjaer A. Monitoring CD8a(+) T Cell Responses to Radiotherapy and CTLA-4 Blockade Using [(64)Cu]NOTA-CD8a PET Imaging. *Mol Imaging Biol* 2020; **22**: 1021-1030 [PMID: 32086762 DOI: 10.1007/s11307-020-01481-0]

52 **Martinez NW**, Sánchez A, Diaz P, Broekhuizen R, Godoy J, Mondaca S, Catenaccio A, Macanas P, Nervi B, Calvo M, Court FA. Metformin protects from oxaliplatin induced peripheral neuropathy in rats. *Neurobiol Pain* 2020; **8**: 100048 [PMID: 32490289 DOI: 10.1016/j.ynpai.2020.100048]

53 **Taylor K**, Loo Yau H, Chakravarthy A, Wang B, Shen SY, Ettayebi I, Ishak CA, Bedard PL, Abdul Razak A, R Hansen A, Spreafico A, Cescon D, Butler MO, Oza AM, Lheureux S, Stjepanovic N, Van As B, Boross-Harmer S, Wang L, Pugh TJ, Ohashi PS, Siu LL, De Carvalho DD. An open-label, phase II multicohort study of an oral hypomethylating agent CC-486 and durvalumab in advanced solid tumors. *J Immunother Cancer* 2020; **8** [PMID: 32753546 DOI: 10.1136/jitc-2020-000883]

54 **Yu W**, Sun J, Liu F, Yu S, Hu J, Zhao Y, Wang X, Liu X. Treating Immunologically Cold Tumors by Precise Cancer Photoimmunotherapy with an Extendable Nanoplatform. *ACS Appl Mater Interfaces* 2020; **12**: 40002-40012 [PMID: 32805869 DOI: 10.1021/acsami.0c09469]

55 **Janji B**, Hasmim M, Parpal S, De Milito A, Berchem G, Noman MZ. Lighting up the fire in cold tumors to improve cancer immunotherapy by blocking the activity of the autophagy-related protein PIK3C3/VPS34. *Autophagy* 2020; **16**: 2110-2111 [PMID: 32892693 DOI: 10.1080/15548627.2020.1815439]

56 **Kleeman SO**, Leedham SJ. Not All Wnt Activation Is Equal: Ligand-Dependent versus Ligand-Independent Wnt Activation in Colorectal Cancer. *Cancers (Basel)* 2020; **12** [PMID: 33202731 DOI: 10.3390/cancers12113355]

57 **Biasci D**, Smoragiewicz M, Connell CM, Wang Z, Gao Y, Thaventhiran JED, Basu B, Magiera L, Johnson TI, Bax L, Gopinathan A, Isherwood C, Gallagher FA, Pawula M, Hudecova I, Gale D, Rosenfeld N, Barmpounakis P, Popa EC, Brais R, Godfrey E, Mir F, Richards FM, Fearon DT, Janowitz T, Jodrell DI. CXCR4 inhibition in human pancreatic and colorectal cancers induces an integrated immune response. *Proc Natl Acad Sci U S A* 2020; **117**: 28960-28970 [PMID: 33127761 DOI: 10.1073/pnas.2013644117]

58 **Matsumoto T**, Okayama H, Nakajima S, Saito K, Nakano H, Endo E, Kase K, Ito M, Yamauchi N, Yamada L, Kanke Y,

Onozawa H, Fujita S, Sakamoto W, Saito M, Saze Z, Momma T, Mimura K, Kono K. Tn Antigen Expression Defines an Immune Cold Subset of Mismatch-Repair Deficient Colorectal Cancer. *Int J Mol Sci* 2020; **21** [PMID: 33260328 DOI: 10.3390/ijms21239081]

59 **Ren J**, Xu M, Chen J, Ding J, Wang P, Huo L, Li F, Liu Z. PET imaging facilitates antibody screening for synergistic radioimmunotherapy with a (177)Lu-labeled αPD-L1 antibody. *Theranostics* 2021; **11**: 304-315 [PMID: 33391476 DOI: 10.7150/thno.45540]

60 **Angelova A**, Ferreira T, Bretscher C, Rommelaere J, Marchini A. Parvovirus-Based Combinatorial Immunotherapy: A Reinforced Therapeutic Strategy against Poor-Prognosis Solid Cancers. *Cancers (Basel)* 2021; **13** [PMID: 33477757 DOI: 10.3390/cancers13020342]

61 **Fabian KP**, Malamas AS, Padget MR, Solocinski K, Wolfson B, Fujii R, Abdul Sater H, Schlom J, Hodge JW. Therapy of Established Tumors with Rationally Designed Multiple Agents Targeting Diverse Immune-Tumor Interactions: Engage, Expand, Enable. *Cancer Immunol Res* 2021; **9**: 239-252 [PMID: 33355290 DOI: 10.1158/2326-6066.CIR-20-0638]

62 **Fabian KP**, Padget MR, Fujii R, Schlom J, Hodge JW. Differential combination immunotherapy requirements for inflamed (warm) tumors versus T cell excluded (cool) tumors: engage, expand, enable, and evolve. *J Immunother Cancer* 2021; **9** [PMID: 33602696 DOI: 10.1136/jitc-2020-001691]

63 **Fathi M**, Pustokhina I, Kuznetsov SV, Khayrullin M, Hojjat-Farsangi M, Karpisheh V, Jalili A, Jadidi-Niaragh F. T-cell immunoglobulin and ITIM domain, as a potential immune checkpoint target for immunotherapy of colorectal cancer. *IUBMB Life* 2021; **73**: 726-738 [PMID: 33686787 DOI: 10.1002/iub.2461]

64 **Chen L**, Chen H, Ye J, Ge Y, Wang H, Dai E, Ren J, Liu W, Ma C, Ju S, Guo ZS, Liu Z, Bartlett DL. Intratumoral expression of interleukin 23 variants using oncolytic vaccinia virus elicit potent antitumor effects on multiple tumor models *via* tumor microenvironment modulation. *Theranostics* 2021; **11**: 6668-6681 [PMID: 34093846 DOI: 10.7150/thno.56494]

65 **Fang Y**, He Y, Wu C, Zhang M, Gu Z, Zhang J, Liu E, Xu Q, Asrorov AM, Huang Y. Magnetism-mediated targeting hyperthermia-immunotherapy in "cold" tumor with CSF1R inhibitor. *Theranostics* 2021; **11**: 6860-6872 [PMID: 34093858 DOI: 10.7150/thno.57511]

66 **Lee SJ**, Yang H, Kim WR, Lee YS, Lee WS, Kong SJ, Lee HJ, Kim JH, Cheon J, Kang B, Chon HJ, Kim C. STING activation normalizes the intraperitoneal vascular-immune microenvironment and suppresses peritoneal carcinomatosis of colon cancer. *J Immunother Cancer* 2021; **9** [PMID: 34145029 DOI: 10.1136/jitc-2020-002195]

67 **Chen D**, Bao X, Zhang R, Ding Y, Zhang M, Li B, Zhang H, Li X, Tong Z, Liu L, Zhou X, Wang S, Cheng X, Zheng Y, Ruan J, Fang W, Zhao P. Depiction of the genomic and genetic landscape identifies CCL5 as a protective factor in colorectal neuroendocrine carcinoma. *Br J Cancer* 2021; **125**: 994-1002 [PMID: 34331023 DOI: 10.1038/s41416-021-01501-y]

68 **Huis In 't Veld RV**, Da Silva CG, Jager MJ, Cruz LJ, Ossendorp F. Combining Photodynamic Therapy with Immunostimulatory Nanoparticles Elicits Effective Anti-Tumor Immune Responses in Preclinical Murine Models. *Pharmaceutics* 2021; **13** [PMID: 34575546 DOI: 10.3390/pharmaceutics13091470]

69 **Liu N**, Shan F, Ma M. Strategic enhancement of immune checkpoint inhibition in refractory Colorectal Cancer: Trends and future prospective. *Int Immunopharmacol* 2021; **99**: 108017 [PMID: 34352568 DOI: 10.1016/j.intimp.2021.108017]

70 **Wang Z**, Little N, Chen J, Lambesis KT, Le KT, Han W, Scott AJ, Lu J. Immunogenic camptothesome nanovesicles comprising sphingomyelin-derived camptothecin bilayers for safe and synergistic cancer immunochemotherapy. *Nat Nanotechnol* 2021; **16**: 1130-1140 [PMID: 34385682 DOI: 10.1038/s41565-021-00950-z]

71 **Matsumoto T**, Okayama H, Nakano H, Ito M, Nakajima S, Saito M, Saze Z, Momma T, Mimura K, Kono K. [Immunotherapy Targeting Tumor-Associated Carbohydrate Antigens in Deficient Mismatch Repair Colorectal Cancer]. *Gan To Kagaku Ryoho* 2021; **48**: 1275-1277 [PMID: 34657062]

72 **Baraibar I**, Mirallas O, Saoudi N, Ros J, Salvà F, Tabernero J, Élez E. Combined Treatment with Immunotherapy-Based Strategies for MSS Metastatic Colorectal Cancer. *Cancers (Basel)* 2021; **13** [PMID: 34944931 DOI: 10.3390/cancers13246311]

73 **Gao Y**, Päivinen P, Tripathi S, Domènech-Moreno E, Wong IPL, Vaahtomeri K, Nagaraj AS, Talwelkar SS, Foretz M, Verschuren EW, Viollet B, Yan Y, Mäkelä TP. Inactivation of AMPK Leads to Attenuation of Antigen Presentation and Immune Evasion in Lung Adenocarcinoma. *Clin Cancer Res* 2022; **28**: 227-237 [PMID: 34667030 DOI: 10.1158/1078-0432.CCR-21-2049]

74 **Shang S**, Yang YW, Chen F, Yu L, Shen SH, Li K, Cui B, Lv XX, Zhang C, Yang C, Liu J, Yu JJ, Zhang XW, Li PP, Zhu ST, Zhang HZ, Hua F. TRIB3 reduces CD8(+) T cell infiltration and induces immune evasion by repressing the STAT1-CXCL10 axis in colorectal cancer. *Sci Transl Med* 2022; **14**: eabf0992 [PMID: 34985967 DOI: 10.1126/scitranslmed.abf0992]

75 **Liu Z**, Guo Y, Yang X, Chen C, Fan D, Wu X, Si C, Xu Y, Shao B, Chen Z, Dang Q, Cui W, Han X, Ji Z, Sun Z. Immune Landscape Refines the Classification of Colorectal Cancer With Heterogeneous Prognosis, Tumor Microenvironment and Distinct Sensitivity to Frontline Therapies. *Front Cell Dev Biol* 2021; **9**: 784199 [PMID: 35083217 DOI: 10.3389/fcell.2021.784199]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2023 February 24; 14(2): 89-98

DOI: 10.5306/wjco.v14.i2.89

ISSN 2218-4333 (online)

MINIREVIEWS

New trends in the surgical management of soft tissue sarcoma: The role of preoperative biopsy

Efstathios T Pavlidis, Theodoros E Pavlidis

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Elkady N, Egypt; Wiemer EA, Netherlands

Received: October 21, 2022
Peer-review started: October 21, 2022
First decision: December 26, 2022
Revised: December 26, 2022
Accepted: January 9, 2023
Article in press: January 9, 2023
Published online: February 24, 2023

Efstathios T Pavlidis, Theodoros E Pavlidis, 2nd Propedeutic Department of Surgery, Hippocration Hospital, School of Medicine, Aristotle University of Thessaloniki, Thessaloniki 54642, Greece

Corresponding author: Theodoros E Pavlidis, Doctor, PhD, Full Professor, Surgeon, 2nd Propedeutic Department of Surgery, Hippocration Hospital, School of Medicine, Aristotle University of Thessaloniki, Konstantinoupoleos 49, Thessaloniki 54642, Greece.
pavlidth@auth.gr

Abstract

Soft tissue sarcoma (STS) accounts for 1% of all malignant neoplasms in adults. Their diagnosis and management constitute a challenging target. They originate from the mesenchyme, and 50 subtypes with various cytogenetic profiles concerning soft tissue and bones have been recognized. These tumors mainly affect middle-aged adults but may be present at any age. Half of the patients have metastatic disease at the time of diagnosis and require systemic therapy. Tumors above 3-5 cm in size must be suspected of potential malignancy. A thorough history, clinical examination and imaging that must precede biopsy are necessary. Modern imaging techniques include ultrasound, computed tomography (CT), new magnetic resonance imaging (MRI), and positron emission tomography/CT. MRI findings may distinguish low-grade from high-grade STS based on a diagnostic score (tumor heterogeneity, intratumoral and peritumoral enhancement). A score ≥ 2 indicates a high-grade lesion, and a score ≤ 1 indicates a low-grade lesion. For disease staging, abdominal imaging is recommended to detect early abdominal or retroperitoneal metastases. Liquid biopsy by detecting genomic material in serum is a novel diagnostic tool. A preoperative biopsy is necessary for diagnosis, prognosis and optimal planning of surgical intervention. Core needle biopsy is the most indicative and effective. Its correct performance influences surgical management. An unsuccessful biopsy means the dissemination of cancer cells into healthy anatomical structures that ultimately affect resectability and survival. Complete therapeutic excision (R0) with an acceptable resection margin of 1 cm is the method of choice. However, near significant structures, *i.e.*, vessels, nerves, an R2 resection (macroscopic margin involvement) preserving functionality but having a risk of local recurrence can be an acceptable choice, after informing the patient, to prevent an unavoidable amputation. For borderline resectability of the tumor, neoadjuvant chemo/radiotherapy has a place. Likewise, after surgical excision, adjuvant therapy is indicated, but chemotherapy in nonmetastatic disease is still debatable. The five-year survival

rate reaches up to 55%. Reresection is considered after positive or uncertain resection margins. Current strategies are based on novel chemotherapeutic agents, improved radiotherapy applications to limit local side effects and targeted biological therapy or immunotherapy, including vaccines. Young age is a risk factor for distant metastasis within 6 mo following primary tumor resection. Neoadjuvant radiotherapy lasting 5-6 wk and surgical resection are indicated for high-grade STS (grade 2 or 3). Wide surgical excision alone may be acceptable for patients older than 70 years. However, locally advanced disease requires a multidisciplinary task of decision-making for amputation or limb salvage.

Key Words: Soft tissue sarcoma; Soft tissue tumors; Sarcomas; Oncology; Preoperative biopsy; Surgical management

Core Tip: The diagnosis and treatment of soft tissue sarcoma are multidisciplinary tasks, and wide surgical resection is an absolute necessity. Modern imaging, especially magnetic resonance imaging, is valuable, and preoperative core needle biopsy is the most indicated and effective diagnostic tool. Its correct planning affects surgical management because the opposite means dissemination of cancer cells into healthy anatomical structures influencing resectability and survival. New therapeutic modalities, including chemoradiation, biological agents and immunotherapy, can improve the outcomes of the main surgical management. In any case, the management policy is personalized.

Citation: Pavlidis ET, Pavlidis TE. New trends in the surgical management of soft tissue sarcoma: The role of preoperative biopsy. *World J Clin Oncol* 2023; 14(2): 89-98
URL: https://www.wjgnet.com/2218-4333/full/v14/i2/89.htm
DOI: https://dx.doi.org/10.5306/wjco.v14.i2.89

INTRODUCTION

Soft tissue sarcomas (STSs) are rare tumors that originate from the mesenchyme (embryonic mesoderm) and affect children more often than adults[1]. They represent aggressive lesions accounting for approximately 1% of all adult malignancies and 7% of pediatric neoplasms[2,3]. Their incidence is calculated to affect 4-5 individuals *per* 100000 *per* year in Europe[4]; annually in the United States, there have been approximately 10000 new cases of soft tissue and bone sarcomas[5]. Likewise, in 2019, approximately 13000 new cases of ST and bone sarcomas were recognized in the United States with a main location (60%) in the limbs and trunk[6]. A French nationwide registry showed a continuing increase in incidence that is higher than reported and varies among different countries; however, the pathology evaluation should be made by sarcoma experts to avoid misdiagnosis which can occur in up to 30% of cases[7].

Limb STS has a rather better prognosis than retroperitoneal or pelvic STS. The most predominant pathologic type of STS is liposarcoma and leiomyosarcoma in adults and rhabdomyosarcoma in children[4]. Overall, 50 histopathologic subtypes with various cytogenetic profiles concerning soft tissue and bones have been recognized. The location in the vast majority concerns limbs, trunk, head and less often retro peritoneum and abdominal cavity[2]. These tumors mainly affect middle-aged adults but may be present at any age. Half of the patients have metastatic disease (first in the lungs and second in the liver) and intermediate-high grade STS at the time of diagnosis and require systemic therapy. The 5-year overall survival is approximately 55%[7-9].

Tumors above 3-5 cm in size, fast growing, deeply located, solid, cumbersome, possibly accompanied by palpable lymph nodes and causing or not causing pain must be suspected of potential malignancy. Then, an imaging evaluation [ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI)] is required and must precede biopsy[10]. Preoperative biopsy (percutaneous core needle, preferably) is a crucial diagnostic tool since there has been progress in planning multimodality management, which ensures improved outcomes[6,11]. The Ki-67 proliferation index has been proposed as a prognostic biomarker that, in addition to survival prediction, may determine the indication for lung or liver metastasectomy in carefully selected patients, improving the treatment[12].

Surgical intervention constitutes the cornerstone of management aiming at therapeutic wide excision with adequate margins[2]. Recurrence occurs in up to 50% of cases after surgery, mainly in the lungs[6]. Any effort must be made for limb salvage to avoid amputation. Neoadjuvant or adjuvant radiotherapy or chemotherapy has contributed to current progress[2]. Likewise, immunotherapy is a promising novel

therapeutic option[1]. Young age is the only known risk factor for distant metastasis within 6 mo following curative resection[13]. Diabetes mellitus has a negative influence on the clinical outcome after therapeutic excision of STS[14].

Modern imaging, including positron emission tomography (PET)/CT and regular follow-up (every 3 mo for the first 3 years, every 6 mo for the following 2 years and then once every year for the next 10 years), nomograms and artificial intelligence for local recurrence or distant metastasis after surgery, have assisted further and improved the outcome[4,12].

In this narrative review, we highlight the current data on the diagnosis and treatment of STS, providing comprehensive, complete and modern knowledge to manage them.

DIAGNOSIS

A thorough history, clinical examination and imaging are necessary requirements. Modern imaging techniques include US, CT, new MRI, and PET/CT. Imaging findings of limb STS correlate with the histopathologic findings[15]. According to the United Kingdom guidelines for the management of STS, any soft tissue lump more than 5 cm in size and, most importantly, increasing rapidly in size or painful must be considered malignant until assessed otherwise on imaging. Therefore, immediate US is mandatory. If the lesion seems to be benign, then the investigation will be terminated. Otherwise, a CT will follow and then MRI if it is indicated. When positive for malignancy or equivocal imaging findings exist, a preoperative biopsy will always be performed to confirm the diagnosis of STS[8], as described in detail below.

However, MRI is currently the method of choice. It provides accurate location, architecture, and vascularization of the tumor and determines the relationships with neighboring vital anatomic structures to plan the operative strategy and the extent of resection[16]. MRI findings may also distinguish low-grade from high-grade STS based on a diagnostic score (tumor heterogeneity, intratumoral and peritumoral enhancement). A score of 2 or 3 indicates a high-grade lesion, and a score of 0 or 1 indicates a low-grade lesion[16] . MRI radiomics and machine learning may accurately predict the tumor grade[17]. MRI is useful not only because it can guide preoperative biopsy[6] but also because high-grade sarcomas need neoadjuvant chemoradiation therapy[16]. It is known that preoperative biopsy may underassess the real grade of the definite complete specimen pathology due to the heterogeneity of STS[17]. Additionally, novel multiparametric MRI has provided promising results for the selection of patients who need neoadjuvant radiotherapy[9]. Preoperative imaging assessment of margin infiltration degree is essential for STS prognosis. MRI using the radiomics mode is a novel promising tool[18]. In addition, MRI using a deep learning radiomics nomogram can accurately predict preoperative lung metastases[19].

Preoperative imaging, pathologic subtypes and molecular findings are crucial. Mutations in the tumor suppressor genes, *i.e.*, the *Rb1* gene (retinoblastoma 1) and *TP53* gene (tumor protein 53) can exist [12]. Liquid biopsy by detecting genomic material in serum is a novel diagnostic, prognostic and staging tool. Genetic material mainly from blood but also from other body fluids (cerebrospinal fluid, saliva, urine, or feces) may be useful for the discovery of circulating tumor cells, cell-free DNA, exosomes, or metabolites[2]. These biomarkers provide valuable information regarding the tumor genetic profile and the status of the disease to ensure optimal monitoring and to identify the mechanisms implicating treatment resistance. The preliminary results are promising despite the technical difficulties, and liquid biopsy could replace invasive tissue biopsy in the future[20]. The heterogeneity of sarcomas poses further prognostic limitations. Furthermore, circulating tumor noncoding RNAs are promising biomarkers. However, all the above research efforts are in the preclinical stage for sarcomas[21]. In addition, the genomic profile may determine the adjuvant treatment choices[22].

For disease staging, the following imaging is necessary: (1) CT chest to detect lung metastases, since they are the most common metastatic involvement; and (2) CT abdomen to detect early hepatic or pelvic metastasis, particularly for the lower limb location of the primary focus to detect retroperitoneal lymph node involvement[4,8]. Based on relevant indications, the following imaging is recommended: (1) Whole-body scintigraphy for possible bone metastases; (2) CT or preferably MRI brain for possible metastases; (3) Whole-body MRI may be useful for occult metastases[8]; and (4) Likewise, for this reason, 18F-Fluoro-2-deoxyglucose PET/CT is currently more often in use[3]. However, it is absolutely indicated before making decisions for amputation or after postoperative recurrence[8]. After neoadjuvant radiation therapy, approximately 20% of patients with limb and trunk STS require a change in the management strategy because of distant lung metastases. The followed scheme includes a total dose of 50 Gy in 25 sessions of 2 Gy within a period of five weeks and then surgical intervention after an elapse of approximately ten weeks. Therefore, chest CT is reasonable for restaging after such a long time of 15 wk[23].

Histopathologic diagnosis is based on morphological, immunohistochemical and molecular pathologic features[10]. It should be made according to the latest World Health Organization classification of soft tissue tumors. Liposarcoma, leiomyosarcoma, myxofibrosarcoma, pleomorphic undifferentiated sarcoma and synovial sarcoma constitute 75% of all STSs[15]. A second opinion of a

pathologist expert may be valuable. There are three malignancy grades based on differentiation, necrosis and mitotic rate according to the Federation of the French Cancer Centres histological grading criteria for STS[8,10]. These parameters are scored 1 to 3 for differentiation and mitotic index and 0 to 2 for necrosis. A 3-grade system is obtained by summing the scores obtained for each of these 3 parameters, as shown in Table 1[8]. The Ki-67 proliferation index grading system may be useful for the evaluation of the histological grade of STS[24]. The staging of STS is based on the Tumor-Node-Metastasis classification system according to the American Joint Committee on Cancer 8th edition, as shown in Table 2[25].

PREOPERATIVE BIOPSY

Diagnosis and management of STS should be performed by experienced centers[26]. A preoperative biopsy is necessary to establish the diagnosis after the imaging evaluation. Imaging should be performed first to avoid any interference with the anatomical integrity of the region by the biopsy manipulations. The biopsy ensures diagnosis of histological type and staging, predicts the biological behavior of the tumor, indicates the need for preoperative (neoadjuvant) or even intraoperative radiation treatment, and neoadjuvant systemic chemotherapy, determines the best planning of the operative strategy and offers better patient information (reassuring) by weighing the risks and expectations[8,10,11,27]. A preoperative frozen section for immediate diagnosis is not recommended. It has no practical value since the regular review of a core needle biopsy (CNB) will safely establish the diagnosis [10].

The primary method of the first choice is CNB with needles of 14-18 gauges. Several needle samples (4-10) are required to increase the maximum chance of a correct diagnosis[6,8,10,28]. It was performed under imaging guidance (US, CT) and achieved adequate specimens for complete histopathologic evaluation along with immunohistochemical assays. Most cases are performed under local anesthesia, but sedation may be required in some cases. The complications (hemorrhage or infection) are minimal [11]. A large series from Royal Marsden Hospital United Kingdom including 530 cases of CNB performed under local anesthesia showed that it was diagnostic in 93% of cases, needed to be repeated in 7% of cases, had a complication rate of 0.4%, had a diagnostic accuracy rate of 97.6% in distinguishing STS from benign lesions (sensitivity of 96.3%, specificity of 99.4%, positive predictive value of 99.5%, negative predictive value of 95.1%) and had a grade accuracy rate of 86.3%[29]. Adequate tissue samples must be obtained in different directions within the tumor through a single skin incision; to avoid rare needle tract recurrence, the selection of the biopsy site should be planned so that it is included in the subsequent resection, if required[29].

Preoperative CT-guided CNB is accurate and valuable for intraabdominal and retroperitoneal sarcomas[30]. A recent study from the United States based on the National Cancer Database including 2620 patients who underwent surgery for nonmetastatic retroperitoneal sarcoma showed that preoperative biopsy (performed in 42.4% of cases) was proven useful with better outcomes and improved survival[31].

Fine needle aspiration does not provide tissue samples and offers cytologic rather than histologic information. Its utility is limited only to recurrence cases of an already known STS[11]. Open biopsy techniques include incisional biopsy by removing a small part of the tumor. It is associated with a 2% possibility of complications (inflammation, hematoma) but most importantly dissemination of malignant cells and delay in the treatment. Its rare indication is limited to failure of CNB. Excisional biopsy by whole tumor removal does not have any place in suspected STS but only in superficial small soft tissue tumors (less than 2 cm in size), which have minimal malignant potential. The basic principles of open biopsy are meticulous hemostasis and avoidance of drain placement[8,11].

MANAGEMENT

The management of abdominal STS at an experienced center with a multidisciplinary approach provides improved outcomes and better prognosis[32]. The initial referral, even based on suspicion, to such a center is of great importance to ensure the optimal chance in accurate diagnosis and proper management[22]. Surgery is the standard treatment and must be performed by an experienced surgeon. Wide excision with adequate margins at least 1 cm or even 2 cm, free of involvement, constitutes the operative target to achieve a residual zero (R0) resection[2,33-35]. However, vital neighboring anatomical structures may sometimes restrict the resection margin, and microscopic infiltration may be found within it (R1 resection). Further treatment is needed for positive resection margins to restrict recurrence[36]. It has been reported that high-grade tumors have a negative effect on overall survival, but resection margins do not. The 5-year overall survival was 71.1% for R0 resection and 70.2% for R1 resection[37]. Lymph node metastases are rare in STS, and sentinel lymph node biopsy and lymphadenectomy are limited and debatable[38]. Neoadjuvant radiotherapy and wide excision have been widely used but are associated with wound complications[39], reaching up to 39%[40]. This rate is limited to

Table 1 Federation of the French Cancer Centres histological grading criteria

Differentiation (score)	Necrosis (score)	Mitotic count (score)
Well (1)	Absent (0)	$n < 10^1$ (1)
Moderate (2)	< 50% (1)	$n = 10–19^1$ (2)
Poor (anaplastic) (3)	≥ 50% (2)	$n \geq 20^1$ (3)

[1]Number of mitoses *per* 10 high power fields.
After summing the three scores, grade 1 is defined as a total score of 2 or 3; grade 2 as a total score of 4 or 5; and grade 3 as a total score of 6 to 8.

Table 2 American Joint Committee on Cancer classification and staging for soft tissue sarcoma, 8th Edition

TNM classification	Stage
T1: Tumor ≤ 5 cm	IA: T1; N0; M0; G1
T2: Tumor > 5 cm and ≤ 10 cm	IB: T2, T3, T4; N0; M0; G1
T3: Tumor > 10 cm and ≤ 15 cm	II: T1; N0; M0; G2/3
T4: Tumor > 15 cm	IIIA: T2; N0; M0; G2/3
N0: No regional lymph node metastasis or unknown lymph node status	IIIB: T3, T4; N0; M0; G2/3
N1: Regional lymph node metastasis	IV: Any T; N1; M0; any G Any T; any N; M1; any G
M0: No distant metastasis	
M1: Distant metastasis	

G expresses the histological grading sum score. TNM: Tumor-Node-Metastasis.

half at experienced centers[40]. Neoadjuvant radiotherapy tends to replace adjuvant radiotherapy and is strongly recommended[41,42]. Concurrent neoadjuvant chemoradiation therapy increases the chance of R0 resection[43]. For high-grade deep tumors, T2 or more (stage II or III), wide excision and adjuvant radiation therapy (external beam 60-76 Gy) for local control is the indicated policy[2,10,44,45]. Limb sparing surgery combined with radiotherapy is the current preferable method for such tumors of limbs [46]. It must precede preoperative traditional fractioned radiotherapy of 50-50.4 Gy with a daily dose of 1.8-2 Gy over 5-6 wk[47-49]. Generally, a daily dose > 2.2 Gy is usually hypofractionated radiotherapy [47]. Novel techniques for radiotherapy, including intensity-modulated radiation therapy, proton beam therapy, intraoperative electron radiotherapy and postoperative brachytherapy (*via* catheters in the surgical field), promise to decrease the side effects of standard radiotherapy while achieving better local control[2,8,10,50].

Chemotherapy with doxorubicin alone or in combination with ifosfamide is the basic scheme as a neo-adjuvant or adjuvant[2]. However, there have been conflicting aspects for adjuvant chemotherapy after R0 resection[51]. Tyrosine-kinase inhibitors (pazopanib, sunitinib, imatinib) have been indicated in some specific types[2]. In advanced metastatic cases, gemcitabine has been used in combination with docetaxel, vinorelbine, or dacarbazine, but with limited results[2]. Isolated hyperthermic limb perfusion (IHLP) with tumor necrosis factor-alpha and melphalan is another proposed option for limb STS[2,52]. A recent nationwide multicenter study from the Netherlands showed that in unresectable limb STS, preoperative IHLP or neoadjuvant radiotherapy avoided both amputations with acceptable oncological outcomes[53]. Wide surgical excision alone without neoadjuvant or adjuvant chemotherapy may be acceptable for patients over 70 years of age, providing comparable survival[54]. Frail very elderly patients (more than 80 years old) can tolerate an operative intervention for limb STS well[55,56].

Overall, unplanned excisions were 18.2% among 2187 primary operations for STS in the Netherlands Cancer Registry database[57]. It is known that unplanned surgical excision is related to an increased risk of local recurrence despite any adjuvant oncologic therapy[58]. For this reason, reresection is an option after positive or uncertain resection margins, but it is associated with increased morbidity and residual disease, which requires complete information for the patient[59]. However, a recent large study from Japan including 4483 operations (4128 planned excisions and 355 unplanned excisions) for limb STS showed that additional excision after unplanned excision was not associated with increased mortality and local recurrence compared to planned excision[60]. Furthermore, in the case of R1 or even R2 resection, reresection in combination with perioperative radiotherapy must be considered[61]. Surgical resection of lung metastases has improved overall survival (49 mo median and 42% 5-year). However, R1 resection of the primary tumor and ≥ 2 metastases decrease it[62]. Pulmonary metastasectomy

improves the prognosis compared to conservative treatment[63].

The comprehensive assessment of recurrence risk has led to an increasing number of personalized management tools[64], including surgical operation, radiotherapy, novel promising targeted biological agents and immunotherapy (monoclonal antibodies, cellular therapies with modified T cells and natural killer cells, or vaccines)[1,2,12,65,66]. For retroperitoneal STS, aggressive surgical management has been recommended, since it showed satisfactory results for primary tumors but not for recurrence[67-70]. Likewise, for abdominal STS, surgery is the standard treatment[71]. Operative intervention and radiotherapy maximize local control[72]. For abdominal wall STS, extensive surgery is indicated for local control despite the rate but acceptability of incisional hernia[73]. For metastatic STS, systemic therapy and local control by surgical resection, usually or recently by stereotactic body radiation therapy, have been recommended[74]. MRI-guided radiotherapy is another recent alternative modality [75]. For advanced retroperitoneal liposarcoma, the most common subtype of retroperitoneal STS, treatment based on targetable molecular pathways may be the future perspective[76].

A recent systematic review showed that patients with hepatic, abdominal or retroperitoneal metastasis undergoing metastasectomy have a survival benefit for a long period of time compared with those undergoing chemotherapy[4]. A multicenter retrospective cohort study from the United States using the National Cancer Database including 8953 cases showed that younger adult patients under 40 years old had a notable proportion (14.3%) of limb STS and more challenging management. They received chemotherapy more often than radiotherapy *vs* older patients[77]. A study including 1124 patients with distant metastases at diagnosis, stage IV STS, from the United States National Cancer Database showed that metastasectomy after resection of the primary site increased survival[78]. In any case, regardless of the subsequent kind of metastasis management, primary tumor resection is necessary to improve survival[79].

Visceral obesity is common in retroperitoneal and trunk sarcoma, and it has a negative effect on surgical results but not on oncologic outcomes[80]. A recent international multicenter study using clinical data as prognostic factors of 493 patients with STS found that increased modified Glasgow prognostic score (used in various malignancies and based on preoperative C-reactive protein and albumin levels to calculate a score from 0 to 2), tumor size, grade, neutrophil/lymphocyte ratio, and recurrence were associated with reduced survival[81]. Likewise, another study found a predictive effect on survival of retroperitoneal STS using body mass index, total protein serum levels and blood white cell count by performing prognostic models[82].

The 5-year survival for limb and trunk STS was found to be 71.6% in local recurrence-free patients, 75.7% in metastasis-free and 84.7% in disease-specific[83]. The 3-year overall survival for head and neck STS was 68%, for disease specific 71% and recurrence free 61%. Higher tumor grade and tumor size greater than 5 cm were associated with reduced disease-specific survival[26].

CONCLUSION

Any suspected soft tissue lump above 5 cm in size must be investigated thoroughly, first by US and CT. For further detailed information, if needed, modern MRI prevails among the imaging modalities and constitutes the method of the first option. Preoperative CNB, always after imaging, is essential in confirming the diagnosis and determining the staging with prognosis and the optimal planning of the management policy. Liquid biopsy and genomic profiling will likely be useful in diagnosis, prognosis and treatment. A multidisciplinary approach is valuable and mandatory. Wide surgical excision with an acceptable healthy margin of 1 cm is the method of choice in management. In locally borderline tumors affecting limb vessels or nerves, modern neoadjuvant or adjuvant chemoradiation therapy may ensure limb savings by downstaging the tumor, thus avoiding amputation. Additionally, this therapy in the advanced metastatic stage improves surgical outcomes after mandatory primary tumor excision. Novel targeted biological agents and immunotherapy may contribute further. Detailed follow-up for a long time is recommended because of the outstanding possibility of recurrence, in which the chance of reresection or stereotactic radiotherapy exists. However, in any case, the management of STS should be personalized and performed by an expert team.

FOOTNOTES

Author contributions: Pavlidis TE designed research, contributed new analytic tools, analyzed data and review; Pavlidis ET performed research, analyzed data review and wrote the paper.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country/Territory of origin: Greece

ORCID number: Efstathios T Pavlidis 0000-0002-7282-8101; Theodoros E Pavlidis 0000-0002-8141-1412.

S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

REFERENCES

1 **Ghosn M**, El Rassy E, Kourie HR. Immunotherapies in sarcoma: Updates and future perspectives. *World J Clin Oncol* 2017; **8**: 145-150 [PMID: 28439495 DOI: 10.5306/wjco.v8.i2.145]
2 **Gómez J**, Tsagozis P. Multidisciplinary treatment of soft tissue sarcomas: An update. *World J Clin Oncol* 2020; **11**: 180-189 [PMID: 32355640 DOI: 10.5306/wjco.v11.i4.180]
3 **Benz MR**, Crompton JG, Harder D. PET/CT Variants and Pitfalls in Bone and Soft Tissue Sarcoma. *Semin Nucl Med* 2021; **51**: 584-592 [PMID: 34238508 DOI: 10.1053/j.semnuclmed.2021.06.009]
4 **Smolle MA**, Leithner A, Bernhardt GA. Abdominal metastases of primary extremity soft tissue sarcoma: A systematic review. *World J Clin Oncol* 2020; **11**: 74-82 [PMID: 32133276 DOI: 10.5306/wjco.v11.i2.74]
5 **Blank AT**, Larson BM, Shaw S, Wakefield CJ, King T, Jones KB, Randall RL. National Comprehensive Cancer Network guidelines compliance of a sarcoma service: A retrospective review. *World J Clin Oncol* 2020; **11**: 389-396 [PMID: 32874952 DOI: 10.5306/wjco.v11.i6.389]
6 **Roland CL**. Soft Tissue Tumors of the Extremity. *Surg Clin North Am* 2020; **100**: 669-680 [PMID: 32402308 DOI: 10.1016/j.suc.2020.02.015]
7 **de Pinieux G**, Karanian M, Le Loarer F, Le Guellec S, Chabaud S, Terrier P, Bouvier C, Batistella M, Neuville A, Robin YM, Emile JF, Moreau A, Larousserie F, Leroux A, Stock N, Lae M, Collin F, Weinbreck N, Aubert S, Mishellany F, Charon-Barra C, Croce S, Doucet L, Quintin-Rouet I, Chateau MC, Bazille C, Valo I, Chetaille B, Ortonne N, Brouchet A, Rochaix P, Demuret A, Ghnassia JP, Mescam L, Macagno N, Birtwisle-Peyrottes I, Delfour C, Angot E, Pommepuy I, Ranchere D, Chemin-Airiau C, Jean-Denis M, Fayet Y, Courrèges JB, Mesli N, Berchoud J, Toulmonde M, Italiano A, Le Cesne A, Penel N, Ducimetiere F, Gouin F, Coindre JM, Blay JY; NetSarc/RePPS/ResSos and French Sarcoma Group-Groupe d'Etude des Tumeurs Osseuses (GSF-GETO) networks. Nationwide incidence of sarcomas and connective tissue tumors of intermediate malignancy over four years using an expert pathology review network. *PLoS One* 2021; **16**: e0246958 [PMID: 33630918 DOI: 10.1371/journal.pone.0246958]
8 **Dangoor A**, Seddon B, Gerrand C, Grimer R, Whelan J, Judson I. UK guidelines for the management of soft tissue sarcomas. *Clin Sarcoma Res* 2016; **6**: 20 [PMID: 27891213 DOI: 10.1186/s13569-016-0060-4]
9 **Kershaw L**, Forker L, Roberts D, Sanderson B, Shenjere P, Wylie J, Coyle C, Kochhar R, Manoharan P, Choudhury A. Feasibility of a multiparametric MRI protocol for imaging biomarkers associated with neoadjuvant radiotherapy for soft tissue sarcoma. *BJR Open* 2021; **3**: 20200061 [PMID: 35707756 DOI: 10.1259/bjro.20200061]
10 **Casali PG**, Blay JY; ESMO/CONTICANET/EUROBONET Consensus Panel of experts. Soft tissue sarcomas: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2010; **21** Suppl 5: v198-v203 [PMID: 20555081 DOI: 10.1093/annonc/mdq209]
11 **Tuttle R**, Kane JM 3rd. Biopsy techniques for soft tissue and bowel sarcomas. *J Surg Oncol* 2015; **111**: 504-512 [PMID: 25663366 DOI: 10.1002/jso.23870]
12 **Brennan MF**, Singer S. Five decades of sarcoma care at Memorial Sloan Kettering Cancer Center. *J Surg Oncol* 2022; **126**: 896-901 [PMID: 36087086 DOI: 10.1002/jso.27032]
13 **Tsuchie H**, Emori M, Nagasawa H, Murahashi Y, Mizushima E, Shimizu J, Yamashita T, Miyakoshi N. Risk Factors of Early Distant Metastasis After Primary Tumor Treatment in Soft Tissue Sarcoma. *In Vivo* 2022; **36**: 2260-2264 [PMID: 36099122 DOI: 10.21873/invivo.12954]
14 **Stelzl A**, Aziz F, Riedl JM, Posch F, Smolle MA, Stojakovic T, Terbuch A, Pichler M, Bergovec M, Leithner A, Liegl-Atzwanger B, Stotz M, Gerger A, Sourij H, Szkandera J. Diabetes mellitus is independently associated with adverse clinical outcome in soft tissue sarcoma patients. *Sci Rep* 2020; **10**: 12438 [PMID: 32709908 DOI: 10.1038/s41598-020-69237-y]
15 **Ramakrishnan K**, Levy N, Goldbach A, Nagarathinam R, Ali S, Ling S, Jonnalagadda P. Imaging of soft tissue sarcomas of the extremities with radiologic-pathologic correlation. *Curr Probl Diagn Radiol* 2022; **51**: 868-877 [PMID: 35654634 DOI: 10.1067/j.cpradiol.2022.04.005]
16 **Boudabbous S**, Hamard M, Saiji E, Gorican K, Poletti PA, Becker M, Neroladaki A. What morphological MRI features enable differentiation of low-grade from high-grade soft tissue sarcoma? *BJR Open* 2022; **4**: 20210081 [PMID: 36105415 DOI: 10.1259/bjro.20210081]
17 **Xu W**, Hao D, Hou F, Zhang D, Wang H. Soft Tissue Sarcoma: Preoperative MRI-Based Radiomics and Machine Learning May Be Accurate Predictors of Histopathologic Grade. *AJR Am J Roentgenol* 2020; **215**: 963-969 [PMID: 32755226 DOI: 10.2214/AJR.19.22147]
18 **Lee S**, Jung JY, Nam Y, Jung CK, Lee SY, Lee J, Shin SH, Chung YG. Diagnosis of Marginal Infiltration in Soft Tissue Sarcoma by Radiomics Approach Using T2-Weighted Dixon Sequence. *J Magn Reson Imaging* 2022 [PMID: 35808915 DOI: 10.1002/jmri.28331]
19 **Liang HY**, Yang SF, Zou HM, Hou F, Duan LS, Huang CC, Xu JX, Liu SL, Hao DP, Wang HX. Deep Learning

Radiomics Nomogram to Predict Lung Metastasis in Soft-Tissue Sarcoma: A Multi-Center Study. *Front Oncol* 2022; **12**: 897676 [PMID: 35814362 DOI: 10.3389/fonc.2022.897676]

20 **van der Laan P**, van Houdt WJ, van den Broek D, Steeghs N, van der Graaf WTA. Liquid Biopsies in Sarcoma Clinical Practice: Where Do We Stand? *Biomedicines* 2021; **9** [PMID: 34680432 DOI: 10.3390/biomedicines9101315]

21 **Wei J**, Liu X, Li T, Xing P, Zhang C, Yang J. The new horizon of liquid biopsy in sarcoma: the potential utility of circulating tumor nucleic acids. *J Cancer* 2020; **11**: 5293-5308 [PMID: 32742476 DOI: 10.7150/jca.42816]

22 **Kirchberg J**, Blum SFU, Pablik J, Herold S, Hoffmann RT, Baretton G, Weitz J. [Preoperative diagnostics and typing of abdominal soft tissue sarcomas]. *Chirurg* 2022; **93**: 5-15 [PMID: 34757436 DOI: 10.1007/s00104-021-01528-0]

23 **Acem I**, Schultze BTA, Schoonbeek A, van Houdt WJ, van de Sande MAJ, Visser JJ, Grünhagen DJ, Verhoef C. The added value of chest imaging after neoadjuvant radiotherapy for soft tissue sarcoma of the extremities and trunk wall: A retrospective cohort study. *Eur J Surg Oncol* 2022; **48**: 1543-1549 [PMID: 35393169 DOI: 10.1016/j.ejso.2022.03.231]

24 **Tanaka K**, Hasegawa T, Nojima T, Oda Y, Mizusawa J, Fukuda H, Iwamoto Y. Prospective evaluation of Ki-67 system in histological grading of soft tissue sarcomas in the Japan Clinical Oncology Group Study JCOG0304. *World J Surg Oncol* 2016; **14**: 110 [PMID: 27091124 DOI: 10.1186/s12957-016-0869-6]

25 **Cates JMM**. The AJCC 8th Edition Staging System for Soft Tissue Sarcoma of the Extremities or Trunk: A Cohort Study of the SEER Database. *J Natl Compr Canc Netw* 2018; **16**: 144-152 [PMID: 29439175 DOI: 10.6004/jnccn.2017.7042]

26 **Roos JH**, Mäkitie AA, Tarkkanen J, Ilmarinen TT. Pretreatment tumor sampling and prognostic factors in patients with soft-tissue sarcoma of the head and neck. *Eur Arch Otorhinolaryngol* 2022; **279**: 3147-3155 [PMID: 34773167 DOI: 10.1007/s00405-021-07162-0]

27 **MacGillis KJ**, Heaberlin J, Mejia A. Clinical Decision Making for a Soft Tissue Hand Mass: When and How to Biopsy. *J Hand Surg Am* 2018; **43**: 1123-1129 [PMID: 29908925 DOI: 10.1016/j.jhsa.2018.03.032]

28 **Young R**, Snow H, Hendry S, Mitchell C, Slavin J, Schlicht S, Na L, Hofman MS, Gyorki DE. Correlation between percutaneous biopsy and final histopathology for retroperitoneal sarcoma: a single-centre study. *ANZ J Surg* 2020; **90**: 497-502 [PMID: 32064728 DOI: 10.1111/ans.15723]

29 **Strauss DC**, Qureshi YA, Hayes AJ, Thway K, Fisher C, Thomas JM. The role of core needle biopsy in the diagnosis of suspected soft tissue tumours. *J Surg Oncol* 2010; **102**: 523-529 [PMID: 20872955 DOI: 10.1002/jso.21600]

30 **Luca Alatzides G**, Luisa Steinberg H, Schildhaus HU, Hamacher R, Kaths M, Grueneisen J, Treckmann J, Bauer S, Umutlu L, Schaarschmidt B. Is preoperative CT-guided biopsy a valuable tool in the diagnostic workup of patients with visceral and retroperitoneal sarcoma? *Eur J Radiol* 2022; **155**: 110470 [PMID: 35985092 DOI: 10.1016/j.ejrad.2022.110470]

31 **Straker RJ 3rd**, Song Y, Shannon AB, Marcinak CT, Miura JT, Fraker DL, Karakousis GC. Preoperative Biopsy in Patients with Retroperitoneal Sarcoma: Usage and Outcomes in a National Cohort. *Ann Surg Oncol* 2021; **28**: 6868-6879 [PMID: 33591480 DOI: 10.1245/s10434-021-09691-8]

32 **Acem I**, Smit MM, Verhoef C, van Houdt WJ, Haas RL, van der Hage JA, Grünhagen DJ, van de Sande MAJ. Management of Soft Tissue Sarcomas in Extremities: Variation in Treatment Recommendations and Surveillance According to Specialty and Continent. *Ann Surg Oncol* 2021; **28**: 7923-7936 [PMID: 33970372 DOI: 10.1245/s10434-021-09946-4]

33 **Patel A**, Kane JM 3rd. Wide Resection of Extremity/Truncal Soft Tissue Sarcomas. *Surg Clin North Am* 2022; **102**: 551-565 [PMID: 35952687 DOI: 10.1016/j.suc.2022.05.002]

34 **Kheiran A**, Eastley NC, Hanson JR, McCulloch TA, Allen PE, Ashford RU. The importance of the early appropriate management of foot and ankle soft tissue sarcomas - experiences of a regional sarcoma service. *Foot (Edinb)* 2022; **50**: 101866 [PMID: 35219135 DOI: 10.1016/j.foot.2021.101866]

35 **Gronchi A**. Surgery in soft tissue sarcoma: the thin line between a surgical or more conservative approach. *Future Oncol* 2021; **17**: 3-6 [PMID: 34107729 DOI: 10.2217/fon-2021-0449]

36 **Matheron G**, Ardakani A, Nasir A, Gikas P. Positive Margins Following Excision of Primary Bone & Soft Tissue Tumours in a Tertiary Centre and the Impact on Patient Outcomes. *Cureus* 2022; **14**: e21235 [PMID: 35186531 DOI: 10.7759/cureus.21235]

37 **Shafiq MB Sr**, Rafi I, Shoaib A, Ali S, Iqbal F, Latif T, Mushtaq U. The Outcome of Extremity Soft Tissue Sarcomas in Terms of Resection Margins: A Study From a Cancer Dedicated Center. *Cureus* 2022; **14**: e26086 [PMID: 35875266 DOI: 10.7759/cureus.26086]

38 **Witt RG**, Cope B, Erstad DJ, Chiang YJ, Nassif EF, Scally CP, Torres KE, Hunt KK, Feig BW, Roland CL, Keung EZ. Sentinel Lymph Node Biopsy and Formal Lymphadenectomy for Soft Tissue Sarcoma: A Single Center Experience of 86 Consecutive Cases. *Ann Surg Oncol* 2022; **29**: 7092-7100 [PMID: 35501583 DOI: 10.1245/s10434-022-11803-x]

39 **Kungwengwe G**, Clancy R, Vass J, Slade R, Sandhar S, Dobbs TD, Bragg TWH. Preoperative versus Post-operative Radiotherapy for Extremity Soft tissue Sarcoma: a Systematic Review and Meta-analysis of Long-term Survival. *J Plast Reconstr Aesthet Surg* 2021; **74**: 2443-2457 [PMID: 34266806 DOI: 10.1016/j.bjps.2021.05.043]

40 **Ellison C**, King DM, Neilson JC, Wooldridge A, Charlson JA, Hackbarth DA, Johnstone C, Bedi M. Preoperative Radiation Performed at a Nonsarcoma Center May Lead to Increased Wound Complications Following Resection in Patients With Soft Tissue Sarcomas. *Am J Clin Oncol* 2021; **44**: 619-623 [PMID: 34753886 DOI: 10.1097/COC.0000000000000870]

41 **Van Meekeren M**, Fiocco M, Ho VKY, Bovée JVMG, Gelderblom H, Haas RL. Patterns of Perioperative Treatment and Survival of Localized, Resected, Intermediate- or High-Grade Soft Tissue Sarcoma: A 2000-2017 Netherlands Cancer Registry Database Analysis. *Sarcoma* 2021; **2021**: 9976122 [PMID: 34335076 DOI: 10.1155/2021/9976122]

42 **Salerno KE**, Alektiar KM, Baldini EH, Bedi M, Bishop AJ, Bradfield L, Chung P, DeLaney TF, Folpe A, Kane JM, Li XA, Petersen I, Powell J, Stolten M, Thorpe S, Trent JC, Voermans M, Guadagnolo BA. Radiation Therapy for Treatment of Soft Tissue Sarcoma in Adults: Executive Summary of an ASTRO Clinical Practice Guideline. *Pract Radiat Oncol* 2021; **11**: 339-351 [PMID: 34326023 DOI: 10.1016/j.prro.2021.04.005]

43 **Attal J**, Cabarrou B, Valentin T, Nesseler JP, Stoeckle E, Ducassou A, Filleron T, Le Guellec S, Boulet B, Vogin G, Ferron G, Moyal EC, Delannes M, Chevreau C. Evaluation of two modalities of perioperative treatment in the management

of extremity and truncal soft tissue sarcomas: neoadjuvant concurrent chemoradiotherapy and sequential treatment. *Strahlenther Onkol* 2021; **197**: 1051-1062 [PMID: 34673991 DOI: 10.1007/s00066-021-01847-5]

44 **Lawrenz JM**, Johnson SR, Zhu K, McKeon M, Moran CP, Vega J, Hajdu KS, Norris JP, Luo LY, Shinohara ET, Cates JMM, Rubin BP, Reith JD, Halpern JL, Mesko NW, Schwartz HS, Nystrom LM, Holt GE. Adjuvant Radiation after Primary Resection of Atypical Lipomatous Tumors of the Extremity Reduces Local Recurrence but Increases Complications: A Multicenter Evaluation. *Sarcoma* 2022; **2022**: 2091677 [PMID: 36046749 DOI: 10.1155/2022/2091677]

45 **Levy A**, Honoré C, Dumont S, Bourdais R, Cavalcanti A, Faron M, Ngo C, Haddag-Miliani L, Le Cesne A, Mir O, Le Péchoux C. [Preoperative versus postoperative radiotherapy in soft tissue sarcomas: State of the art and perspectives]. *Bull Cancer* 2021; **108**: 868-876 [PMID: 34246458 DOI: 10.1016/j.bulcan.2021.03.012]

46 **Cammelli S**, Cortesi A, Buwenge M, Zamagni A, Ferioli M, Ghigi G, Romeo A, Morganti AG. The role of radiotherapy in adult soft tissues sarcoma of the extremities. *Eur J Orthop Surg Traumatol* 2021; **31**: 1583-1596 [PMID: 33954820 DOI: 10.1007/s00590-021-02990-6]

47 **Roohani S**, Ehret F, Kobus M, Flörcken A, Märdian S, Striefler JK, Rau D, Öllinger R, Jarosch A, Budach V, Kaul D. Preoperative hypofractionated radiotherapy for soft tissue sarcomas: a systematic review. *Radiat Oncol* 2022; **17**: 159 [PMID: 36104789 DOI: 10.1186/s13014-022-02072-9]

48 **Kaiser D**, Schelm M, Gerber C, Brown ML, Müller DA. The effect of preoperative radiotherapy on surgical resectability, tumor volume and the necrosis rate of soft tissue sarcomas: A retrospective single-center analysis. *Surg Oncol* 2021; **39**: 101668 [PMID: 34653769 DOI: 10.1016/j.suronc.2021.101668]

49 **Dei Tos AP**, Bonvalot S, Haas R. Evolution in the management of soft tissue sarcoma: classification, surgery and use of radiotherapy. *Expert Rev Anticancer Ther* 2020; **20**: 3-13 [PMID: 32293209 DOI: 10.1080/14737140.2020.1753509]

50 **Laughlin BS**, Golafshar MA, Ahmed S, Prince M, Anderson JD, Vern-Gross T, Seetharam M, Goulding K, Petersen I, DeWees T, Ashman JB. Early Experience Using Proton Beam Therapy for Extremity Soft Tissue Sarcoma: A Multicenter Study. *Int J Part Ther* 2022; **9**: 1-11 [PMID: 35774491 DOI: 10.14338/IJPT-21-00037.1]

51 **Eraslan E**, Ilhan Gulesen A, Yildiz F, Tufan G, Yalcintas Arslan U, Alkis N. The effect of adjuvant chemotherapy on the survival of patients with high-risk soft tissue sarcomas: Single center experience. *J BUON* 2021; **26**: 2169-2175 [PMID: 34761631]

52 **Lindner LH**, Blay JY, Eggermont AMM, Issels RD. Perioperative chemotherapy and regional hyperthermia for high-risk adult-type soft tissue sarcomas. *Eur J Cancer* 2021; **147**: 164-169 [PMID: 33684876 DOI: 10.1016/j.ejca.2021.02.002]

53 **van Praag VM**, Fiocco M, Bleckman RF, van Houdt WJ, Haas RLM, Verhoef C, Grunhagen DJ, van Ginkel RJ, Bonenkamp JJ, van de Sande MAJ. The oncological outcomes of isolated limb perfusion and neo-adjuvant radiotherapy in soft tissue sarcoma patients - A nationwide multicenter study. *Eur J Surg Oncol* 2022 [PMID: 36085118 DOI: 10.1016/j.ejso.2022.08.018]

54 **Aoki Y**, Tome Y, Oshiro H, Katsuki R, Tamaki T, Wada N, Karube K, Nishida K. Wide excision alone for elderly patients aged > 70 years old with soft tissue sarcomas. *Medicine (Baltimore)* 2022; **101**: e30127 [PMID: 36086737 DOI: 10.1097/MD.0000000000030127]

55 **Sivarajah G**, Davies E, Hurley A, Strauss DC, Smith MJF, Hayes AJ. Frailty in Very Elderly Patients is Not Associated with Adverse Surgical or Oncological Outcomes in Extremity Surgery for Soft Tissue Sarcoma. *Ann Surg Oncol* 2022; **29**: 3982-3990 [PMID: 35118523 DOI: 10.1245/s10434-021-11292-4]

56 **Hartley LJ**, AlAqeel M, Kurisunkal VJ, Evans S. Outcomes of soft-tissue sarcoma in nonagenarians. *Bone Joint J* 2022; **104-B**: 177-182 [PMID: 34969278 DOI: 10.1302/0301-620X.104B1.BJJ-2021-0761.R1]

57 **Melis AS**, Vos M, Schuurman MS, van Dalen T, van Houdt WJ, van der Hage JA, Schrage YM, Been LB, Bonenkamp JB, Bemelmans MHA, Grünhagen DJ, Verhoef C, Ho VKY; Dutch Sarcoma Group (DSG). Incidence of unplanned excisions of soft tissue sarcomas in the Netherlands: A population-based study. *Eur J Surg Oncol* 2022; **48**: 994-1000 [PMID: 34848102 DOI: 10.1016/j.ejso.2021.11.123]

58 **Grignol VP**, Lopez-Aguiar AG. The Implications of an Unplanned Sarcoma Excision (the "Whoops" Operation). *Surg Clin North Am* 2022; **102**: 529-538 [PMID: 35952685 DOI: 10.1016/j.suc.2022.04.002]

59 **Traweek RS**, Martin AN, Rajkot NF, Guadagnolo BA, Bishop AJ, Lazar AJ, Keung EZ, Torres KE, Hunt KK, Feig BW, Roland CL, Scally CP. Re-excision After Unplanned Excision of Soft Tissue Sarcoma is Associated with High Morbidity and Limited Pathologic Identification of Residual Disease. *Ann Surg Oncol* 2023; **30**: 480-489 [PMID: 36085392 DOI: 10.1245/s10434-022-12359-6]

60 **Nakamura T**, Kawai A, Hagi T, Asanuma K, Sudo A. A comparison of clinical outcomes between additional excision after unplanned and planned excisions in patients with soft-tissue sarcoma of the limb : a propensity matching cohort study. *Bone Joint J* 2021; **103-B**: 1809-1814 [PMID: 34847719 DOI: 10.1302/0301-620X.103B12.BJJ-2021-0037.R1]

61 **Le Péchoux C**, Llacer C, Sargos P, Moureau-Zabotto L, Ducassou A, Sunyach MP, Biston MC, Thariat J. Conformal radiotherapy in management of soft tissue sarcoma in adults. *Cancer Radiother* 2022; **26**: 377-387 [PMID: 34961656 DOI: 10.1016/j.canrad.2021.11.023]

62 **Lee RM**, Ethun CG, Gamboa AC, Turgeon MK, Tran T, Poultsides G, Grignol V, Bedi M, Mogal H, Clarke CN, Tseng J, Roggin KK, Chouliaras K, Votanopoulos K, Krasnick BA, Fields RC, Oskouei SV, Monson DK, Reimer NB, Maithel SK, Pickens A, Cardona K. A novel preoperative risk score to guide patient selection for resection of soft tissue sarcoma lung metastases: An analysis from the United States Sarcoma Collaborative. *J Surg Oncol* 2021; **124**: 1477-1484 [PMID: 34374088 DOI: 10.1002/jso.26635]

63 **Gusho CA**, Seder CW, Lopez-Hisijos N, Blank AT, Batus M. Pulmonary metastasectomy in bone and soft tissue sarcoma with metastasis to the lung. *Interact Cardiovasc Thorac Surg* 2021; **33**: 879-884 [PMID: 34516633 DOI: 10.1093/icvts/ivab178]

64 **Acem I**, van de Sande MAJ. Prediction tools for the personalized management of soft-tissue sarcomas of the extremity. *Bone Joint J* 2022; **104-B**: 1011-1016 [PMID: 36047022 DOI: 10.1302/0301-620X.104B9.BJJ-2022-0647]

65 **Banks LB**, D'Angelo SP. The Role of Immunotherapy in the Management of Soft Tissue Sarcomas: Current Landscape and Future Outlook. *J Natl Compr Canc Netw* 2022; **20**: 834-844 [PMID: 35830892 DOI: 10.6004/jnccn.2022.7027]

66 **Yuan J**, Li X, Yu S. Molecular targeted therapy for advanced or metastatic soft tissue sarcoma. *Cancer Control* 2021; **28**:

10732748211038424 [PMID: 34844463 DOI: 10.1177/10732748211038424]
67 **Lv A**, Li Y, Li ZW, Mao LL, Tian XY, Hao CY. Treatment algorithm and surgical outcome for primary and recurrent retroperitoneal sarcomas: A long-term single-center experience of 242 cases. *J Surg Oncol* 2022; **126**: 1288-1298 [PMID: 35943840 DOI: 10.1002/jso.27040]
68 **Siew CCH**, Cardona K, van Houdt WJ. Management of recurrent retroperitoneal sarcomas. *Eur J Surg Oncol* 2022 [PMID: 35810040 DOI: 10.1016/j.ejso.2022.06.008]
69 **Danieli M**, Swallow CJ, Gronchi A. How to treat liposarcomas located in retroperitoneum. *Eur J Surg Oncol* 2022 [PMID: 35623985 DOI: 10.1016/j.ejso.2022.04.020]
70 **Willis F**, Schneider M. [Retroperitoneal soft tissue sarcoma: surgical management]. *Chirurg* 2022; **93**: 16-26 [PMID: 34596706 DOI: 10.1007/s00104-021-01506-6]
71 **Djafarrian R**, Zingg T, Digklia A, Becce F, Özsahin EM, La Rosa S, Demartines N, Matter M. [Management of abdominal soft tissue sarcomas]. *Rev Med Suisse* 2021; **17**: 1172-1176 [PMID: 34133095]
72 **Rust DJ**, Kato T, Yoon SS. Treatment for local control of retroperitoneal and pelvis sarcomas: A review of the literature. *Surg Oncol* 2022; **43**: 101814 [PMID: 35834940 DOI: 10.1016/j.suronc.2022.101814]
73 **Neuberg M**, Mir O, Levy A, Sourrouille I, Dumont S, Haddag-Miliani L, Ngo C, Mihoubi F, Rimareix F, Le Péchoux C, Adam J, Honart JF, Ceribelli C, Le Cesne A, Leymarie N, Faron M, Honoré C. Surgical management of soft tissue tumors of the abdominal wall: A retrospective study in a high-volume sarcoma center. *J Surg Oncol* 2021; **124**: 679-686 [PMID: 34120344 DOI: 10.1002/jso.26566]
74 **Gutkin PM**, von Eyben R, Chin A, Donaldson SS, Oh J, Jiang A, Ganjoo KN, Avedian RS, Bruzoni M, Steffner RJ, Moding EJ, Hiniker SM. Local Control Outcomes Using Stereotactic Body Radiation Therapy or Surgical Resection for Metastatic Sarcoma. *Int J Radiat Oncol Biol Phys* 2022; **114**: 771-779 [PMID: 35643255 DOI: 10.1016/j.ijrobp.2022.05.017]
75 **Blitzer GC**, Yadav P, Morris ZS. The Role of MRI-Guided Radiotherapy for Soft Tissue Sarcomas. *J Clin Med* 2022; **11** [PMID: 35207317 DOI: 10.3390/jcm11041042]
76 **Casadei L**, de Faria FCC, Lopez-Aguiar A, Pollock RE, Grignol V. Targetable Pathways in the Treatment of Retroperitoneal Liposarcoma. *Cancers (Basel)* 2022; **14** [PMID: 35326514 DOI: 10.3390/cancers14061362]
77 **Seldon C**, Shrivastava G, Al-Awady A, Asher D, Ramey S, Fernandez M, Dooley S, Kwon D, Zhao W, Goel N, Diwanji T, Subhawong T, Trent J, Yechieli R. Variation in Management of Extremity Soft-Tissue Sarcoma in Younger vs Older Adults. *JAMA Netw Open* 2021; **4**: e2120951 [PMID: 34415314 DOI: 10.1001/jamanetworkopen.2021.20951]
78 **Abugideiri M**, Janopaul-Naylor J, Switchenko J, Tian S, Read W, Press R, Oskouei S, Reimer N, Ferris M, Cassidy RJ, Behera M, Monson D, Landry J, Godette KD, Patel PR. Impact of Metastasectomy and Aggressive Local Therapy in Newly Diagnosed Metastatic Soft Tissue Sarcoma: An Analysis of the NCDB. *Ann Surg Oncol* 2022; **29**: 649-659 [PMID: 34272614 DOI: 10.1245/s10434-021-10466-4]
79 **Matsuoka M**, Onodera T, Yokota I, Iwasaki K, Matsubara S, Hishimura R, Kondo E, Iwasaki N. Surgical resection of primary tumor in the extremities improves survival for metastatic soft-tissue sarcoma patients: a population-based study of the SEER database. *Clin Transl Oncol* 2021; **23**: 2474-2481 [PMID: 34060011 DOI: 10.1007/s12094-021-02646-1]
80 **Boyle EA**, Elliott JA, McIntyre TV, Barnes ME, Donlon NE, Umair M, Gillis AE, Ridgway PF. Body composition is associated with operative and oncologic outcomes in the management of retroperitoneal and trunk soft tissue sarcoma. *Am J Surg* 2022; **223**: 729-737 [PMID: 34389158 DOI: 10.1016/j.amjsurg.2021.08.005]
81 **Spence S**, Doonan J, Farhan-Alanie OM, Chan CD, Tong D, Cho HS, Sahu MA, Traub F, Gupta S; The MPGS Study Group. Does the modified Glasgow Prognostic Score aid in the management of patients undergoing surgery for a soft-tissue sarcoma? *Bone Joint J* 2022; **104-B**: 168-176 [PMID: 34969280 DOI: 10.1302/0301-620X.104B1.BJJ-2021-0874.R1]
82 **Yao Y**, Wang Z, Yong L, Yao Q, Tian X, Wang T, Yang Q, Hao C, Zhou T. Longitudinal and time-to-event modeling for prognostic implications of radical surgery in retroperitoneal sarcoma. *CPT Pharmacometrics Syst Pharmacol* 2022; **11**: 1170-1182 [PMID: 35758865 DOI: 10.1002/psp4.12835]
83 **Morii T**, Anazawa U, Sato C, Iwata S, Nakagawa M, Endo M, Nakamura T, Ikuta K, Nishida Y, Nakayama R, Udaka T, Kawamoto T, Kito M, Sato K, Imanishi J, Akiyama T, Kobayashi H, Nagano A, Outani H, Toki S, Nishisho T, Sasa K, Suehara Y, Kawano H, Ueda T, Morioka H. Dedifferentiated liposarcoma in the extremity and trunk wall: A multi-institutional study of 132 cases by the Japanese Musculoskeletal Oncology Group (JMOG). *Eur J Surg Oncol* 2022 [PMID: 36088237 DOI: 10.1016/j.ejso.2022.08.024]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com