

# World Journal of *Clinical Oncology*

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



## Contents

Monthly Volume 14 Number 2 February 24, 2023

## REVIEW

- 40 Hereditary cancer syndromes  
*Imyanitov EN, Kuligina ES, Sokolenko AP, Suspitsin EN, Yanus GA, Iyevleva AG, Ivantsov AO, Aleksakhina SN*
- 69 Significance of music therapy in treating depression and anxiety disorders among people with cancer  
*Eseadi C, Ngwu MO*

## MINIREVIEWS

- 81 Therapeutic challenge for immunotherapy targeting cold colorectal cancer: A narrative review  
*Ma SX, Li L, Cai H, Guo TK, Zhang LS*
- 89 New trends in the surgical management of soft tissue sarcoma: The role of preoperative biopsy  
*Pavlidis ET, Pavlidis TE*

**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**

Production Editor: Xiang-Di Zhang; Production Department Director: Xu Guo; Editorial Office Director: Yu-Jie Ma.

**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.wjnet.com/2218-4333/editorialboard.htm>

**PUBLICATION DATE**

February 24, 2023

**COPYRIGHT**

© 2023 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjnet.com/bpg/gerinfo/240>

**PUBLICATION ETHICS**

<https://www.wjnet.com/bpg/GerInfo/288>

**PUBLICATION MISCONDUCT**

<https://www.wjnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>



## 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](mailto: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

©The Author(s) 2023. Published by Baishideng Publishing Group Inc. All rights reserved.

**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].

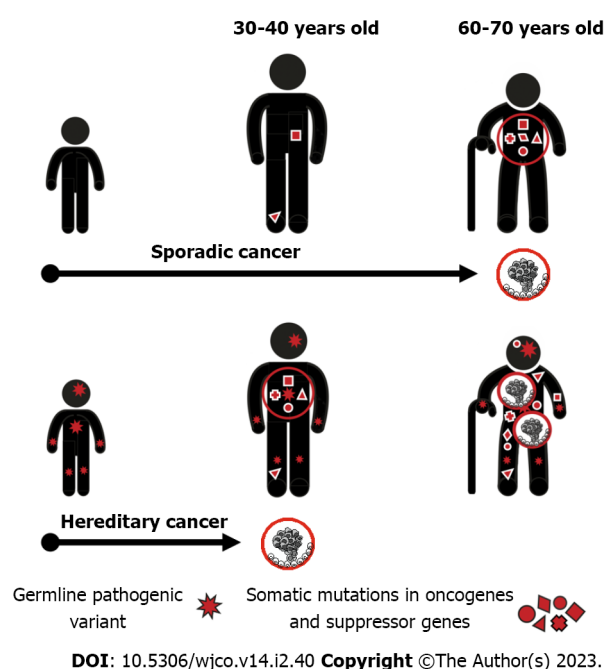
Earlier studies on HCSs usually assumed that almost all carriers of pathogenic alleles are destined to develop cancer, *i.e.* they considered mainly families and genes with almost 100% disease penetrance. The development of genetic technologies and the availability of large collections of cancer patients 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



**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]. *BRIPI* 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].

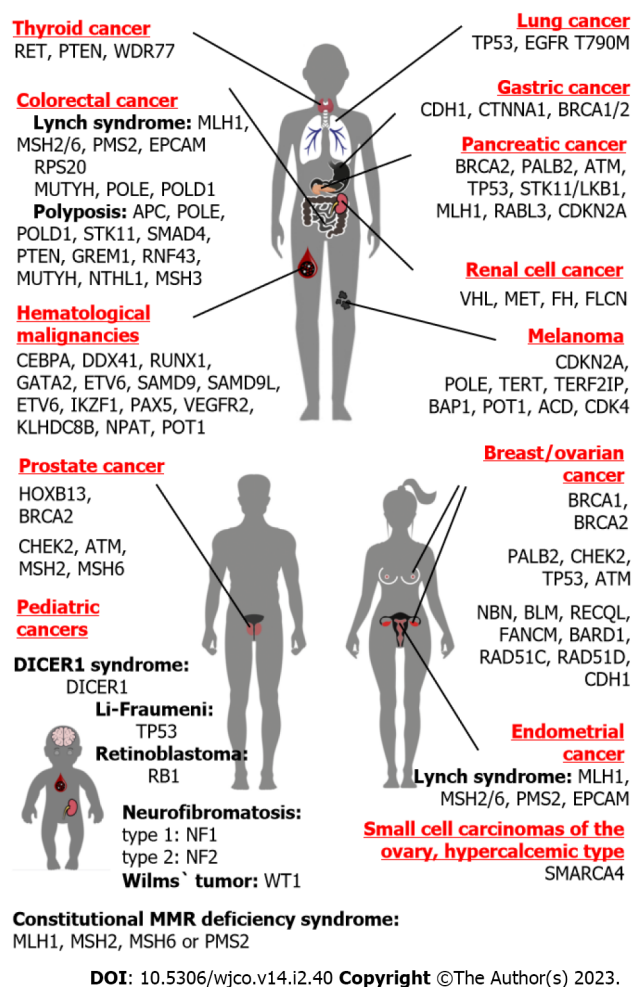
**Table 1 Health impact of major hereditary cancer genes: Frequency of pathogenic variants in non-selected subjects and oncological patients**

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

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 transmethylease 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 *SMARCB1* 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].

---

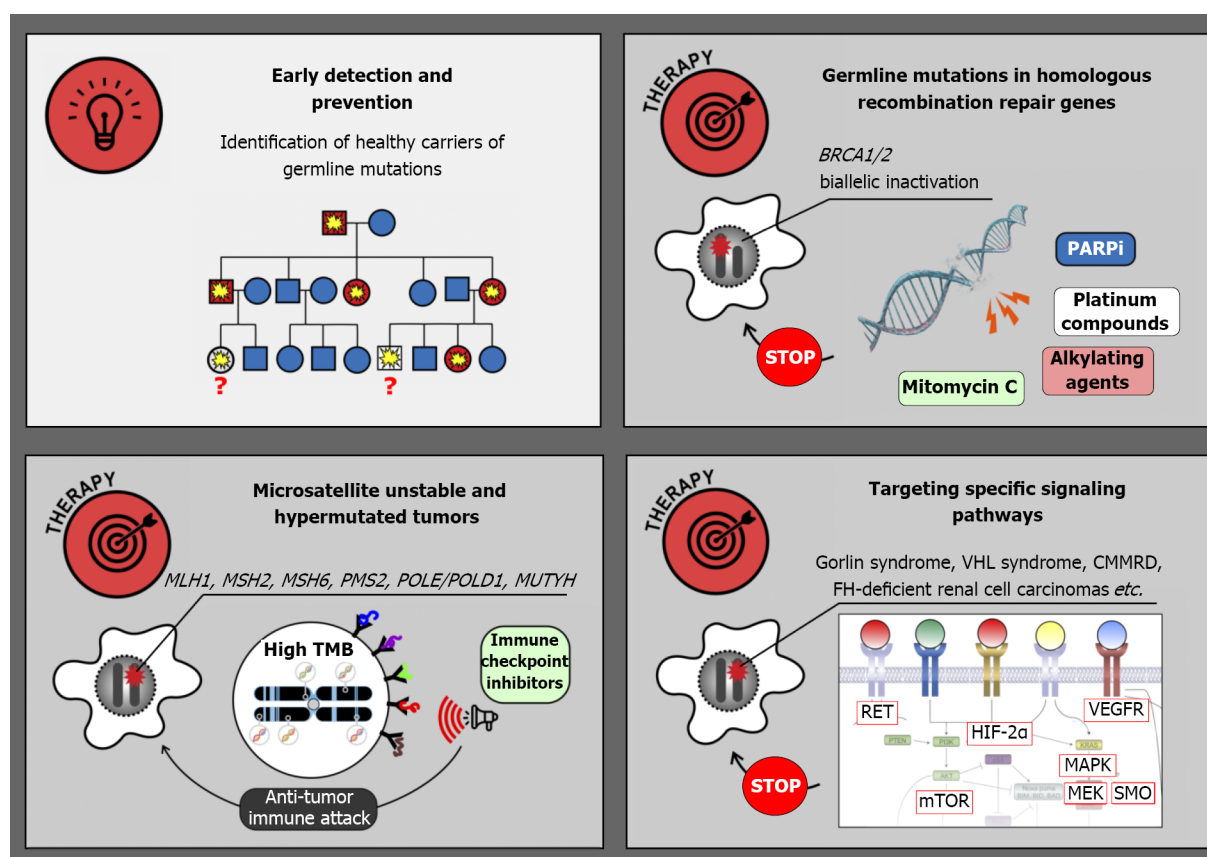
## **MANAGEMENT OF HEREDITARY TUMORS**

---

### **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.           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------|----------------|
| <i>BRCA1/2</i> -driven carcinomas and their phenocopies                                                                                                                                                       | <i>BRCA1/2</i> 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; <i>POLD1/POLE</i> -deficient cancers; <i>MUTYH</i> -associated colorectal carcinomas; tumors in patients with CMMRD syndrome) | High tumor mutation burden resulting in excessive number of neoantigens                           | Immune checkpoint inhibitors                                             | [199-206]      |
| <i>RET</i> -associated malignancies                                                                                                                                                                           | <i>RET</i> tyrosine kinase                                                                        | <i>RET</i> inhibitors                                                    | [207-209]      |
| Neurofibromatosis, type 1                                                                                                                                                                                     | Upregulation of RAS/RAF/MEK pathway due to <i>NF1</i> 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-2 $\alpha$ due to <i>VHL</i> gene inactivation                               | HIF-2 $\alpha$ inhibitors                                                | [216]          |

HIF-2 $\alpha$ : Hypoxia inducible factor-2 $\alpha$ ; PARPi: Poly (ADP-ribose) polymerase inhibitors; CMMRD: Constitutional mismatch repair deficiency syndrome; MEK: Mitogen-activated protein kinase; SMO: Smoothed; 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 syndrome[214,215]. There are promising results of the treatment of

VHL syndrome related tumors by hypoxia-inducible factor-2 $\alpha$  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.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution NonCommercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <https://creativecommons.org/licenses/by-nc/4.0/>

**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

- 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]
- 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]
- Valle L, de Voer RM, Goldberg Y, Sijrsen 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]
- Peltonmäki 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]
- 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, Herrera 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, Anttonenkov 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, Georgoulas V, Gil F, Giles GG, Glendon G, Garcia EBG, Alnæs GIG, Guénel P, Hadjisavvas A, Haerle 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, Hoening 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, Prajzandanc 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, Thanastithichai 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, Garcia-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]
- 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, Lindstrom 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, Martjanov 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.32383](#)]

- 10.1002/jc.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, Laloo 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**, Jooisse 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, Benitez 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, Castela 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, Manoochhehri 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-Askmalin 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, Ejlersen 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 García 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, Ziłowska-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, Gschwanter-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, Kemal 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, Pykäs 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, Mannerman 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: [25000000](#) DOI: [10.1056/NEJMoa1310000](#)]

- 25099575 DOI: [10.1056/NEJMoa1400382](https://doi.org/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 Oudenhoove 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](https://pubmed.ncbi.nlm.nih.gov/32546565/) DOI: [10.1136/jmedgenet-2019-106739](https://doi.org/10.1136/jmedgenet-2019-106739)]
- 52 **Sokolenko AP**, Iyevleva AG, Preobrazhenskaya EV, Mitushkina NV, Aysheva 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](https://pubmed.ncbi.nlm.nih.gov/21815139/) DOI: [10.1002/ijc.26342](https://doi.org/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, Swiec 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](https://pubmed.ncbi.nlm.nih.gov/25915596/) DOI: [10.1038/ng.3284](https://doi.org/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, Jensen 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](https://pubmed.ncbi.nlm.nih.gov/28033443/) DOI: [10.1001/jamaoncol.2016.5592](https://doi.org/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](https://pubmed.ncbi.nlm.nih.gov/23028338/) DOI: [10.1371/journal.pgen.1002894](https://doi.org/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](https://pubmed.ncbi.nlm.nih.gov/33326660/) DOI: [10.1002/humu.24158](https://doi.org/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](https://pubmed.ncbi.nlm.nih.gov/31754952/) DOI: [10.1007/s10549-019-05492-6](https://doi.org/10.1007/s10549-019-05492-6)]
- 58 **Koivuluoma S**, Tervasmäki A, Kauppila S, Winqvist R, Kumpula T, Kuismäki 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](https://pubmed.ncbi.nlm.nih.gov/33279852/) DOI: [10.1016/j.ejca.2020.10.033](https://doi.org/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](https://pubmed.ncbi.nlm.nih.gov/31719101/) DOI: [10.1158/0008-5472.CAN-19-0728](https://doi.org/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](https://pubmed.ncbi.nlm.nih.gov/28486781/) DOI: [10.1002/ijc.30771](https://doi.org/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](https://pubmed.ncbi.nlm.nih.gov/30240537/) DOI: [10.1002/humu.23656](https://doi.org/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](https://pubmed.ncbi.nlm.nih.gov/29529297/) DOI: [10.1093/jnci/djy001](https://doi.org/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](https://pubmed.ncbi.nlm.nih.gov/34709361/) DOI: [10.1001/jamaoncol.2021.4398](https://doi.org/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, Calvillo 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](https://pubmed.ncbi.nlm.nih.gov/32560361/) DOI: [10.3390/cancers12061598](https://doi.org/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-Osae 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](https://pubmed.ncbi.nlm.nih.gov/21642682/) DOI: [10.1001/jama.2011.743](https://doi.org/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, Möslin G, Mecklin JP, Nielsen M, Möller 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-Garyayev 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**, Capellà 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, Kinnarsley 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**, Akhaphkina TA, Ivantsov AO, Preobrazhenskaya EV, Aleksakhina SN, Bizin IV, Sokolenko AP, Mitushkina 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, Scouler 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 A, 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, Pykäs 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 A, 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, Mebrouk 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, Permeth 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, Hebbinger 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, Wucherpennig 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, Ejlersen B, Engel C, Evans DG, Feliubadaló 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, Spiegelman 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, Arden-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, Cadranet 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, Mitushkina 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, Dhooze M, Tlemsani C, Léna H, Teulé A, Álvarez JV, Raimbourg J, Hiret S, Lacroix L, Menéndez M, Saldaña J, Brunet J, Lianes P, Coupiet I, Auclin E, Recondo G, Friboulet L, Adam J, Green E, Planchard D, Frébourg T, Capella 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, Sherif 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/nrcclinonc.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 Askmalin 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, Cavaleiro 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, Susptsin 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, Pajtlar 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, Schreiber 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, Mikaelisdottir 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, Klcio 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, Brugieres 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 **Klcio 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, Pastorcak 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.mmrrev.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, Royle 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, Kovácsázi 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 L, 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/encr.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, Ledoine 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, Anstas 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, Aljelaifi 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, Leblouille 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, Sudhama 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, Tamake 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, Aysheva SN, Preobrazhenskaya EV, Gorodnova TV, Yanus GA, Togo AV, Cherdynseva 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, Vrolijk 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**, Ejlersen B, Albrechtsen A, Bergsten E, Bjerregaard P, Hansen T, Myrhaøj 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, Ejlersen 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, Rehms 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, Velthuis 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](#)]



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](mailto:bpgoffice@wjgnet.com)

**Help Desk:** <https://www.f6publishing.com/helpdesk>

<https://www.wjgnet.com>

