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REVIEW

Hereditary cancer syndromes

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Abstract

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

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

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

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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

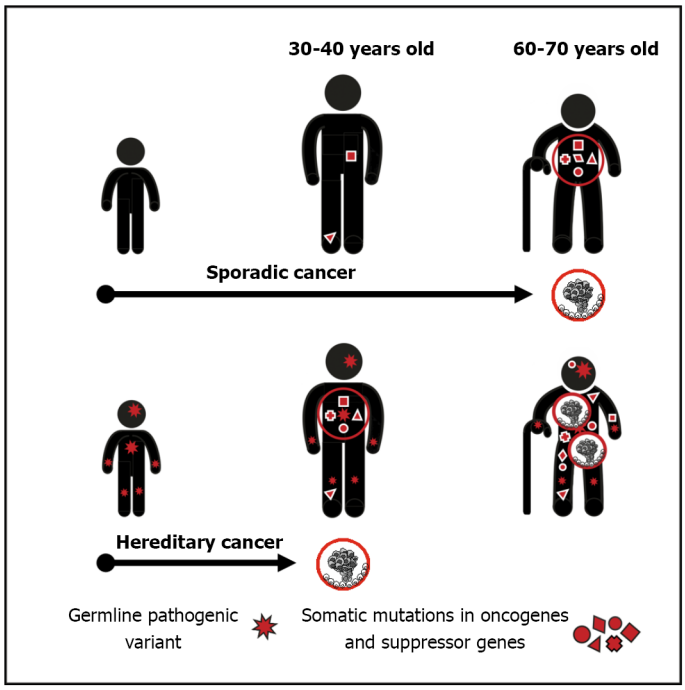

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Figure 1 Mechanisms of hereditary cancer predisposition. Single cancer-driving mutation is usually fully compensated, therefore carriers of germline pathogenic variants may remain healthy during a prolonged period of time. However, since every cell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

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

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

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

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

MAJOR TYPES OF HCSS

Breast and ovarian carcinomas

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

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

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

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

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

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

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

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

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

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

Colorectal tumors

The accumulation of multiple cases of colorectal cancer (CRC) in pedigrees was systematically described in 1967 by Lynch *et al*[73]. Lynch syndrome, also called hereditary non-polyposis colorectal cancer (HNPCC), is the best-known genetic cause of CRC predisposition. HNPCC is associated with heterozygous germline inactivation of genes involved in DNA mismatch repair (MMR), namely *MLH1*, *MSH2*, *MSH6* or *PMS2* (Table 1). In addition, some Lynch syndrome patients carry deletion of the last portion of epithelial cell adhesion molecule (*EPCAM*), a gene located upstream to the *MSH2* genomic segment. This deletion results in the loss of transcription of 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

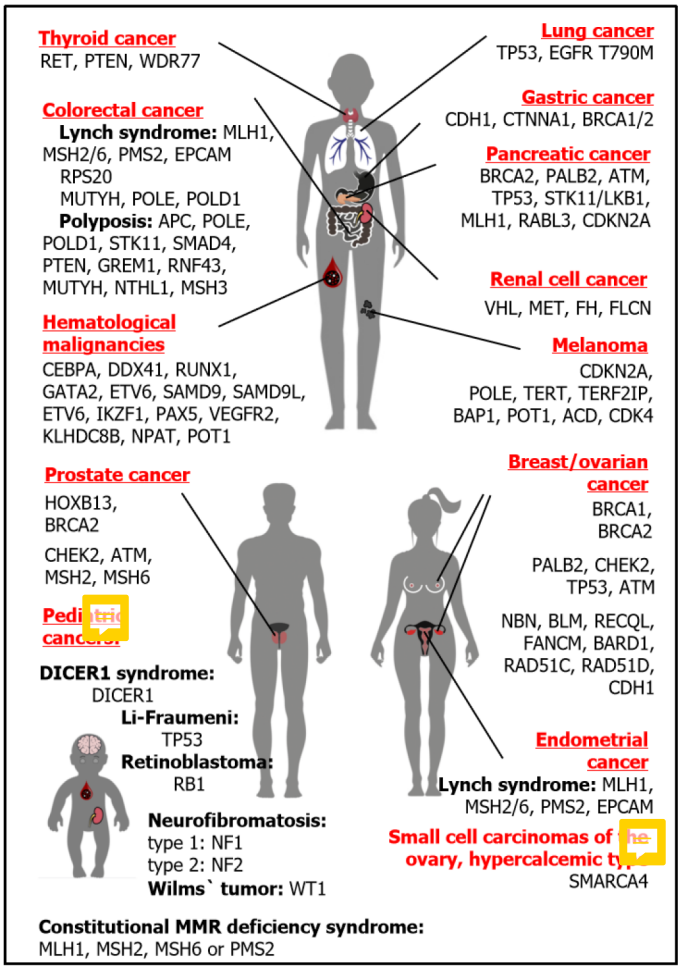

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Figure 2 Main hereditary cancer genes and organs at risk. This figure illustrates major hereditary cancer types observed in females, males, adults of both genders, and children.

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

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

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

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

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

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

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

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

Gastric cancer

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

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

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

Pancreatic cancer

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

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

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

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

Prostate cancer

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

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

Renal cell cancer

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

Lung cancer

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

Melanoma

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

Multiple endocrine neoplasia

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

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

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

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

Li-Fraumeni syndrome

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

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

PTEN hamartoma tumor syndrome

PTEN hamartoma tumor syndrome (PHTS) is manifested by multiple benign and malignant tumors affecting breast, thyroid, endometrium, skin, kidney, colon and some other organs[151-153]. It is caused by heterozygous inactivating PVs in the *PTEN* gene, which is involved in the negative regulation of phosphatidylinositol 3-kinase/AKT/mechanistic target of rapamycin (mTOR) pathways 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, Cowden, PJSs, neurofibromatosis, *RET*-related malignancies, *etc.* Expectedly, NGS analysis of non-selected patients with pediatric cancers revealed elevated frequency of PVs in known cancer-predisposing genes[161,162].

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

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

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

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

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

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

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

Hematological malignancies

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

MANAGEMENT OF HCSS

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].

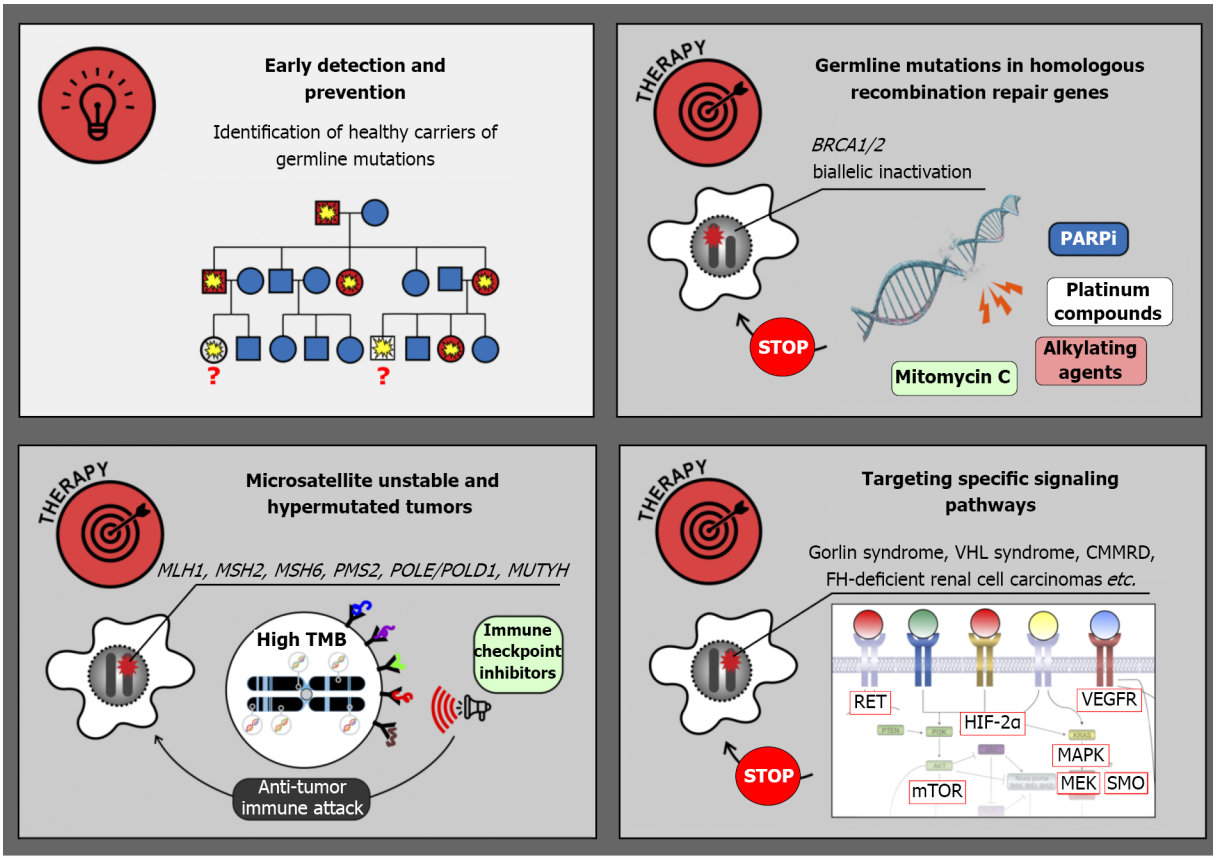

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Figure 3 Management of hereditary cancer syndromes. PARPi: Poly (ADP-ribose) polymerase inhibitors; TMB: Tumor mutation burden; ~~HIF-2α: Hypoxia inducible factor-2α~~; VHL: von Hippel-Lindau; ~~mTOR: Mechanistic target of rapamycin~~; MAPK: Mitogen-activated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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSION

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

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

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

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

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

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

FOOTNOTES

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