Cancer Predisposition

Genetic Pathway Reference

8 Functional Categories • ~120 SNPs Catalogued

Educational reference document | No personal genotype data

1. Purpose and Scope

This document is a standalone educational reference describing the biology of cancer predisposition, the functional gene categories that determine genomic integrity and carcinogen handling, the well-studied common and rare germline variants in those genes, the cofactors each enzyme requires, and the nutritional or supplemental targets that map to each cofactor and pathway. It is intended for use by clinicians, researchers, or interested non-specialists who want a compact pathway primer that can later be paired with personal genotype results.

All variant interpretations are based on peer-reviewed GWAS literature, mechanistic studies, and major clinical consortia (CIMBA, BCAC, PRACTICAL, CORECT, NHGRI-EBI GWAS Catalog). The document contains no personal genotype data, no medication or supplement regimens, and no individualized clinical recommendations. Penetrance varies enormously by gene: classic high-penetrance syndromes (BRCA1/2, Lynch, Li-Fraumeni, FAP, Cowden, Peutz-Jeghers, HDGC) carry lifetime cancer risks of 40 to 85 percent for carriers; moderate-penetrance genes (ATM, CHEK2, PALB2, BRIP1) confer 2 to 4 fold relative risks; and common low-penetrance GWAS variants confer per-allele odds ratios of 1.05 to 1.5, aggregating into polygenic risk scores that can still meaningfully shift lifetime incidence.

2. Pathway Biology

2.1 The hallmarks framework

Cancer arises through the sequential or parallel acquisition of a defined set of cellular capabilities. Hanahan and Weinberg (Cell 2011) describe ten hallmarks: sustained proliferative signaling, evasion of growth suppressors, resistance to cell death, replicative immortality, angiogenesis, invasion and metastasis, deregulated energetics, immune evasion, genome instability, and tumor-promoting inflammation. Hereditary cancer predisposition almost always traces to the genome-instability hallmark: a germline defect in a gene whose job is to maintain DNA fidelity, followed over a lifetime by a somatic second hit (Knudson's two-hit model, PNAS 1971) in the same or an epistatic gene.

2.2 DNA damage response and repair as the core axis

The human genome sustains tens of thousands of lesions per cell per day: oxidative base damage, single-strand breaks, double-strand breaks, replication errors, deaminations, and bulky adducts from exogenous carcinogens. Five coordinated repair systems keep the genome stable: homologous recombination (HR) for double-strand breaks during S/G2, non-homologous end joining (NHEJ) for double-strand breaks in G1, mismatch repair (MMR) for replication errors, base excision repair (BER) for oxidative and small base lesions, and nucleotide excision repair (NER) for bulky adducts. ATM and ATR sit at the apex of the DNA damage response, sensing breaks and stalled replication forks, phosphorylating CHEK2 and CHEK1, which in turn

activate p53 and enforce cell-cycle arrest or apoptosis. Germline loss of any component elevates cancer risk; the magnitude depends on which tissues are most exposed to the corresponding damage type.

2.3 Carcinogen metabolism

The liver, lung, and gut metabolize xenobiotics through a two-phase system. Phase I enzymes, dominated by the cytochrome P450 family, oxidize lipophilic compounds to make them more polar. This process often activates pro-carcinogens into reactive electrophiles: benzo[a]pyrene from tobacco smoke becomes BPDE via CYP1A1 and CYP1B1; aflatoxin B1 becomes AFB1-exo-8,9-epoxide via CYP3A4; heterocyclic amines from charred meat are N-hydroxylated by CYP1A2. Phase II enzymes (glutathione-S-transferases, N-acetyltransferases, UDP-glucuronosyltransferases, sulfotransferases, NQO1) conjugate these reactive intermediates to glutathione, acetate, glucuronate, or sulfate for excretion. The ratio of Phase I activation to Phase II detoxification, governed partly by polymorphisms in these enzymes, determines the effective carcinogen load delivered to DNA (Nebert and Dalton, Nat Rev Cancer 2006).

2.4 Hormonal carcinogenesis

Estrogens and androgens promote cell proliferation in hormone-responsive tissues. Estradiol is hydroxylated at C2 (protective, via CYP1A1/1A2) or C4 (genotoxic, via CYP1B1) to catechol estrogens, which COMT then methylates for safe excretion; unmethylated catechol estrogens can redox-cycle to quinones and form depurinating DNA adducts (Cavalieri and Rogan, J Steroid Biochem Mol Biol 2011). Aromatase (CYP19A1) sets tissue estrogen synthesis; 17-beta-hydroxysteroid dehydrogenases and 5-alpha-reductase govern androgen flux. Variants in these enzymes shift the lifetime hormonal exposure curve and modulate breast, endometrial, and prostate cancer risk.

2.5 Folate, methylation, and nucleotide supply

One-carbon metabolism delivers methyl groups for DNA methylation (tumor suppressor silencing when dysregulated) and precursors for thymidylate and purine synthesis. MTHFR partitions flux between dTMP synthesis and homocysteine remethylation. Inadequate folate causes uracil misincorporation into DNA and double-strand breaks during repair. The relationship between MTHFR C677T and cancer risk is bidirectional and context-dependent: in folate-replete states, the TT genotype is modestly protective for colorectal cancer (more dUMP available), whereas in folate-deplete states it is a risk factor (Kim, JNCI 2005 review). This is the clearest example of a gene-nutrient interaction in cancer genetics and is the basis for the cross-reference to the Homocysteine Regulation pathway.

2.6 Clinical integration

Cancer predisposition testing historically focused on single-gene assays for the highest-penetrance syndromes. Multi-gene panel testing now identifies pathogenic variants in 8 to 12 percent of unselected cancer patients (Mandelker et al., JAMA 2017; LaDuca et al., Genet Med 2020), and a further substantial fraction harbor moderate-penetrance variants and common low-penetrance alleles that aggregate into polygenic risk scores. The most actionable findings change clinical management: BRCA1/2 for risk-reducing surgery and PARP inhibitor eligibility; Lynch genes for enhanced colonoscopy and endometrial surveillance; Li-Fraumeni (TP53) for whole-body MRI protocols; FAP (APC) for colectomy timing; CDH1 for prophylactic gastrectomy; MUTYH biallelic for aggressive colon surveillance. Moderate-penetrance genes (ATM, CHEK2, PALB2) guide enhanced breast imaging. Common GWAS variants mostly do not

change individual management but contribute to polygenic risk scores that are being incorporated into screening programs.

3. Functional Categories

The cancer predisposition pathway is organized here into eight functional categories, each corresponding to a distinct molecular job. The categories below are used as the organizing scaffold for the SNP catalog in Section 4.

#	Category	Function	Key genes
1	HR repair	Double-strand break repair via sister chromatid	BRCA1, BRCA2, PALB2, RAD51, BRIP1, NBN, BARD1, RAD51C, RAD51D
2	Mismatch repair (Lynch)	Correct replication errors and IDL loops	MLH1, MSH2, MSH6, PMS2, EPCAM
3	BER and NER	Repair oxidative and bulky lesions	MUTYH, OGG1, XRCC1, XPC, ERCC2, ERCC5
4	DDR checkpoints	Sense damage, arrest cycle, trigger apoptosis	ATM, CHEK2, TP53, MDM2, ATR
5	Tumor suppressors	Restrain proliferation; classic syndromes	APC, PTEN, STK11, CDH1, CDKN2A, VHL, RB1, NF1, NF2
6	Carcinogen metabolism	Phase I activation and Phase II detoxification	CYP1A1, CYP1A2, CYP1B1, CYP2E1, GSTM1, GSTT1, GSTP1, NAT1, NAT2, NQO1, SULT1A1, UGT1A1
7	Hormonal and folate	Sex steroid flux, one-carbon metabolism	CYP17A1, CYP19A1, ESR1, ESR2, SRD5A2, COMT, MTHFR, MTRR, TYMS
8	Common GWAS loci	Low-penetrance polygenic risk signals	8q24, TERT, FGFR2, TOX3, CASP8, SMAD7, HNF1B, MSMB, VDR

4. Gene and Variant Catalog

4.1 Homologous recombination repair

HR is the high-fidelity pathway for repairing double-strand breaks during S/G2 phase, using the sister chromatid as template. BRCA1 coordinates damage signaling and end resection; BRCA2 loads RAD51 filaments onto single-stranded DNA; PALB2 is the physical bridge between them. Loss of any component forces the cell onto error-prone alternative pathways and defines BRCAness, which is therapeutically actionable via PARP inhibitor synthetic lethality.

Gene	rsID	Variant	Functional consequence	Cofactor
BRCA1	rs80357906	185delAG (founder)	Frameshift, truncated protein. Lifetime breast ~72%, ovarian ~44% (Kuchenbaecker, JAMA 2017).	(protein)
BRCA1	rs80357713	5382insC (founder)	Frameshift. Similar penetrance to 185delAG.	(protein)
BRCA1	rs28897672	C61G (RING domain)	Disrupts BARD1 binding, abolishes E3 ligase activity.	(protein)
BRCA2	rs80359550	6174delT (founder)	Frameshift. Breast ~69%, ovarian ~17% (Kuchenbaecker 2017).	(protein)
BRCA2	rs11571833	K3326X (truncation)	Removes last 93 aa. OR ~1.4 breast, ~2.4 ovarian, ~2.1 lung squamous (Michailidou, Nature 2017).	(protein)
PALB2	rs180177102	c.1592delT	Frameshift; abolishes BRCA2 recruitment. ~35% lifetime breast cancer (Antoniou, NEJM 2014).	(protein)
RAD51	rs1801320	135G>C (5'UTR)	Modifier of BRCA1/2 carrier risk; altered mRNA levels.	(protein)
BRIP1	rs4988344	R798X	Truncation of BRCA1-interacting helicase. OR ~2 breast, higher ovarian (Seal, Nat Genet 2006).	Fe-S cluster
NBN	rs1805794	E185Q	Mild destabilization of MRN complex. OR ~1.4 breast, ~2.6 prostate.	(protein)
RAD51C	Truncations	Multiple	Loss of HR paralog. OR ~5.9 ovarian (Loveday, Nat Genet 2011).	(protein)

HR is a protein machine and has few classical small-molecule cofactors. The most relevant metabolic tie-in is NAD+ biology: PARP1 is the primary damage sensor for single-strand breaks and its PARylation activity consumes NAD+, linking repair capacity indirectly to niacin and NR/NMN status. Zinc is structural in BRCA1's RING domain. Iron-sulfur clusters are required by BRIP1/FANCJ and other DNA helicases.

4.2 Mismatch repair (Lynch syndrome axis)

MMR corrects base-base mismatches and small insertion-deletion loops introduced by replicative polymerases. MSH2-MSH6 recognizes mismatches; MLH1-PMS2 initiates strand excision. Germline loss causes Lynch syndrome, characterized by microsatellite instability (MSI-H) in tumors and dramatically elevated colorectal, endometrial, ovarian, gastric, urothelial, small bowel, and brain cancer risk. Gene-specific penetrance differs: MLH1 and MSH2 carry the highest risks; MSH6 is milder and later-onset; PMS2 is the mildest. EPCAM 3' deletions silence MSH2 via promoter methylation.

Gene	rsID	Variant	Functional consequence	Cofactor
MLH1	Multiple	Truncations / splice	Classic Lynch. Lifetime CRC 46-61%, endometrial 34-54% (Moller, Gut 2018, PLSD).	(protein)
MLH1	rs1800734	-93G>A promoter	Common promoter variant; modest CRC modifier. OR ~1.15 (Raptis, JNCI 2007).	(protein)
MSH2	rs63751660	A636P (Ashkenazi)	Pathogenic founder missense. Classic Lynch.	(protein)
MSH2	Multiple	Truncations	Lifetime CRC ~46%, endometrial ~51%.	(protein)
MSH6	Multiple	Truncations	Milder Lynch, later onset. CRC ~20%, endometrial ~44%.	(protein)
PMS2	Multiple	Truncations (pseudogene-complicated)	Mildest Lynch gene. CRC ~10-20%, endometrial ~15%.	(protein)
EPCAM	3' deletions	Large deletions	Silences MSH2 via promoter methylation. GI-predominant Lynch.	(protein)

There are no direct small-molecule cofactors for the MMR proteins themselves, but folate status (via MTHFR and MTR) modulates the background mutation rate by controlling dUMP/dTMP ratios and therefore the uracil-misincorporation pressure on MMR capacity. This is the mechanistic bridge between the Homocysteine Regulation pathway and MMR carrier phenotype severity.

4.3 Base excision repair and nucleotide excision repair

BER repairs single-base oxidative damage, principally 8-oxoguanine (the product of reactive oxygen species reacting with guanine in DNA). MUTYH excises adenine mispaired with 8-oxoG; OGG1 excises 8-oxoG itself. NER removes bulky, helix-distorting lesions: UV photoproducts, polycyclic aromatic hydrocarbon adducts, and cisplatin crosslinks. Biallelic MUTYH causes MUTYH-associated polyposis (MAP) and is the clearest mendelian example of failed oxidative BER.

Gene	rsID	Variant	Functional consequence	Cofactor
MUTYH	rs36053993	G396D	Impaired excision of A:8-oxoG. Biallelic MAP, CRC OR ~28; monoallelic OR ~1.15-1.5 (Win, Gastro 2014).	Mg2+
MUTYH	rs34612342	Y179C	More severe loss of glycosylase activity. Biallelic MAP, more severe than G396D.	Mg2+
OGG1	rs1052133	S326C	Reduced 8-oxoguanine glycosylase activity. OR ~1.2 lung cancer (Weiss meta-analysis).	Mg2+
XRCC1	rs25487	R399Q	Scaffold for BER; altered interaction with PARP1. Mixed modest risk.	(protein)
XPC	rs2228001	K939Q	NER damage recognition. OR ~1.2 bladder, lung.	(protein)

Gene	rsID	Variant	Functional consequence	Cofactor
ERCC2/XPD	rs13181	K751Q	NER helicase. OR ~1.2 lung, bladder.	Fe-S, ATP
ERCC5/XPG	rs17655	D1104H	NER 3' endonuclease. Modest risk modifier.	(protein)

BER and NER glycosylases and polymerases require Mg2+ for catalysis; helicases (ERCC2, BRIP1) require Fe-S clusters and ATP. Zinc is structural in XPA (not shown) and other NER scaffolds. Riboflavin supports flavin-dependent lesion recognition in some pathways. The functional output of BER depends critically on the steady-state ROS load, which is determined by the antioxidant-defense genes catalogued in the Endothelial Health and Glycation Pathways references.

4.4 DNA damage response checkpoints

ATM and ATR are the apical kinases of the DDR. ATM responds primarily to double-strand breaks, phosphorylating CHEK2, p53, BRCA1, and H2AX. ATR responds to stalled replication forks. CHEK2 and CHEK1 execute cell-cycle arrest via CDC25 inhibition and amplify the p53 signal. TP53 integrates damage signals and chooses between cell-cycle arrest, senescence, and apoptosis. MDM2 is p53's principal negative regulator; variants that raise MDM2 expression attenuate p53 signaling.

Gene	rsID	Variant	Functional consequence	Cofactor
ATM	rs1800057	P1054R	Modest functional effect. OR ~1.3 breast.	Mg2+, ATP
ATM	rs1801516	D1853N	Common missense; mixed breast/pancreatic association.	Mg2+, ATP
ATM	rs56128736	V2424G (c.7271T>G)	Hypomorph. OR ~8-12 breast in families, ~1.6 population (Goldgar, BCR 2011).	Mg2+, ATP
CHEK2	rs555607708	1100delC	Frameshift, kinase-dead. OR ~2.7 unselected breast, ~4.8 familial (Weischer, JCO 2008); OR ~2.1 CRC; OR ~2 prostate.	Mg2+, ATP
CHEK2	rs17879961	I157T	Missense, partial loss. OR ~1.4 breast, ~1.5 CRC, ~1.7 prostate.	Mg2+, ATP
CHEK2	rs137853007	S428F (Ashkenazi)	Loss of kinase activity. OR ~2.0 breast.	Mg2+, ATP
TP53	rs1042522	P72R (codon 72)	Arg more pro-apoptotic, Pro more senescence-inducing. Modifier of mutant TP53 penetrance (Dumont, Nat Genet 2003).	Zn2+
TP53	rs17878362	PIN3 16-bp dup intron 3	Altered splicing; modifier of cancer risk.	Zn2+
MDM2	rs2279744	SNP309 T>G	Raises MDM2 expression, attenuates p53. Accelerates LFS tumor onset; OR ~1.2-1.5 several cancers (Bond, Cell 2004).	(ligase)

ATM, ATR, CHEK1, CHEK2, and DNA-PK are all Mg2+-ATP-dependent serine-threonine kinases. p53's DNA-binding domain is a zinc-coordinated beta-sandwich: zinc deficiency can cause p53 to mis-fold and functionally behave like a mutant, which links dietary zinc status to p53 activity even in wild-type carriers (Puca, Oncotarget 2011). CHEK2 1100delC is the single most common moderate-penetrance breast cancer allele in Northern European populations and has the largest effect size in this category.

4.5 Tumor suppressors and cell cycle

These genes encode the classic Knudson two-hit tumor suppressors. Germline loss of one allele creates a predisposed tissue; somatic loss of the second allele initiates the tumor. Most of the classical cancer syndromes map here.

Gene	rsID / variant	Syndrome	Functional consequence	Cofactor
APC	rs1801155	I1307K (Ashkenazi)	Hypermutable A8 tract. OR ~2 CRC in Ashkenazim; ~7% carrier rate (Laken, Nat Genet 1997). Not polyposis.	(scaffold)
APC	Truncations	FAP / AFAP	Near-100% CRC penetrance in classic FAP.	(scaffold)
PTEN	Truncations	Cowden (PHTS)	Breast ~85%, thyroid ~35%, endometrial ~28%.	(lipid phosphatase)
STK11	Truncations	Peutz-Jeghers	GI hamartomas; breast, pancreas, cervical cancer spectrum.	Mg2+, ATP
CDH1	Truncations	HDGC	Diffuse gastric ~42% men, ~33% women; lobular breast ~55% women (Hansford, JAMA Oncol 2015).	Ca2+
CDKN2A	Multiple	Familial melanoma/pancreatic	Melanoma ~67% lifetime in high-risk families.	(CDK inhibitor)
VHL	Missense and truncations	VHL syndrome	Clear cell RCC, pheochromocytoma, hemangioblastoma.	(E3 ligase)
RB1	Truncations	Retinoblastoma	Near-100% retinoblastoma; secondary sarcomas.	(pocket protein)
NF1	Truncations	NF1	Neurofibromas, MPNST, optic glioma.	(GAP)
NF2	Truncations	NF2	Vestibular schwannoma, meningioma.	(scaffold)

Apart from STK11 (an ATP-dependent kinase) and CDH1 (calcium-dependent homophilic adhesion), this category has few targetable small-molecule cofactors. Clinical management depends overwhelmingly on early identification and surveillance or risk-reducing surgery. APC I1307K is the one variant in this category that is common enough to warrant routine consideration in people of Ashkenazi descent.

4.6 Carcinogen metabolism

4.6.1 Phase I activation

Cytochrome P450 enzymes oxidize lipophilic xenobiotics to more polar, often more reactive metabolites. In the cancer context, this is a double-edged sword: the same enzymes that clear drugs also activate pro-carcinogens into genotoxic electrophiles.

Gene	rsID	Variant	Functional consequence	Cofactor
CYP1A1	rs4646903	m1 / *2A (T>C 3'UTR)	Higher inducibility; more BPDE from PAHs in smokers.	heme, O2, NADPH
CYP1A1	rs1048943	m2 / *2C (I462V)	Higher catalytic activity.	heme, O2, NADPH
CYP1A2	rs762551	*1F (-163C>A)	Higher inducibility in smokers; N-hydroxylates heterocyclic amines.	heme, O2, NADPH
CYP1B1	rs1056836	L432V	Activates PAHs and hydroxylates estradiol to genotoxic 4-OH-estradiol.	heme, O2, NADPH
CYP2E1	rs2031920	RsaI / *5 (c1/c2)	Ethanol-inducible; activates nitrosamines.	heme, O2, NADPH
CYP2D6	rs3892097	*4 splice loss	Poor metabolizer phenotype; affects tamoxifen and many drugs.	heme, O2, NADPH
CYP3A4	rs2740574	*1B (-392A>G)	Promoter variant; modest activity difference.	heme, O2, NADPH

4.6.2 Phase II detoxification

Phase II enzymes conjugate reactive intermediates to glutathione, acetate, glucuronate, or sulfate, producing water-soluble excretable products. Null alleles in GSTM1 and GSTT1 are deletions (not SNPs) and are present in 30 to 50 percent of the population, with substantial ethnic variation.

Gene	rsID	Variant	Functional consequence	Cofactor
GSTM1	CNV	Null deletion	Absent GSTM1 protein; reduced PAH conjugation. Elevated lung, bladder, H&N cancer risk in smokers (Hashibe, CEBP 2003).	GSH
GSTT1	CNV	Null deletion	Absent GSTT1 protein; reduced small-electrophile clearance.	GSH
GSTP1	rs1695	I105V	Reduced PAH-diolepoxide conjugation (Val allele).	GSH

Gene	rsID	Variant	Functional consequence	Cofactor
NAT1	rs4986782	R187Q	Slow N-acetylation of aromatic amines.	Acetyl-CoA
NAT2	rs1799930	*6A (R197Q)	Slow acetylator. Elevated bladder cancer risk with aromatic amine exposure.	Acetyl-CoA
NAT2	rs1799931	*7 (G286E)	Slow acetylator allele.	Acetyl-CoA
NAT2	rs1801280	*5 (I114T)	Slow acetylator allele; common in Europeans.	Acetyl-CoA
NQO1	rs1800566	P187S (*2)	Reduced quinone reductase activity; lower protection from quinone electrophiles.	FAD, NAD(P)H
SULT1A1	rs9282861	R213H	Reduced sulfation of heterocyclic amines.	PAPS
UGT1A1	rs8175347	TA7 (*28, Gilbert)	Reduced glucuronidation; modifier of bilirubin, irinotecan toxicity, and some cancer risks.	UDPGA

This category has the richest nutritional tie-in. Phase II glutathione conjugation depends on steady-state GSH availability, which in turn depends on cysteine (supportable by N-acetylcysteine, whey protein), glycine, and glutamate. NQO1 is a flavoprotein (riboflavin) that uses NAD(P)H (niacin). Sulfation needs sulfate precursors (cysteine, MSM). Cruciferous vegetables induce Phase II enzymes via Nrf2 activation through sulforaphane and indole-3-carbinol, providing a dietary lever on the whole category. The clinical significance of individual phase I/II variants is typically modest in isolation but becomes meaningful in the context of high carcinogen exposure (smoking, occupational, dietary).

4.7 Hormonal and folate-mediated carcinogenesis

Estrogens, androgens, and methylation status together modulate risk for hormone-dependent cancers (breast, endometrial, ovarian, prostate) and the background mutation rate affecting all tissues. The folate sub-axis is shared with the Homocysteine Regulation pathway and provides a direct bridge between the two reports.

Gene	rsID	Variant	Functional consequence	Cofactor
CYP17A1	rs743572	T>C (-34 promoter)	Altered 17-alpha-hydroxylase expression; mixed breast/prostate modifier.	heme, NADPH
CYP19A1	rs10046	3'UTR	Altered aromatase expression; OR ~1.1 breast.	heme, NADPH
CYP19A1	rs700519	C264R	Aromatase missense; weak breast modifier.	heme, NADPH
ESR1	rs2234693	PvuII intronic	Altered estrogen receptor alpha levels; modest breast/endometrial effect.	(receptor)
ESR1	rs9340799	XbaI intronic	Altered ESR1 expression.	(recepto

Gene	rsID	Variant	Functional consequence	Cofactor
				r)
ESR2	rs1256049	intronic	Altered ER-beta signaling; weak breast modifier.	(receptor)
SRD5A2	rs523349	V89L	5-alpha-reductase activity; prostate risk modifier.	NADPH
HSD17B1	rs605059	S312G	Altered sex steroid interconversion.	NAD(P)H
COMT	rs4680	V158M	Low-activity Met allele slows catechol estrogen methylation; OR ~1.1 breast.	SAMe, Mg2+
MTHFR	rs1801133	C677T (A222V)	Thermolabile enzyme. TT protective for CRC (~0.85) at adequate folate; OR ~1.2 breast. Context-dependent (Kim, JNCI 2005).	FAD, folate
MTHFR	rs1801131	A1298C (E429A)	Milder enzyme defect.	FAD, folate
MTRR	rs1801394	I22M (A66G)	Methionine synthase reductase; weak CRC modifier.	FAD, B12
TYMS	5'UTR	2R/3R tandem repeat	Thymidylate synthase expression level; weak CRC modifier.	folate

This is the category with the richest nutritional cofactor structure and the most direct link to the Homocysteine and Glycation pathways. Folate (as 5-methyl-THF, not folic acid), methylcobalamin and adenosylcobalamin, pyridoxal-5-phosphate (B6), and riboflavin (FAD) are all required for full MTHFR, MTR, and MTRR function. SAMe supports COMT methylation of catechol estrogens. Choline and betaine are alternative methyl donors. Inadequate folate raises dUMP/dTMP ratios, increasing uracil misincorporation and double-strand breaks. Excess unmetabolized folic acid may have opposite effects on established neoplasms. This bidirectional relationship (Kim, JNCI 2005) means the clinically useful form is 5-MTHF, calibrated to homocysteine and serum folate.

4.8 Common low-penetrance GWAS loci

These are the most-replicated common variants from the NHGRI-EBI GWAS Catalog. Each confers a small per-allele effect (OR 1.1-1.5) but together they form the backbone of modern polygenic risk scores, which can meaningfully shift lifetime incidence and are being incorporated into national screening programs (Mavaddat, AJHG 2019; Kachuri, Nat Commun 2020).

Locus / Gene	rsID	Cancer	OR per allele	Source
8q24 region 3	rs6983267	Colorectal, prostate	~1.2	Tomlinson, Nat Genet 2007
8q24	rs1447295	Prostate	~1.3	Amundadottir, Nat Genet 2006
TERT-CLPTM1L	rs401681	Multiple (lung, bladder, melanoma, glioma)	~1.15	Rafnar, Nat Genet 2009

Locus / Gene	rsID	Cancer	OR per allele	Source
TERT-CLPTM1L	rs2736098	Multiple	~1.15	Rafnar, 2009
FGFR2	rs2981582	Breast (ER+)	~1.26	Easton, Nature 2007
FGFR2	rs1219648	Breast	~1.20	Easton, 2007
TOX3/TNRC9	rs3803662	Breast	~1.20	Easton, 2007
CASP8	rs1045485	Breast (protective)	~0.88	Cox, Nat Genet 2007
MAP3K1	rs889312	Breast	~1.13	Easton, 2007
LSP1	rs3817198	Breast	~1.07	Easton, 2007
SMAD7 (5q31)	rs4939827	Colorectal	~1.18	Broderick, Nat Genet 2007
11q23	rs3802842	Colorectal	~1.15	Tenesa, Nat Genet 2008
HNF1B	rs4430796	Prostate (T2D inverse)	~1.22	Gudmundsson, Nat Genet 2007
MSMB	rs10993994	Prostate	~1.25	Eeles, Nat Genet 2008
KLK3	rs2735839	Prostate	~1.20	Eeles, 2008
CDKN2A/B (9p21)	rs1011970	Melanoma, breast	~1.15	Turnbull, Nat Genet 2010
VDR	rs731236	Breast, CRC, prostate	~1.1	Meta-analyses (mixed)
VDR	rs2228570	Multiple	~1.1	Meta-analyses

Common GWAS loci have small individual effects that do not change individual management in isolation. Their value lies in polygenic risk scores that aggregate hundreds of variants. Note that the 9p21 CDKN2A/B locus overlaps with the 9p21 coronary artery disease signal catalogued in the Endothelial Health reference, making this chromosomal region a convergence point between cardiovascular and cancer biology. TERT-CLPTM1L is pleiotropic across many cancer types and also modifies leukocyte telomere length.

5. Category → Genes → Cofactors → Nutritional Targets

Summary table linking each functional category to the cofactors required and the dietary or supplemental nutrients that support them. This is a conceptual map, not an individualized prescription. Personal supplementation depends on genotype, intake, lab values, and clinical context.

Category	Key cofactors	Nutritional / supplement targets
1. HR repair	NAD+ (PARP1), Zn (BRCA1 RING), Fe-S (BRIP1)	Niacin/NR/NMN; zinc; iron sufficiency
2. Mismatch repair	Mg2+, folate (indirect)	Magnesium; 5-MTHF; B12
3. BER and NER	Mg2+, Zn, Fe-S, ATP	Magnesium; zinc; iron sufficiency

Category	Key cofactors	Nutritional / supplement targets
4. DDR checkpoints	Mg2+-ATP (kinases), Zn (p53 DBD)	Magnesium; zinc (critical for p53 folding)
5. Tumor suppressors	Ca2+ (CDH1), ATP (STK11)	Adequate calcium; no specific supplement
6. Carcinogen metabolism	Heme, O2, NADPH, GSH, FAD, PAPS, UDPGA, AcCoA	NAC / whey (GSH precursor); riboflavin; niacin; cruciferous vegetables (Nrf2); cysteine; sulforaphane
7. Hormonal and folate	NADPH, SAMe, FAD, folate, B12, B6, heme	5-MTHF; methylcobalamin; adenosylcobalamin; P5P (B6); riboflavin; choline; betaine; DIM / I3C for estrogen 2/16 ratio
8. Common GWAS loci	Variable by gene	Vitamin D (VDR); general anti-inflammatory diet

6. Complete SNP Lookup Table

Quick reference for all rsIDs catalogued in this document, sorted alphabetically by gene. Coordinates are GRCh38 and represent the common-variant position for look-up purposes. For rare pathogenic variants in BRCA1/2, Lynch genes, APC, TP53, PTEN, STK11, CDH1, VHL, RB1, and NF1/2, the relevant changes are typically truncating variants distributed across the gene and are not captured by single rsIDs; these require full gene sequencing interpretation rather than SNP lookup. Representative variants are listed here where a single rsID anchors them.

Gene / locus	rsID	GRCh38 position	Category / variant
APC	rs1801155	5:112839514	Tumor suppressor (I1307K)
ATM	rs1800057	11:108267071	DDR checkpoint (P1054R)
ATM	rs1801516	11:108304796	DDR checkpoint (D1853N)
ATM	rs56128736	11:108326213	DDR checkpoint (V2424G)
BRCA1	rs28897672	17:43115746	HR repair (C61G)
BRCA1	rs80357906	17:43124027	HR repair (185delAG)
BRCA1	rs80357713	17:43091983	HR repair (5382insC)
BRCA2	rs11571833	13:32398489	HR repair (K3326X)
BRCA2	rs80359550	13:32340301	HR repair (6174delT)
BRIP1	rs4988344	17:61754379	HR repair (R798X)
CASP8	rs1045485	2:201284586	GWAS breast (protective)
CDKN2A/B	rs1011970	9:22051670	GWAS 9p21 melanoma/breast
CHEK2	rs17879961	22:28725099	DDR checkpoint (I157T)

Gene / locus	rsID	GRCh38 position	Category / variant
CHEK2	rs137853007	22:28695232	DDR checkpoint (S428F)
CHEK2	rs555607708	22:28695868	DDR checkpoint (1100delC)
COMT	rs4680	22:19963748	Estrogen methylation (V158M)
CYP17A1	rs743572	10:102830765	Steroidogenesis (-34)
CYP19A1	rs10046	15:51210647	Aromatase 3'UTR
CYP19A1	rs700519	15:51236065	Aromatase C264R
CYP1A1	rs4646903	15:74720644	Phase I (*2A)
CYP1A1	rs1048943	15:74720577	Phase I (*2C / I462V)
CYP1A2	rs762551	15:74749576	Phase I (*1F)
CYP1B1	rs1056836	2:38071060	Phase I (L432V)
CYP2E1	rs2031920	10:133541510	Phase I (RsaI)
CYP2D6	rs3892097	22:42128945	Phase I (*4)
CYP3A4	rs2740574	7:99381814	Phase I (*1B)
ERCC2	rs13181	19:45351661	NER (K751Q)
ERCC5	rs17655	13:102868851	NER (D1104H)
ESR1	rs2234693	6:151842200	ER-alpha (PvuII)
ESR1	rs9340799	6:151842246	ER-alpha (XbaI)
ESR2	rs1256049	14:64232552	ER-beta
FGFR2	rs2981582	10:121592803	GWAS breast
FGFR2	rs1219648	10:121593120	GWAS breast
GSTM1	CNV	1:109687815-109693790	Phase II (null deletion)
GSTT1	CNV	22:24322361-24326106	Phase II (null deletion)
GSTP1	rs1695	11:67585218	Phase II (I105V)
HNF1B	rs4430796	17:37741679	GWAS prostate
HSD17B1	rs605059	17:42537235	Sex steroid (S312G)
KLK3	rs2735839	19:51364623	GWAS prostate
LSP1	rs3817198	11:1895708	GWAS breast
MAP3K1	rs889312	5:56857225	GWAS breast
MDM2	rs2279744	12:68808800	p53 pathway (SNP309)
MLH1	rs1800734	3:36993455	MMR promoter -93

Gene / locus	rsID	GRCh38 position	Category / variant
MSMB	rs10993994	10:46046343	GWAS prostate
MSH2	rs63751660	2:47475100	MMR (A636P)
MTHFR	rs1801133	1:11796321	Folate (C677T)
MTHFR	rs1801131	1:11794419	Folate (A1298C)
MTRR	rs1801394	5:7870973	Folate (I22M)
MUTYH	rs36053993	1:45331833	BER (G396D)
MUTYH	rs34612342	1:45332803	BER (Y179C)
NAT1	rs4986782	8:18079912	Phase II (R187Q)
NAT2	rs1799930	8:18400344	Phase II (*6A)
NAT2	rs1799931	8:18400806	Phase II (*7)
NAT2	rs1801280	8:18400285	Phase II (*5)
NBN	rs1805794	8:89967186	HR repair (E185Q)
NQO1	rs1800566	16:69711242	Phase II (P187S)
OGG1	rs1052133	3:9757089	BER (S326C)
PALB2	rs180177102	16:23629927	HR repair (c.1592delT)
RAD51	rs1801320	15:40695147	HR repair (5'UTR)
SMAD7	rs4939827	18:48927093	GWAS CRC
SRD5A2	rs523349	2:31531620	5-alpha-reductase (V89L)
SULT1A1	rs9282861	16:28605268	Phase II (R213H)
TERT	rs401681	5:1322087	GWAS multi-cancer
TERT	rs2736098	5:1294086	GWAS multi-cancer
TOX3	rs3803662	16:52551427	GWAS breast
TP53	rs1042522	17:7676154	p53 codon 72 (P72R)
TYMS	rs34743033	18:657726	Thymidylate synthase 5'UTR
UGT1A1	rs8175347	2:233760233	Phase II (*28 / TA7)
VDR	rs731236	12:47844974	Vitamin D receptor (TaqI)
VDR	rs2228570	12:47879112	Vitamin D receptor (FokI)
XPC	rs2228001	3:14145327	NER (K939Q)
XRCC1	rs25487	19:43551574	BER (R399Q)
11q23	rs3802842	11:111300984	GWAS CRC
8q24	rs6983267	8:127401060	GWAS CRC/prostate

Gene / locus	rsID	GRCh38 position	Category / variant
8q24	rs1447295	8:127914831	GWAS prostate

7. Bibliography and Source Notes

Key primary sources used in compiling this reference. Full methodological detail is available in the cited papers.

Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell 2011;144:646-674.

Knudson AG. Mutation and cancer: statistical study of retinoblastoma. Proc Natl Acad Sci USA 1971;68:820-823.

Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med 2015;372:2243-2257.

Turnbull C, Rahman N. Genetic predisposition to breast cancer: past, present, and future. Annu Rev Genomics Hum Genet 2008;9:321-345.

Kuchenbaecker KB, Hopper JL, Barnes DR, et al. Risks of breast, ovarian, and contralateral breast cancer for BRCA1 and BRCA2 mutation carriers. JAMA 2017;317:2402-2416.

Michailidou K, Lindstrom S, Dennis J, et al. Association analysis identifies 65 new breast cancer risk loci. Nature 2017;551:92-94.

Antoniou AC, Casadei S, Heikkinen T, et al. Breast-cancer risk in families with mutations in PALB2. N Engl J Med 2014;371:497-506.

Weischer M, Bojesen SE, Ellervik C, et al. CHEK2*1100delC genotyping for clinical assessment of breast cancer risk: meta-analyses of 26,000 cases and 27,000 controls. J Clin Oncol 2008;26:542-548.

Goldgar DE, Healey S, Dowty JG, et al. Rare variants in the ATM gene and risk of breast cancer. Breast Cancer Res 2011;13:R73.

Moller P, Seppala T, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut 2018;67:1306-1316.

Win AK, Dowty JG, Cleary SP, et al. Risk of colorectal cancer for carriers of mutations in MUTYH, with and without a family history of cancer. Gastroenterology 2014;146:1208-1211.

Laken SJ, Petersen GM, Gruber SB, et al. Familial colorectal cancer in Ashkenazim due to a hypermutable tract in APC. Nat Genet 1997;17:79-83.

Bond GL, Hu W, Bond EE, et al. A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. Cell 2004;119:591-602.

Dumont P, Leu JI, Della Pietra AC, et al. The codon 72 polymorphic variants of p53 have markedly different apoptotic potential. Nat Genet 2003;33:357-365.

Hansford S, Kaurah P, Li-Chang H, et al. Hereditary diffuse gastric cancer syndrome: CDH1 mutations and beyond. JAMA Oncol 2015;1:23-32.

Hashibe M, Brennan P, Strange RC, et al. Meta- and pooled analyses of GSTM1, GSTT1, GSTP1 and CYP1A1 genotypes and risk of head and neck cancer. Cancer Epidemiol Biomarkers Prev 2003;12:1509-1517.

Nebert DW, Dalton TP. The role of cytochrome P450 enzymes in endogenous signalling pathways and environmental carcinogenesis. Nat Rev Cancer 2006;6:947-960.

Cavalieri EL, Rogan EG. Unbalanced metabolism of endogenous estrogens in the etiology and prevention of human cancer. J Steroid Biochem Mol Biol 2011;125:169-180.

Kim YI. Role of folate in colon cancer development and progression. J Nutr 2003;133:3731S-3739S; and Kim YI. Folate and DNA methylation: a mechanistic link between folate deficiency and colorectal cancer. Cancer Epidemiol Biomarkers Prev 2004;13:511-519.

Puca R, Nardinocchi L, Porru M, et al. Restoring p53 active conformation by zinc increases the response of mutant p53 tumor cells to anticancer drugs. Oncotarget 2011;2:1106-1116.

Tomlinson I, Webb E, Carvajal-Carmona L, et al. A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21. Nat Genet 2007;39:984-988.

Amundadottir LT, Sulem P, Gudmundsson J, et al. A common variant associated with prostate cancer in European and African populations. Nat Genet 2006;38:652-658.

Rafnar T, Sulem P, Stacey SN, et al. Sequence variants at the TERT-CLPTM1L locus associate with many cancer types. Nat Genet 2009;41:221-227.

Easton DF, Pooley KA, Dunning AM, et al. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007;447:1087-1093.

Broderick P, Carvajal-Carmona L, Pittman AM, et al. A genome-wide association study shows that common alleles of SMAD7 influence colorectal cancer risk. Nat Genet 2007;39:1315-1317.

Tenesa A, Farrington SM, Prendergast JG, et al. Genome-wide association scan identifies a colorectal cancer susceptibility locus on 11q23. Nat Genet 2008;40:631-637.

Eeles RA, Kote-Jarai Z, Giles GG, et al. Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet 2008;40:316-321.

Gudmundsson J, Sulem P, Steinthorsdottir V, et al. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet 2007;39:977-983.

Turnbull C, Ahmed S, Morrison J, et al. Genome-wide association study identifies five new breast cancer susceptibility loci. Nat Genet 2010;42:504-507.

Mavaddat N, Michailidou K, Dennis J, et al. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. Am J Hum Genet 2019;104:21-34.

Seal S, Thompson D, Renwick A, et al. Truncating mutations in the Fanconi anemia J gene BRIP1 are low-penetrance breast cancer susceptibility alleles. Nat Genet 2006;38:1239-1241.

Loveday C, Turnbull C, Ramsay E, et al. Germline mutations in RAD51D confer susceptibility to ovarian cancer. Nat Genet 2011;43:879-882.

Buniello A, MacArthur JAL, Cerezo M, et al. The NHGRI-EBI GWAS Catalog of published genome-wide association studies, targeted arrays and summary statistics. Nucleic Acids Res 2019;47:D1005-D1012.

Raptis S, Mrkonjic M, Green RC, et al. MLH1 -93G>A promoter polymorphism and the risk of microsatellite-unstable colorectal cancer. J Natl Cancer Inst 2007;99:463-474.

End of reference document.