Germline Testing: A Therapeutic Imperative

Too often, germline testing is perceived as an "extra" step. In reality, it is a **therapeutic imperative**: the results alter systemic therapy choices, surgical planning, surveillance intensity, and cascade prevention. When missed, patients don't just lose information — they lose opportunities that could change survival and quality of life.

This document highlights the essential guidelines and implications, designed to support streamlined decision-making in daily practice.

Cancer Type	Who to Test (Key Criteria)	Key Genes/Panels to Consider
Breast Cancer	• TNBC ≤60; early onset; male breast; multiple primaries; testing to inform systemic/surgical decisions; broadened founder mutation ancestries beyond AJ (Polish, Icelandic, French Canadian, Bahamian, Spanish/Mexican/Central–South American, Hungarian, Brazilian [TP53 R337H], Dutch CDKN2A, etc.).	• BRCA1/2; PALB2; TP53; PTEN; CDH1; moderate-penetrance (CHEK2, ATM) with counseling. Notes: variant-specific risk nuances for ATM and BRCA1/2 missense; management individualized.
Ovarian Cancer	• All epithelial ovarian/fallopian/peritoneal cancers; add non-epithelial ovarian (SCTAT; SCCOHT) at any age; STIC lesions may be considered.	• BRCA1/2 core; lynch genes when history overlaps; consider BRIP1/RAD51C/RAD51D; acknowledge appropriateness of DICER1 and SMARCA4 for relevant histologies.
Pancreatic Cancer	• All exocrine pancreatic cancers (explicitly includes acinar cell carcinoma); individuals with qualifying family history.	• ATM, BRCA1/2, PALB2, CDKN2A, STK11, TP53, MLH1, MSH2, MSH6, EPCAM. • Screening note: Insufficient data to recommend surveillance for carriers of genes other than ATM, BRCA2, STK11, CDKN2A without close family history.
Prostate Cancer	• mCSPC/mCRPC; high/very-high-risk localized; intraductal/cribriform features; strong FH; early onset.	• BRCA1/2 (very strong for BRCA2); PALB2 (emerging); ATM (rare variants); HOXB13 (early-onset association); TP53 newly tied to risk with screening from age 40
Colorectal Cancer (CRC)	• CRC ≤50; multiple LS-related primaries; ≥1 FDR/SDR with CRC or EC plus another LS-related cancer; sebaceous neoplasms—consider tumor screening for dMMR; polyposis (≥10).	• MMR genes (MLH1, MSH2, MSH6, PMS2) and EPCAM; polyposis genes (APC, MUTYH, BMPR1A, SMAD4, STK11, PTEN) as indicated. • Nuance: For PMS2, extracolonic risks are uncertain —surveillance beyond CRC/EC should be individualized.
Urothelial Cancer (UC)	• All patients who meet the Amsterdam/Bethesda criteria or Hereditary breast and ovarian cancer/BRCA guidelines or have a close relative who would have met guidelines • All patients with MSI-H or MMR-deficient tumors • Early onset (<45y)	• All UTUC tumors → screen for dMMR/MSI. • If abnormal → germline testing (MLH1, MSH2, MSH6, PMS2, EPCAM). • If family history of Lynch cancers → germline testing regardless of tumor findings.
Endometrial Cancer	• EC ≤50; EC with synchronous/metachronous LS-related cancers; strong FH; dMMR/MSI-H tumors.	• MLH1, MSH2, MSH6, PMS2, EPCAM.
Gastric Cancer	• Diffuse/signet-ring gastric cancer at young age; families with multiple diffuse GC cases; scenarios with lobular breast + gastric combinations as per HDGC criteria.	• CDH1
Thyroid Cancer	• All patients with medullary thyroid carcinoma (MTC) should undergo germline RET testing as part of initial work-up (to diagnose MEN2; cascade testing for relatives. • Cowden/PTEN: thyroid US age 7–12.	• RET (germline); additional somatic RET testing when germline wild-type per guideline.
Melanoma	• Consider genetic evaluation when there are multiple primary melanomas in an individual, ≥3 melanomas in a family, or melanoma + pancreatic cancer clusters.	• CDKN2A, CDK4 (± BAP1, ± MITF p.E318K in select contexts).
Renal (Kidney) Cancer	• Suspect hereditary RCC with early onset, bilateral/multifocal tumors, non–clear cell histology, or family history of RCC; refer for genetics and panel testing.	• VHL, FLCN, FH, SDHx, BAP1, TSC1/2 (panel guided by histology and syndromic features).
Lung Cancer	• If EGFR T790M is identified de novo (no prior EGFR-TKI exposure), genetic counseling and possible germline testing are warranted.	• EGFR (germline T790M); consider broader assessment based on family history.
Adrenal/NETs	• All patients with PPGL (any age) should be considered for germline testing given high heritability; tailor panel based on tumor location, catecholamine phenotype, and family history.	• SDHB, SDHC, SDHD, SDHA, VHL, RET, NF1, MAX, TMEM127, FH (panel selection per phenotype)

Key clinical highlights include:

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1. Treatment-Altering Implications

a. PARP Inhibitor Eligibility

- **Breast cancer:** Olaparib and talazoparib improve survival in BRCA+ patients across early and metastatic stages.
- **Ovarian cancer:** BRCA+ patients achieve enhanced platinum sensitivity; PARP inhibitors provide effective maintenance.
- **Pancreatic cancer:** BRCA/PALB2 carriers show enhanced platinum response vs controls; olaparib maintenance extends survival.
- **Prostate cancer:** BRCA2+ mCRPC patients respond well to PARP inhibitors; both olaparib and rucaparib are FDA-approved.

b. Immunotherapy Eligibility

- **Lynch syndrome:** Checkpoint inhibitors yield 46–71% response in CRC, 14–100% in non-CRC Lynch cancers.
- **MSI-High tumors:** Pembrolizumab and other agents achieve durable responses, sometimes complete pathological remissions.

c. Targeted Therapy Access

- **RET-positive thyroid cancer:** Selective RET inhibitors (selpercatinib, pralsetinib) deliver superior efficacy and fewer side effects than multi-kinase inhibitors.

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2. Prevention and Cascade Testing

- **BRCA carriers:** 50% inheritance risk; enhanced screening (annual MRI age 25–30), prophylactic mastectomy, pancreatic/prostate screening in men.
- **Lynch syndrome:** Colonoscopy every 1–2 years from age 20–25; endometrial surveillance; prophylactic hysterectomy considered.
- **CDKN2A carriers:** ~90% melanoma risk; dermatologic exams every 6 months.

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3. Prophylactic Surgery Options

- Risk-reducing salpingo-oophorectomy (BRCA, RAD51C/D)
- Prophylactic thyroidectomy (RET-positive children)
- Bilateral mastectomy for high-risk BRCA carriers

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4. Enhanced Surveillance Protocols

- VHL syndrome: Multi-organ monitoring (kidney, CNS, adrenal).
- Lynch syndrome: Annual endometrial biopsy (age 30–35+), intensified colonoscopy.
- Hereditary renal cancers: Subtype-specific imaging surveillance.

Bottom line: Germline testing is not optional screening—it is a frontline decision tool that reshapes therapy, prevention, and outcomes for both patients and their families.

Key References:

1. Adjuvant Olaparib for Patients with BRCA1- or BRCA2-Mutated Breast Cancer
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3. PARP Inhibition in Prostate Cancer With Homologous Recombination Repair Alterations
4. Long-Term Efficacy of Pembrolizumab and the Clinical Utility of ctDNA in Locally Advanced dMMR/MSI-H Solid Tumors
5. An Update on Immune Checkpoint Therapy for the Treatment of Lynch Syndrome
6. NCCN Genetic/ Familial High-Risk Assessment: Breast, Ovarian, Pancreatic, and Prostate
7. NCCN Genetic/ Familial High-Risk Assessment: CRC, Endometrial, and Gastric
8. The emerging landscape of germline variants in urothelial carcinoma: Implications for genetic testing

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