New Orleans Summer Cancer Meeting

Cancer Genetic Risk Factors:

What's New and What You Need to Know?

SYLVESTER COMPREHENSIVE CANCER CENTER
UNIVERSITY OF MIAMI HEALTH SYSTEM

NCI Designated Cancer Center

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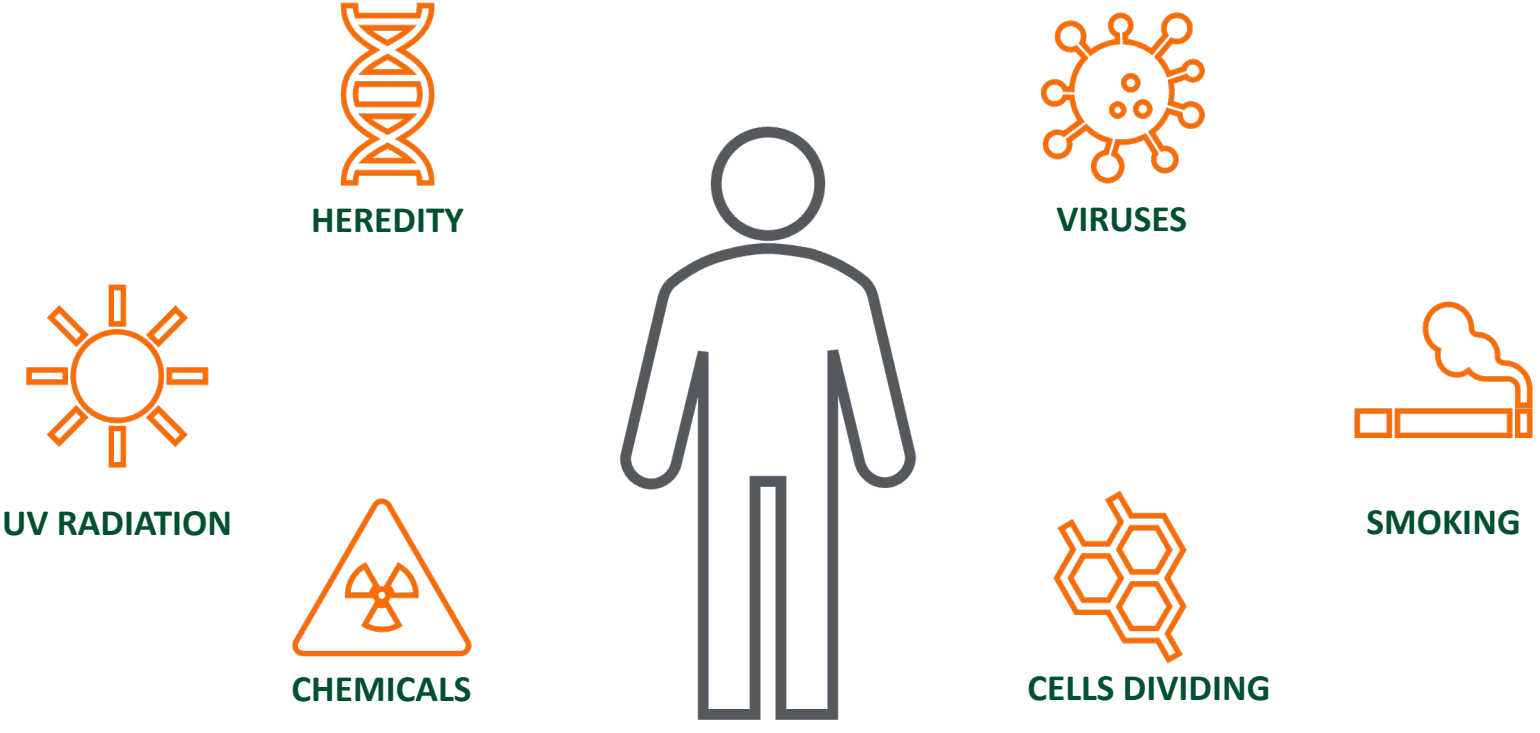
OBJECTIVES

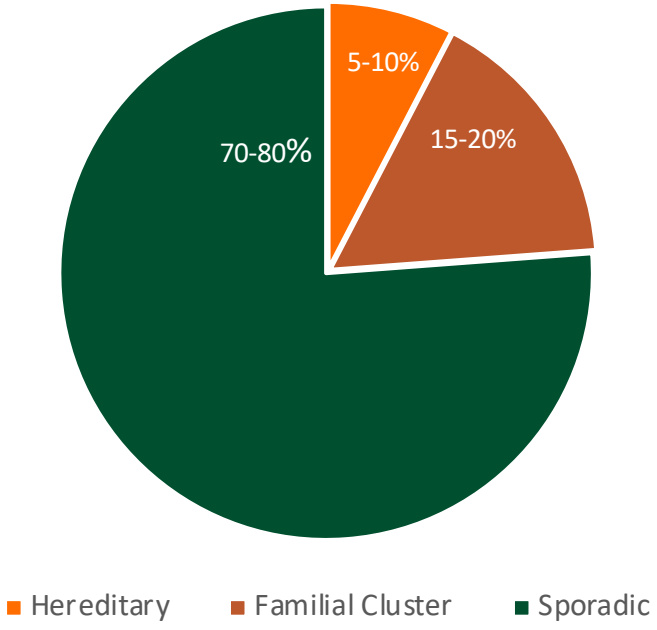
- Identify basics of cancer genetics
- Recognize differences in somatic and germline testing
- Describe possible outcomes in germline testing and interpreting variant of uncertain significance (VUS)
- Demonstrate current NCCN guidelines for germline testing
- Acquire knowledge on ASCO updates for germline testing

CANCER GENETICS

BASICS OF CANCER GENETICS



CAUSES OF CANCER

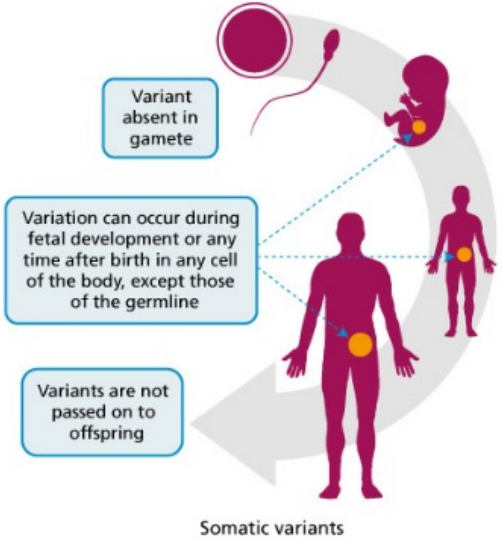


- **SPORADIC:**
  - Majority of cancers
- **HEREDITARY:**
  - >50 single-gene syndromes identified
  - Growing number of low/moderate-risk genes
- **FAMILIAL CLUSTER:**
  - Possible unidentified single-gene pathogenic variant
  - Shared environment or shared genetic

SOMATIC TESTING & GERMLINE TESTING

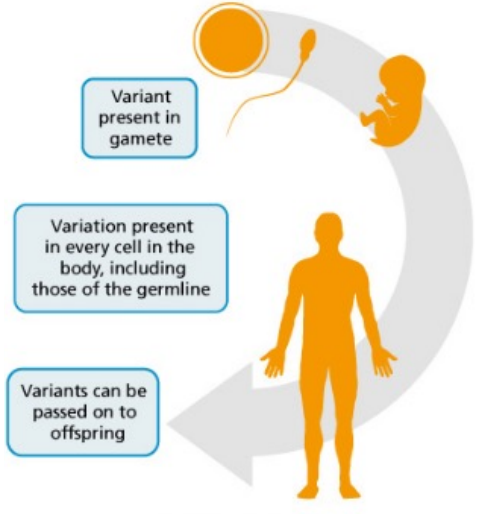
SOMATIC VS GERMLINE

- **SOMATIC MUTATIONS:**
  - Occurs in non-reproductive cells
  - Only affecting the tissues derived from the altered cell
  - Can be used for prediction, prognosis, and diagnosis



Somatic variants

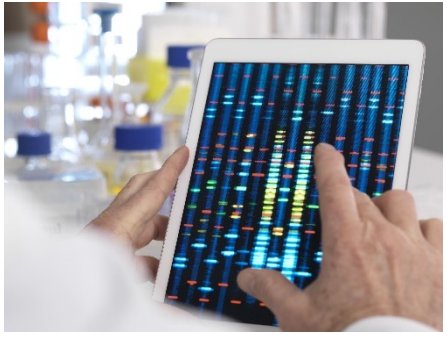
- **GERMLINE MUTATIONS:**
  - Occurs in reproductive cells (sperm or egg cells)
  - Potentially being passed on to subsequent generations



Germline variants

Illustration from : https://www.genomicseducation.hee.nhs.uk/cancer-genomics/

BASIC INDICATIONS FOR GERMLINE TESTING



- Early onset of cancer(s)
- Multiple family members on the same side with same cancer(s)
- Known genetic mutations (or pathogenic variants) in the family
- Ashkenazi Jewish Ancestry
- Multiple cancers in an individual
- Close degree of affected individual(s) or affected individual with diagnosis at any age (pancreatic cancer, ovarian cancer, metastatic prostate cancer, triple negative breast cancer)
- Rare cancers such as breast cancer in male or retinoblastoma
- Cluster of affected individuals on the same side of the family
- Bilateral cancer in the same organ (such as breast or renal cancer)
- Many colon polyps (>20 adenomas)

INTERPRETING GERMLINE TESTING:VARIANT CLASSIFICATIONS

Pathogenic	Likely Pathogenic	Uncertain Significance	Likely Benign	Benign
				
Alteration which directly contributes to disease development	Alteration which is very likely to contribute to disease development, but evidence is insufficient to conclusively prove	Alteration detected but no evidence to support a classification	Alteration which is not likely to contribute to disease development, but evidence is insufficient to conclusively prove	Alteration which does not cause disease

CONSIDERATIONS FOR VARIANTS OF UNCERTAIN SIGNIFANCE (VUS)

- Are common with use of large multi-gene panels
- Are more common in racial and ethnic minorities compared with non-Hispanic white individuals
- When reclassified, approximately 80%–90% are reclassified as likely benign or benign and 10%–20% as P/LP

While VUS are part of genetic testing results, they should be interpreted cautiously and not used in isolation to dictate medical management.

- Collaborate with genetic specialists
- Consider broader health contexts are essential for making informed decisions about screening and risk reduction strategies

CONSIDERATIONS FOR VUS – TO TEST OR NOT TO TEST?

- Base medical management decisions on personal and family medical histories
- Consider factors like symptoms and age of onset
- **TESTING FAMILY MEMBERS FOR VUS**
  - Generally, not recommended unless there is clinical suspicion of a genetic condition that could be clarified by additional testing
  - Specific circumstances include cases where the VUS may explain a genetic condition, providing insight into inheritance patterns or phenotypic expression

VUS: RNA ANALYSIS AND RESEARCH STUDIES

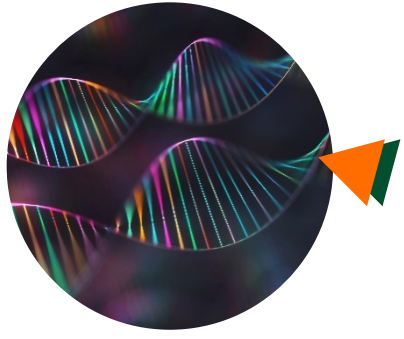
- **RNA CAN BE HELPFUL WITH VUS**
  - Determine whether a variant affects the expression or function of a gene by analyzing how it influences RNA transcripts
  - Useful for variants where the effect on protein function or gene regulation is uncertain based on DNA analysis alone

- **RESEARCH STUDIES IN VUS**
  - Consider referral to research studies aimed at defining the functional impact of variants can be beneficial
  - Often conducted by clinical laboratories or registries specializing in variant reclassification
  - Aim to gather additional data over time to better understand the clinical implications of variants
  - Participation can lead to updated classifications of variants as more evidence becomes available

- **RESOURCES**
  - For current data of classification status such as: https://www.ncbi.nlm.nih.gov/clinvar/, https://brcaexchange.org/about/app and https://www.cangene-canvaruk.org/canvig-uk

CURRENT NCCN GUIDELINES

CURRENT NCCN GUIDELINES FOR HEREDITARY CANCER TESTING- VERSION 3.2024



GENERAL TESTING CRITERIA:

- Individual with any blood relative with a known Pathogenic / Likely Pathogenic (P/LP) variant in cancer susceptibility gene
- Individual with previous limited testing
  - I.e.: single gene/absent deletion/duplication) who meets testing criteria for multigene panel
- P/LP variant identified on tumor genomic testing
- To aid in systemic therapy or surgical decisions
- Individual who meets Li-Fraumeni Syndrome (LFS) or Cowden (PTEN) or Lynch Syndrome (LS) testing criteria
- Testing may be considered in:
  - Ashkenazi Jewish ancestry without other risk factors and personal history of serous endometrial cancer

Genetics_bop.pdf (nccn.org). National Comprehensive Cancer Network. (2024, February 12). https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

CURRENT NCCN GUIDELINES FOR HEREDITARY CANCER TESTING- VERSION 3.2024

OVARIAN:

- Epithelial ovarian (including fallopian tube cancer or peritoneal cancer) at any age

PANCREATIC:

- All individuals diagnosed with exocrine pancreatic cancer

Genetics_bop.pdf (nccn.org). National Comprehensive Cancer Network. (2024, February 12). https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

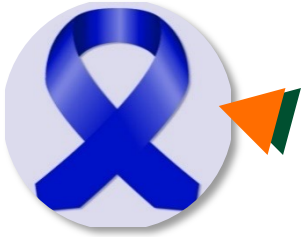
CURRENT NCCN GUIDELINES FOR HEREDITARY CANCER TESTING- VERSION 3.2024

PROSTATE:

- Metastatic (any age)
- High or Very High-risk group: cT3a to cT4, Grade group 4, Grade Group 5, Gleason pattern 5, PSA > 20 ng/mL
- Ancestry: Ashkenazi Jewish ancestry
- Prostate cancer at any age with family history of ≥1 close blood relative with ANY: breast cancer at age ≤50, male breast cancer, triple negative breast cancer, ovarian cancer, pancreatic cancer, prostate cancer with metastatic, or high- or very-high-risk group or ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with prostate cancer

Genetics_bop.pdf (nccn.org). National Comprehensive Cancer Network. (2024, February 12). https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

CURRENT NCCN GUIDELINES FOR HEREDITARY CANCER TESTING- VERSION 3.2024



COLORECTAL- Lynch Syndrome Criteria

- < 50 at diagnosis
- Known MMR deficiency in tumor at any age
- Synchronous or metachronous CRC
- CRC at any age with family history of : ≥1 close blood relative with Lynch Syndrome (LS) cancer at <50 or ≥2 close blood relatives with LS related cancer at any age

COLORECTAL- Adenomatous Polyposis Criteria

- Personal history of ≥ 20 cumulative adenomas
- Known PV/LP in polyposis gene
- Multifocal/bilateral congenital hypertrophy of retinal pigment epithelium (CHRPE)
- Consider testing if: 10-19 cumulative adenomas, desmoid tumor, hepatoblastoma, cribriform-morular variant of papillary thyroid cancer, unilateral CHRPE

Genetics_bop.pdf (nccn.org). National Comprehensive Cancer Network. (2024, February 12). https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

CURRENT NCCN GUIDELINES FOR HEREDITARY CANCER TESTING- VERSION 3.2024

BREAST:

- Diagnosis at ≤50 years
- To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting or adjuvant setting in HER2
- Triple Negative Breast, Multiple primary breast cancers (synchronous or metachronous), Lobular breast cancer with personal or family history of diffuse gastric cancer
- Male breast cancer
- Ancestry: Ashkenazi Jewish ancestry
- Breast cancer at any age with family history of ≥1 close blood relative with ANY: breast cancer at age ≤50, male breast cancer, ovarian cancer, pancreatic cancer, prostate cancer with metastatic, or high- or very-high-risk group or ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer

Genetics_bop.pdf (nccn.org). National Comprehensive Cancer Network. (2024, February 12). https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf

ASCO UPDATES

Germline Testing in Patients With Breast Cancer: ASCO–Society of Surgical Oncology Guideline

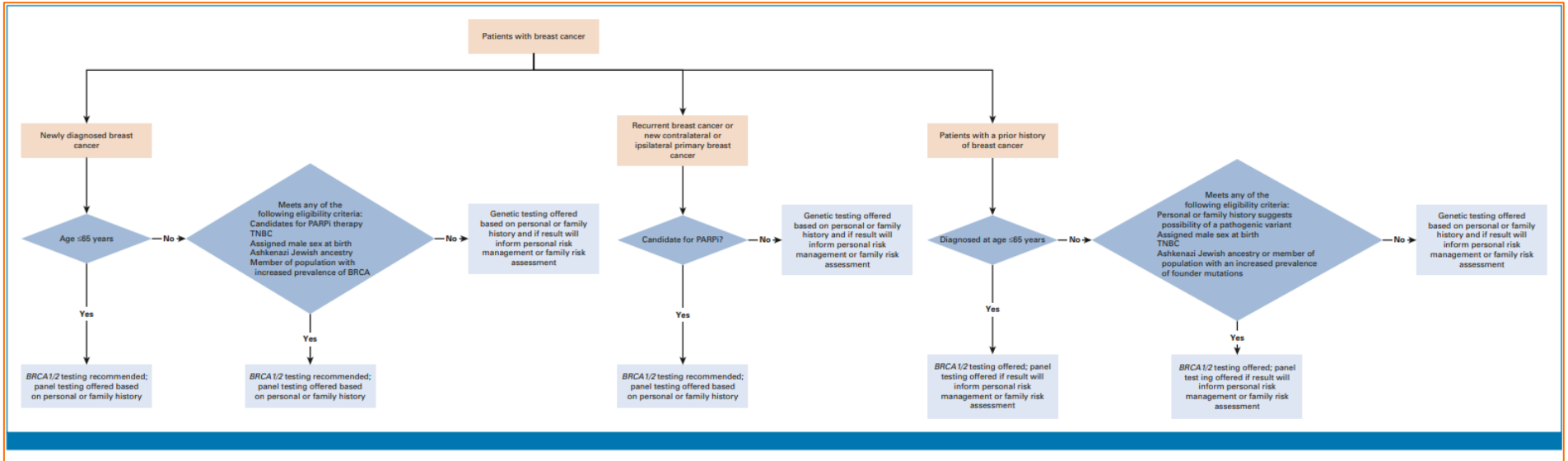


FIG 1. Algorithm for Germline Testing in Patients with Breast Cancer Abbreviations. PARPi, poly(ADP-ribose) polymerase inhibitors; TNBC, triple-negative breast cancer.

Isabelle Bedrosian et al., Germline Testing in Patients With Breast Cancer: ASCO–Society of Surgical Oncology Guideline. *JCO* **42**, 584-604(2024).DOI:10.1200/JCO.23.02225

ASCO Update: Selection of Germline Genetic Testing Panels in Patients With Cancer

KEY CONSIDERATIONS WITH GERMLINE TESTING:

- Detailed family history taken (details of cancer, first- and second-degree relatives and ethnicity)
- Multigene panel should be offered if > 1 gene is relevant based on personal or family history
- Patients who meet criteria for germline genetic testing should be offered germline testing regardless of results from tumor testing
- Patients who would not normally be offered germline genetic testing based on personal and/or family history criteria but who have a pathogenic or likely pathogenic variant identified by tumor testing should be offered germline testing

Nadine Tung et al., Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline. *JCO* **0**, JCO.24.00662DOI:10.1200/JCO.24.00662

ASCO UPDATE: CONTINUED

WHEN CONSIDERING WHAT GENES TO INCLUDE IN THE PANEL, THE MINIMAL PANEL SHOULD INCLUDE:

- The more strongly recommended genes from Table 1 and may include those less strongly recommended.

- A broader panel may be ordered when the potential benefits are clearly identified, and the potential harms from uncertain results should be mitigated.

TABLE 1. Genes Recommended for Testing and Inclusion in Multigene Panels for Selected Cancers

Cancer Type and Specific Population	More Strongly Recommended (higher relative risk of cancer or highly actionable)	Less Strongly Recommended (moderate relative risk of cancer or potential impact for therapy/change in medical management)
Breast cancer	*BRCA1, BRCA2, PALB2* *CDH1*[a], *PTEN*[a], *STK11*[a], *TP53*[a,c]	*ATM, BARD1, CHEK2, RAD51C, RAD51D* *NF1*[a,b]
Colorectal cancer	*APC, EPCAM, MLH1, MSH2, MSH6, MUTYH*[d], *NTHL1*[d], *PMS2, POLD1, POLE* *BMPR1A*[a], *SMAD4*[a], *STK11*[a], *TP53*[a,c]	*AXIN2, CHEK2, MBD4* *GREM1*[a], *MSH3*[a], *PTEN*[a], *RNF43*[a]
Endometrial cancer	*EPCAM, MLH1, MSH2, MSH6, PMS2* *PTEN*[a], *STK11*[a]	NA
Gastric cancer	*APC, CTNNA1, EPCAM, MLH1, MSH2, MSH6, PMS2* *BMPR1A*[a], *CDH1*[a], *SMAD4*[a], *STK11*[a]	NA
Gastrointestinal stromal tumors	*KIT, PDGFRA* If SDH-deficient or *SDH*-mutant tumor: *SDHA, SDHAF2, SDHB, SDHC, SDHD* If *NF1*-mutated tumor: *NF1*	If tumor is not SDH-deficient, *SDH*-mutated, or *NF1*-mutated: *NF1, SDHA, SDHAF2, SDHB, SDHC, SDHD*
Medullary thyroid carcinoma	*RET*	NA
Non–small cell lung cancer—if *EGFR* tumor pathogenic variant (such as p.T790M) found with no previous EGFR-TKI therapy	*EGFR* *STK11*[a]	*TP53*[a,c]
Adrenocortical tumors	*APC, EPCAM, MEN1, MLH1, MSH2, MSH6, PMS2, TP53*	NA
Melanoma, cutaneous	*CDKN2A, CDK4*	*BAP1, MC1R, MITF, POT1, TERT* *PTEN*[a]
Melanoma, uveal	*BAP1*	NA
Ovarian cancer (epithelial)	*BRCA1, BRCA2, BRIP1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, RAD51C, RAD51D*	*ATM*
Pancreatic adenocarcinoma	*ATM, BRCA1, BRCA2, CDK4, CDKN2A, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2* *STK11*[a], *TP53*[a,c]	*APC*
Phaeochromocytomas and paragangliomas	*FH, MAX, RET, SDHA, SDHB, SDHC, SDHD, TMEM127* *NF1*[a], *VHL*[a]	*EGLN1, EPAS1, KIF1B, MET, SDHAF2*
Prostate cancer	*BRCA1, BRCA2, EPCAM, HOXB13, MLH1, MSH2, MSH6, PMS2*	*ATM, CHEK2, PALB2*
Renal cell carcinoma	*BAP1, FH, FLCN, MET, SDHA, SDHAF2, SDHB, SDHC, SDHD* *PTEN*[a], *VHL*[a]	*TSC1*[a], *TSC2*[a]
Sarcoma (soft tissue or osteosarcoma)	*TP53*[a,c]	*NF1*[a], *RB1*[a]

Nadine Tung et al.,Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline. *JCO* **0**, JCO.24.00662DOI:10.1200/JCO.24.00662

ASCO UPDATE: CONTINUED

ALL PATIENTS WITH PATHOGENIC VARIANTS IDENTIFIED IN TUMOR TESTING WHICH WARRANT GERMLINE TESTING:

- BRCA1, BRCA2, BRIP1, MLH1, MSH2, MSH6, MUTYH (when biallelic), PALB2, PMS2, RAD51C, RAD51D, RET, SDHAF2, SDHB, SDHD, TMEM127, TSC2, VHL
- Test only if patient <30 years old: APC, PTEN, RB1, TP53 (brain tumors excluded)

PATIENTS WITH PATHOGENIC VARIANTS IDENTIFIED IN TUMOR TESTING MAY BE OFFERED GERMLINE TESTING:

- ATM, BAP1, BARD1, CHEK2, DICER1, FH, FLCN, NF1, POLD1, POLE, SDHA
- Test only if patient < 30 years old: CDKN2A, SMARCA4

Nadine Tung et al.,Selection of Germline Genetic Testing Panels in Patients With Cancer: ASCO Guideline. *JCO* **0**, JCO.24.00662DOI:10.1200/JCO.24.00662

ARTICLE REVIEWS

Key Points from Universal Germline and Tumor Genomic Testing Needed to Win the War Against Cancer: Genomics is the Diagnosis by Vivek Subbiah et al in the Journal of Clinical Oncology in June 2023

- Updated viewpoint from universal somatic testing to also include universal germline testing to win war against cancer because only somatic testing is insufficient for identifying inherited cancer risks in relatives
- Germline testing allows for proactive management and tailored interventions if predisposition identified and can assist in reducing apprehension about cancer risk in those who are identified as non-carriers
- It transforms outcomes for traditional hereditary syndromes and identifies broader associations and risks from germline variants
- Comprehensive genetic insights are crucial for effective cancer treatment and early detection strategies

Vivek Subbiah et al.,Universal Germline and Tumor Genomic Testing Needed to Win the War Against Cancer: *Genomics Is the Diagnosis*. *JCO* **41**, 3100-3103(2023).DOI:10.1200/JCO.22.02833

Key Points from Universal Germline and Tumor Genomic Testing Needed to Win the War Against Cancer: Continued

- **CHALLENGES IN IMPLEMENTING UNIVERSAL GENOMIC TESTING (SOMATIC AND GERMLINE) INCLUDE:**
  - Logistics
  - Insurance coverage
  - Need for education
- Access to well-trained genetic counselors is crucial for effective family member testing and counseling as part of genomic services
- **INNOVATIVE SOLUTIONS OUTLINED IN THE ASCO EDUCATIONAL HANDBOOK INCLUDE:**
  - Telegenetics
  - Group genetic counseling
  - Collaboration with non-genetics healthcare professionals
  - Genetic counselor extenders
  - Modifications of traditional counseling models

Vivek Subbiah et al.,Universal Germline and Tumor Genomic Testing Needed to Win the War Against Cancer: *Genomics Is the Diagnosis*. *JCO* **41**, 3100-3103(2023).DOI:10.1200/JCO.22.02833

UNIVERSAL TESTING VS GUIDELINE-DIRECTED TESTING IN CANCER

Multisite study (Interrogating Cancer Etiology Using Proactive Genetic Testing [INTERCEPT] program) within Mayo Clinic (Rochester, Minnesota, Jacksonville and Phoenix) in patients with solid tumors from 4/1/18 to 3/31/20.

POPULATION

- Inclusion:
  - English-speaking adult (18-85 years of age)
  - new or active cancer diagnosis of carcinoma
  - treated at any of the Mayo Clinic Cancer Centers
- Exclusion:
  - Hematologic malignant cancers
  - Cancer survivors

METHOD

- Patients were unselected for various items such as:
  - cancer type
  - stage of disease
  - Family history of cancer
  - race/ethnicity
  - age

METHOD

- Patients viewed a standardized pretest education video (also offered additional pretest genetic counseling)
- Testing with panel of 83 genes (84 genes as of July 2019) with Invitae Multi-Cancer panel (at no cost)
- All test results were reviewed by a certified genetic counselor, results disclosed to the patient and those with PGVs were invited for genetic counseling.

Samadder et al., Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients With Hereditary Cancer Syndrome. JAMA Oncol. 2021 Feb 1;7(2):230-237. doi: 10.1001/jamaoncol.2020.6252. Erratum in: JAMA Oncol. 2021 Feb 1;7(2):312. doi: 10.1001/jamaoncol.2020.7373. PMID: 33126242; PMCID: PMC7600058.

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RESULTS

- 2984 patients
- PGV were found in 397 patients (13.3%)
  - 282 moderate to high penetrance genes
- VUS were found in 1415 patients (47.4%)
- Clinically actionable findings in 192 patients (6.4%)
  - Would not have been detected if by phenotype or family history testing criteria
  - 42 patients (28.2%) had modifications to treatment

CONCLUSION

- Universal multigene panel testing in solid tumor patients was noted to have increased detection of PGV over the predicted target testing guidelines alone
- Almost 30% of patients with high penetrant genes had change in therapy

Samadder et al., Comparison of Universal Genetic Testing vs Guideline-Directed Targeted Testing for Patients With Hereditary Cancer Syndrome. JAMA Oncol. 2021 Feb 1;7(2):230-237. doi: 10.1001/jamaoncol.2020.6252. Erratum in: JAMA Oncol. 2021 Feb 1;7(2):312. doi: 10.1001/jamaoncol.2020.7373. PMID: 33126242; PMCID: PMC7600058.


THANK YOU
DAVID BARNES

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