Genetic Counseling: Dealing with Uncertainty

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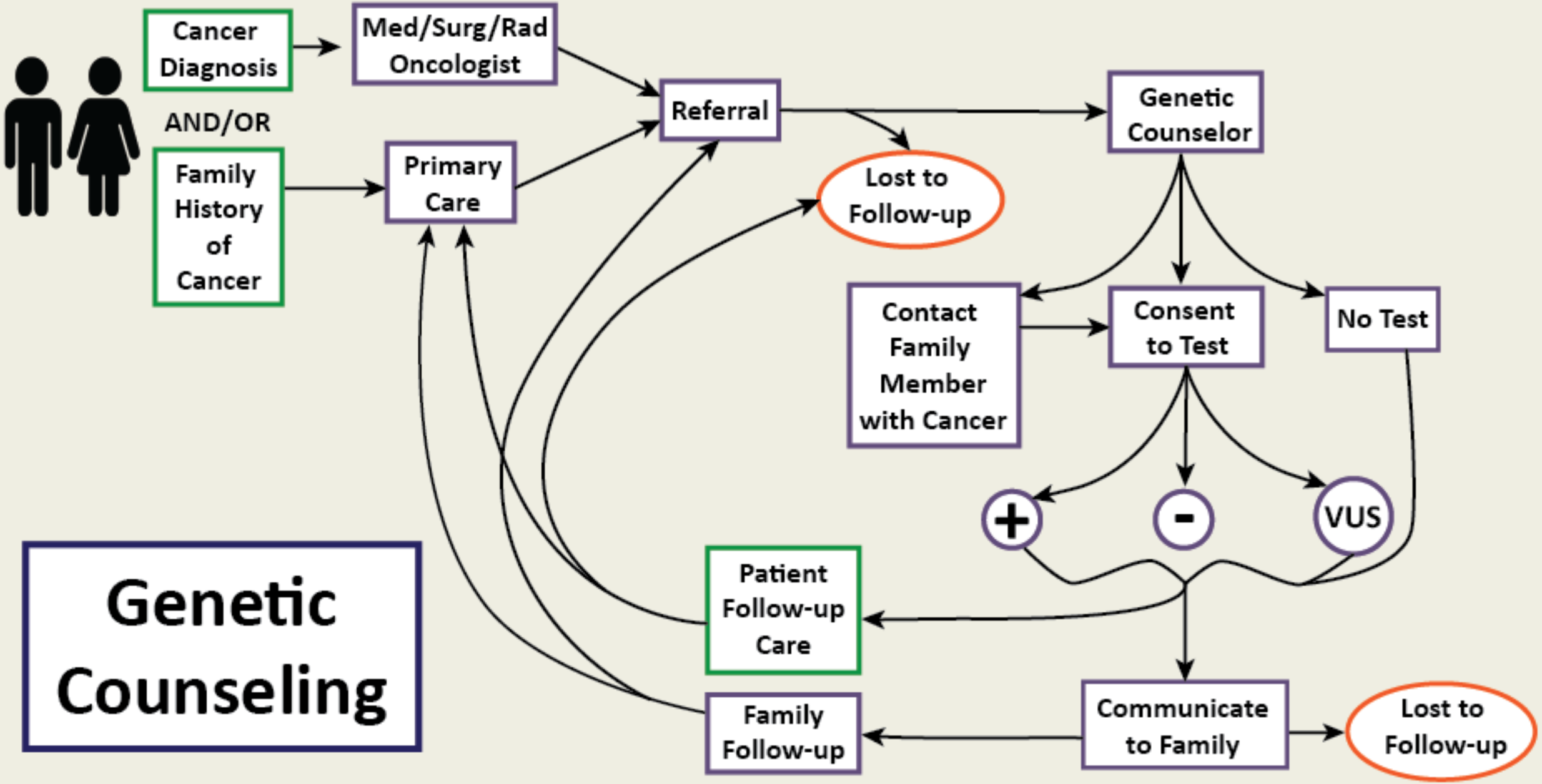
NIH NATIONAL CANCER INSTITUTE


Cancer Diagnosis
Med/Surg/Rad Oncologist
AND/OR
Family History of Cancer
Primary Care
Referral
Lost to Follow-up
Genetic Counselor
Contact Family Member with Cancer
Consent to Test
No Test
+
-
VUS
Patient Follow-up Care
Family Follow-up
Communicate to Family
Lost to Follow-up
Genetic Counseling

Multiple Paths to Genetic Counseling/Testing

- Family history triggers referral
- Cancer Diagnosis
  - Colon – Mismatch repair
  - Tumor sequencing/germline sequencing
- Pre-natal testing
- Direct-to-consumer

From: **Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers**

JAMA. 2017;317(23):2402-2416. doi:10.1001/jama.2017.7112

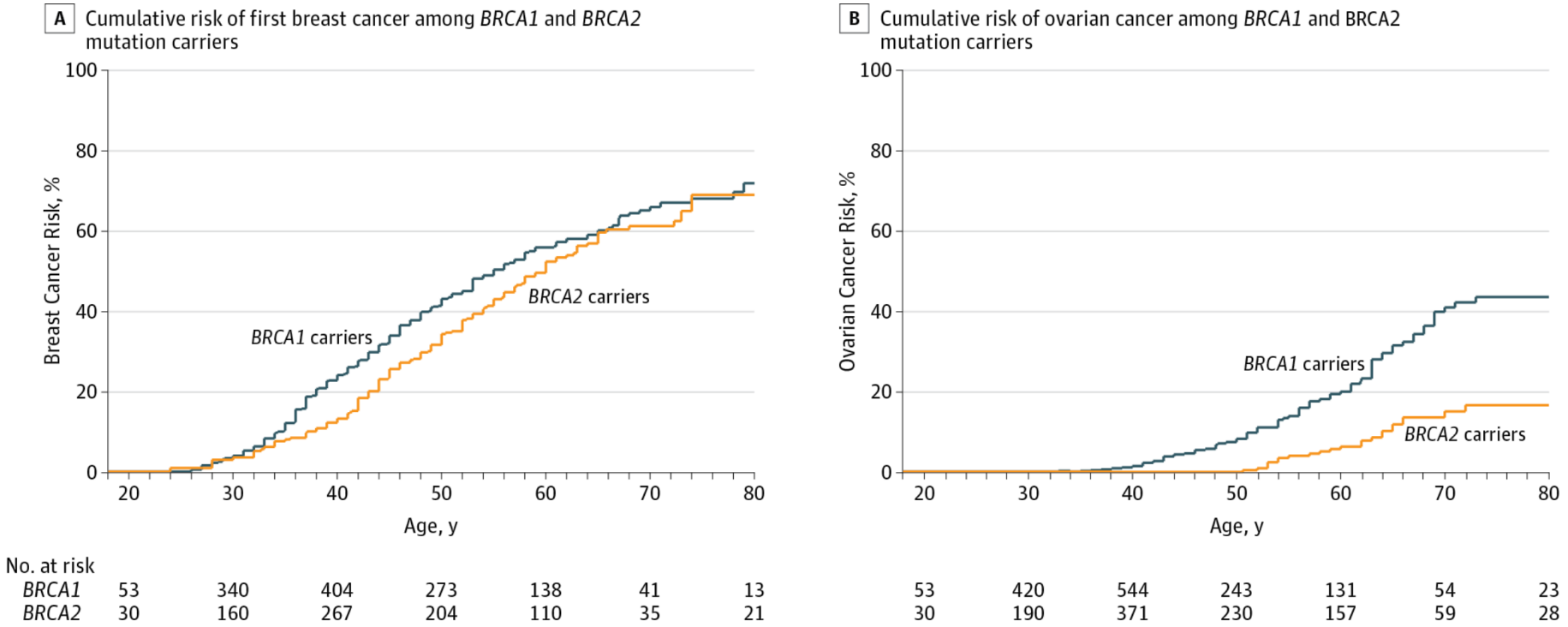


Figure Legend:

Estimated Cumulative Risks of Breast and Ovarian Cancer in Mutation CarriersKaplan-Meier estimates of cumulative risks of breast and ovarian cancers. In the breast cancer analysis, women were censored at risk-reducing bilateral mastectomy. In the ovarian cancer analysis, women were censored for risk-reducing salpingo-oophorectomy. Number at risk indicates the number of women who remained at risk at the end of the 10-year age category (eg, in panel A, there were 138 women with BRCA1 mutations still at risk of breast cancer at the end of the age 50-60 years period). The earliest follow-up started at age 18 years.

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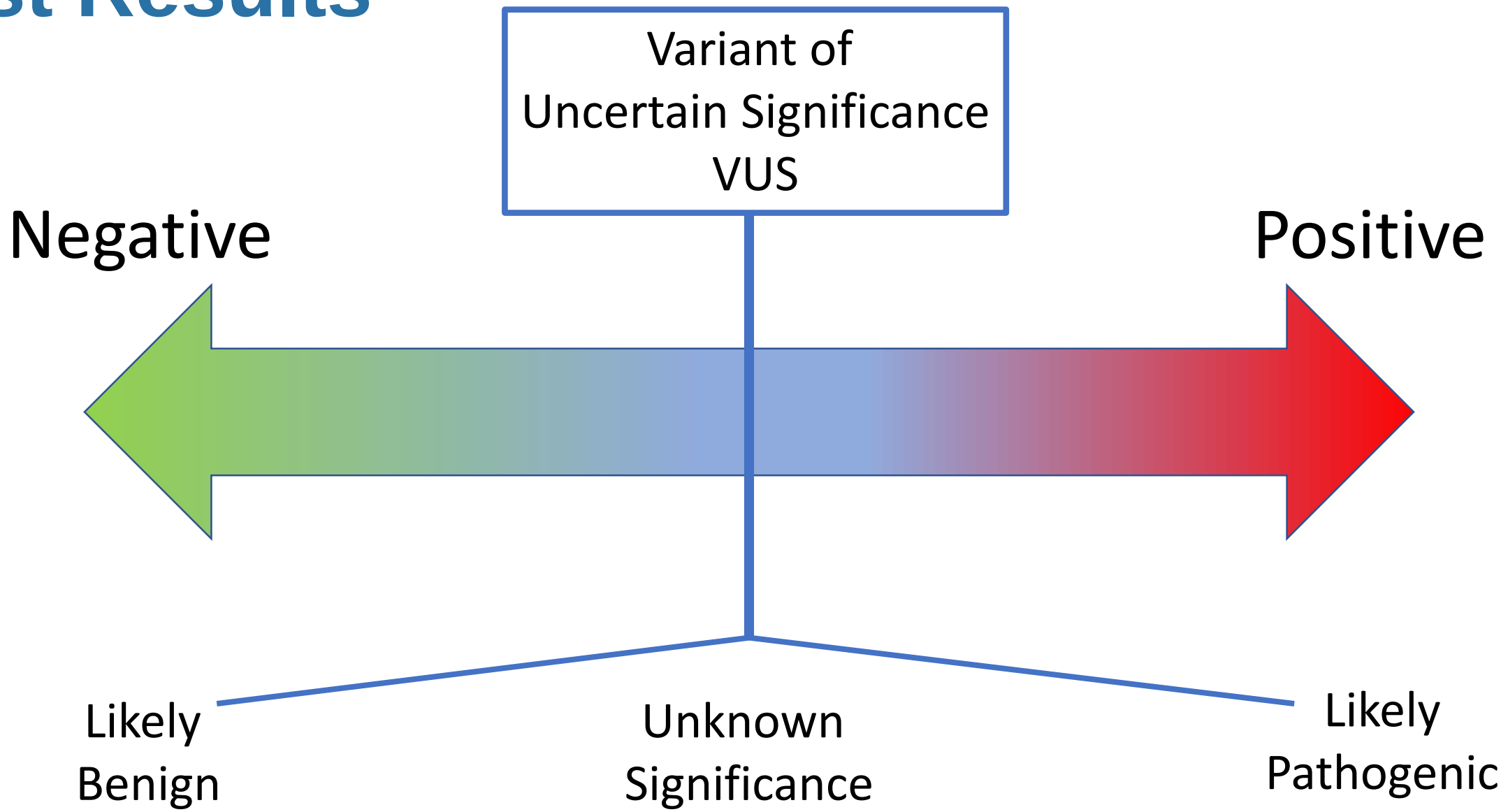
Cancer Risks in Individuals with Lynch Syndrome Age ≤70 Years Compared to the General Population

Cancer Type	General Population Risk	Lynch Syndrome (*MLH1* and *MSH2* heterozygotes)	
		Risk	Mean Age of Onset
Colon	4.8%	52%-82%	44-61 years
Endometrium	2.7%	25%-60%	48-62 years
Stomach	<1%	6%-13%	56 years
Ovary	1.4%	4%-12%	42.5 years
Hepatobiliary tract	<1%	1.4%-4%	Not reported
Urinary tract	<1%	1%-4%	~55 years
Small bowel	<1%	3%-6%	49 years
Brain/central nervous system	<1%	1%-3%	~50 years
Sebaceous neoplasms	<1%	1%-9%	Not reported

https://www.ncbi.nlm.nih.gov/books/NBK1211/

Test Results



52375963

Integrated BRAC*Analysis*® with Myriad myRisk™ Hereditary Cancer

myRisk Genetic Result

MYRIAD myRisk™ Hereditary Cancer | Powered by myVision™

RECEIVING HEALTHCARE PROVIDER	SPECIMEN		PATIENT	
Test HCP, MD	Specimen Type:	**Blood**	Name:	**Pt Last Name, Pt First Name**
Test Medical Center	Draw Date:	**Apr 18, 2016**	Date of Birth:	
123 Main St	Accession Date:	**Apr 18, 2016**	Patient ID:	**Patient id**
Testville, TX 55555	Report Date:	**Apr 19, 2016**	Gender:	**Female**
			Accession #:	**07000983-BLD**
			Requisition #:	**7000983**

RESULT: NEGATIVE - NO CLINICALLY SIGNIFICANT MUTATION IDENTIFIED

Note: "CLINICALLY SIGNIFICANT," as defined in this report, is a genetic change that is associated with the potential to alter medical intervention.

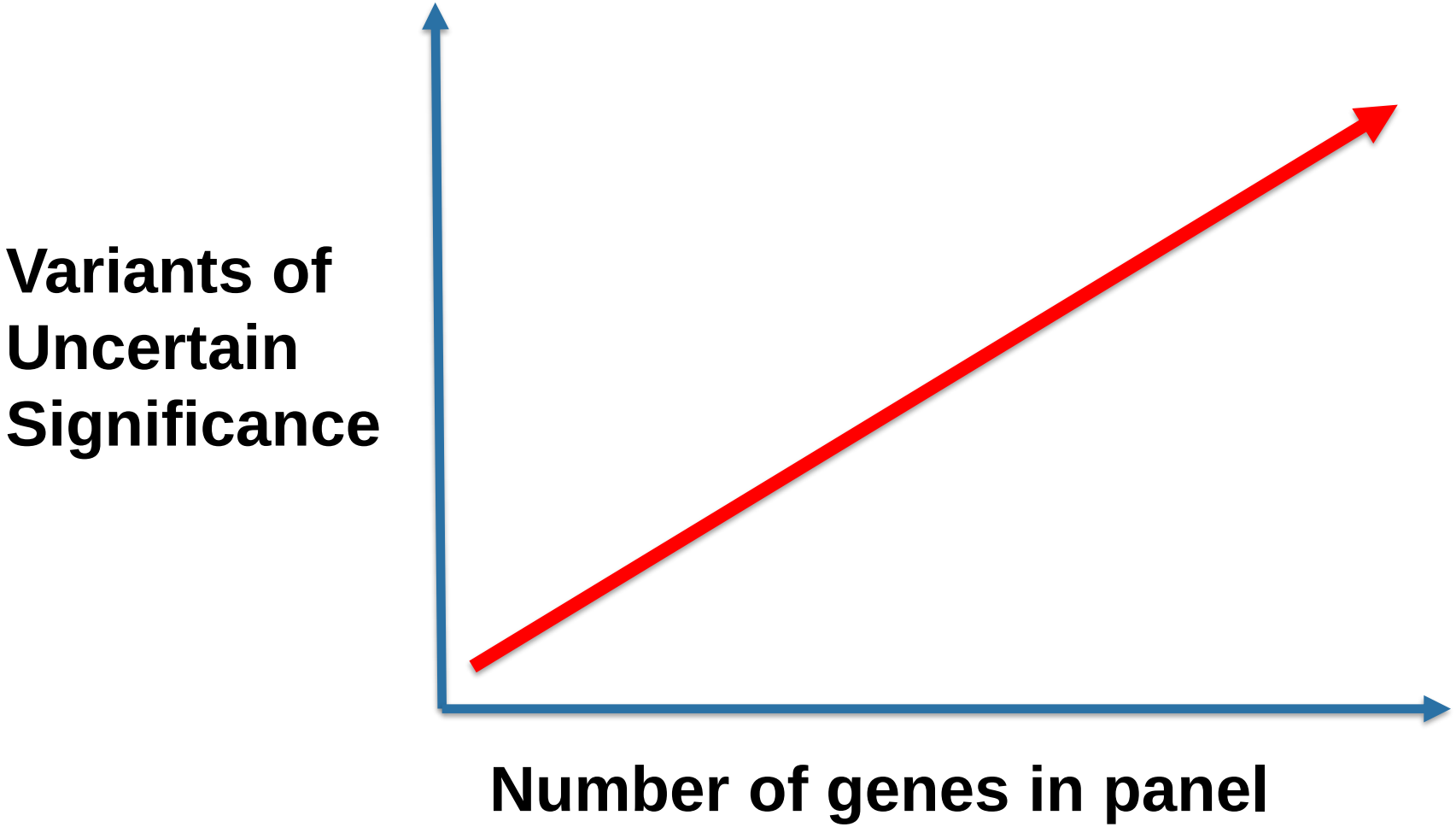
ADDITIONAL FINDINGS: VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

GENE	VARIANT(S) OF UNCERTAIN SIGNIFICANCE	INTERPRETATION
MLH1	c.xxxxx (p.xxxxx) (aka xxxxx)	**UNCERTAIN CLINICAL SIGNIFICANCE** There are currently insufficient data to determine if these variants cause increased cancer risk.
MSH2	c.xxxxx (p.xxxxx) (aka xxxxx)	

Details About Non-Clinically Significant Variants: All individuals carry DNA changes (i.e., variants), and most variants do not increase an individual's risk of cancer or other diseases. When identified, variants of uncertain significance (VUS) are reported. Likely benign variants (Favor Polymorphisms) and benign variants (Polymorphisms) are not reported and available data indicate that these variants most likely do not cause increased cancer risk. Present evidence does not suggest that non-clinically significant variant findings be used to modify patient medical management beyond what is indicated by the personal and family history and any other clinically significant findings.

Variant Classification: Myriad's myVision™ Variant Classification Program performs ongoing evaluations of variant classifications. In certain cases, healthcare providers may be contacted for more clinical information or to arrange family testing to aid in variant classification. When new evidence about a variant is identified and determined to result in clinical significance and management change, that information will automatically be made available to the healthcare provider through an amended report.

Genomic Sequencing/Multi-Gene Panels



Results and Interpretation

- Informative – risk clarified
  - True negative –known familial mutation not inherited
  - True positive - known pathogenic/deleterious mutation – variable penetrance
- Uninformative – risk not clarified
  - Possibility of hereditary cancer cannot be ruled out
    - negative (unaffected and no known familial mutation; family consistent with hereditary cancer syndrome)
    - variants of uncertain clinical significance (VUS)

Sources of Uncertainty

- Incomplete Penetrance
  - Susceptibility (risk) ≠ Disease
- Variations in Penetrance
  - Modifier factors (genes/environment)
- Variants of Uncertain Significance
- Uninformative tests

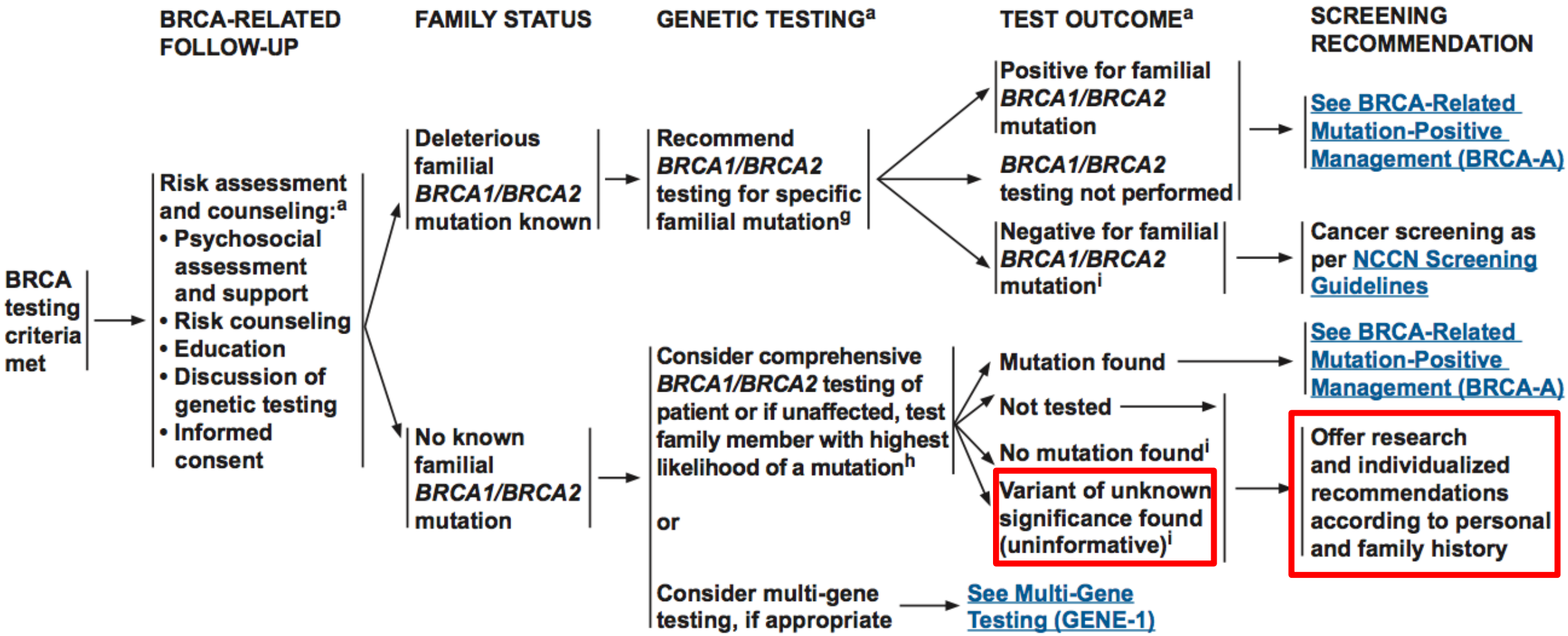
The VUS Challenge

- Lacks adequacy of information to classify as disease-causing or normal variation
- Association with disease risk is unknown
- Limited clinical utility
- No evidence-based guidelines
- Patients and providers may over-interpret the meaning of result

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2017
BRCA-Related Breast and/or Ovarian Cancer Syndrome

NCCN Guidelines Index
Table of Contents
Discussion



NCCN Guidelines: https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#breast_risk

Association between *BRCA* VUS Results and Surgical Decisions

- University of Washington Seattle: *BRCA*
  - 10.3% (11 of 107) of women with a *BRCA* VUS had risk-reducing mastectomy
  - 20.6% (22 of 107) had risk-reducing bilateral salpingo-oophorectomy
- City of Hope compared *BRCA* VUS results (n=71) with Uninformative results (n=714)
  - Similar risk reducing mastectomy (7%)
  - Risk-reducing oophorectomy 5%; 3%
  - More distress among those with VUS

Murray et al Genetic in Medicine 2011; 13:998-105
Culver et al Cin Genet 2013; 84:464-472

Lynch Syndrome: Patient Understanding of VUS

- Qualitative study of 28 individuals with a Lynch Syndrome VUS
  - “I’m just a waiting ticking time bomb for the cancers…”
  - “I would rather believe this is a positive interpretation so that way I could have a follow-up plan.”
  - “And getting my ovaries out – that was a hard decision….I want to live. Definitely safe vs sorry, absolutely.” (37 yo)
  - Pts expressed that ongoing or future contact from their providers would be appreciated, even if no new info
  - Emphasized the benefit from having a plan of action to reduce cancer risk in the face of uncertainty

Solomon et al J. Genet Counsel (2017) 26:866-877)

Integrating into Clinical Practice

Expert Review of Molecular Diagnostics

ISSN: 1473-7159 (Print) 1744-8352 (Online) Journal homepage: http://www.tandfonline.com/loi/ierо20

Toward clinical genomics in everyday medicine: perspectives and recommendations

Susan K. Delaney, Michael L. Hultner, Howard J. Jacob, David H. Ledbetter, Jeannette J. McCarthy, Michael Ball, Kenneth B. Beckman, John W. Belmont, [illegible] Bloss, Michael F. Christman, Andy Cosgrove, Stephen A. [illegible] Danis, Massimo Delledonne, Michael J. Dougherty, Joel [illegible] Jennifer R. Friedman, David H. Haase, Tom S. [illegible] Kaminsky, Nikki Ledbetter, Warren H. [illegible] derman, Richard L. Love, David [illegible] Megill, Helen [illegible] Ratay, Bradley [illegible]

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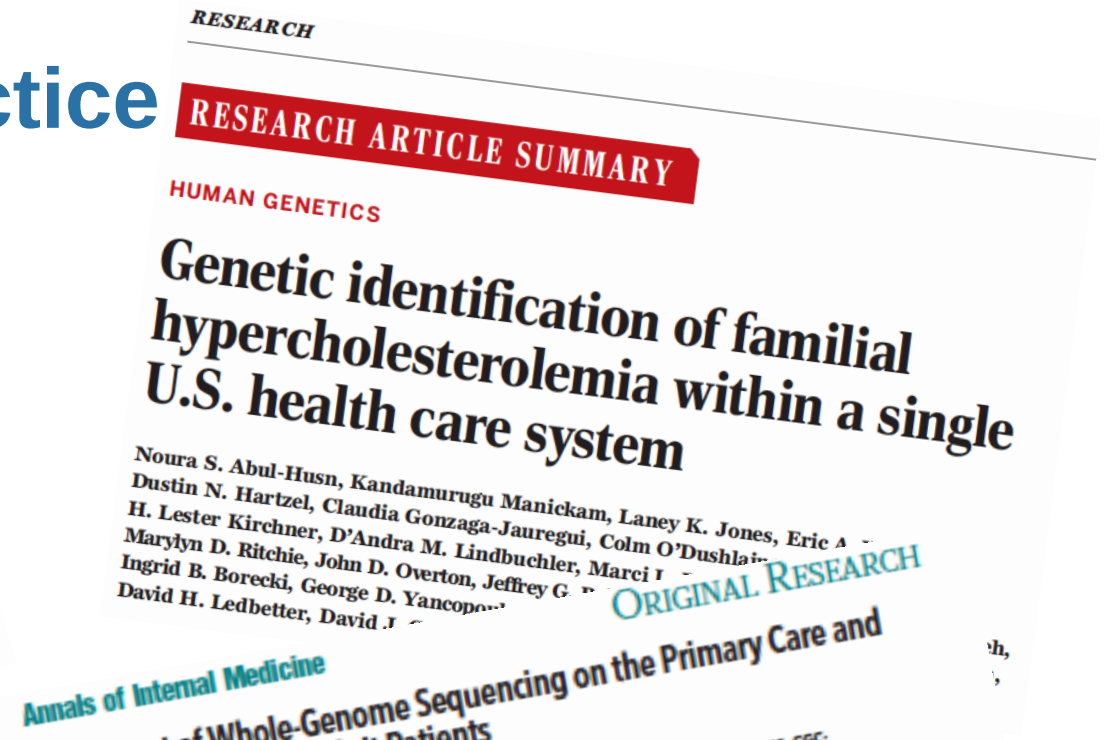

RESEARCH

RESEARCH ARTICLE SUMMARY

HUMAN GENETICS

Genetic identification of familial hypercholesterolemia within a single U.S. health care system

Noura S. Abul-Husn, Kandamurugu Manickam, Laney K. Jones, Eric A. [illegible] Dustin N. Hartzel, Claudia Gonzaga-Jauregui, Colm O'Dushlaine, H. Lester Kirchner, D'Andra M. Lindbuchler, Marci L. [illegible] Marylyn D. Ritchie, John D. Overton, Jeffrey G. [illegible] Ingrid B. Borecki, George D. Yancopoulos, David H. Ledbetter, David J. [illegible]

ORIGINAL RESEARCH

Annals of Internal Medicine

The Impact of Whole-Genome Sequencing on the Primary Care and Outcomes of Healthy Adult Patients

A Pilot Randomized Trial

Jason L. Vassy, MD, MPH, SM; Kurt D. Christensen, PhD, MPH; Erica F. Schonman, MPH; Carrie L. Blout, MS, CGC; Jill O. Robinson, MA; Joel B. Krier, MD; Pamela M. Diamond, PhD; Matthew Lebo, PhD; Kalotina Machini, PhD; Danielle R. Azzariti, MS, CGC; Dmitry Dukhovny, MD, MPH; David W. Bates, MD, MSc; Calum A. MacRae, MD, PhD; Michael F. Murray, MD; Heidi L. Rehm, PhD; Amy L. McGuire, JD, PhD; and Robert C. Green, MD, MPH, for the MedSeq Project*

[illegible] Author manuscript; available in PMC 2017 March 01.

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Genet Med. 2016 September ; 18(9): 906–913. doi:10.1038/gim.2015.187.

Recommendations for the integration of genomics into clinical practice

Sarah Bowdin, MD[1,2], Adel Gilbert, MS[1], Emma Bedoukian, MS[3,4], Christopher Carew, MBA[1], Margaret P. Adam, MD[5], John Belmont, MD, PhD[6], Barbara Bernhardt, MS[7], Leslie Biesecker, MD[8], Hans T. Bjornsson, MD, PhD[9,10], Miriam Blitzer, PhD[11], Lisa C.A. D'Alessandro, MD[12], Matthew A. Deardorff, MD, PhD[3,4,13], Laurie Demmer, MD[14], Alison Elliott, PhD[15], Gerald L. Feldman, MD, PhD[16], Ian A. Glass, MBChB, MD[5], Gail Herman, MD, PhD[17], Lucia Hindorff, PhD[18], Fuki Hisama, MD[19], Louanne Hudgins, MD[20], A. Micheil Innes, MD[21], Laird Jackson, MD[22], Gail Jarvik, MD, PhD[18], Raymond Kim, MD, PhD[22], Bruce Korf, MD, PhD[23], David H. Ledbetter, PhD[24], Mindy Li, MD[25], Eriskay Liston, MS[22], Christian Marshall, PhD[26], Livija Medne, MS[2,3], M. Stephen Meyn, MD, PhD[1,22], Nasim Monfared, MSc[22], Cynthia Morton, PhD[27], John J. Mulvihill, MD[28], Sharon E. Plon, MD, PhD[29], Heidi Rehm, PhD[27], Amy Roberts, MD[30], Cheryl Shuman, MS[1,22], Nancy B. Spinner, PhD[25], D. James Stavropoulos, PhD[26], Kathleen Valverde, MS[31], Darrel J. Waggoner, MD[32], Alisha Wilkens, MS[3,4], Ronald D. Cohn, MD[1,22], Ian D. Krantz, MD[3,13]

The Geisinger MyCode Community Health Initiative: an electronic health record-linked biobank for Precision Medicine research

David J. Carey[*], Samantha N. Fetterolf, F. Daniel Davis, William A. Faucett, H. Lester Kirchner, Uyenlinh Mirshahi, Michael F. Murray, Diane T. Smelser, Glenn S. Gerhard[¶], and David H. Ledbetter

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Integral Role of Primary Care

- Ascertainment/counsel/refer – clinical utility
- Interpretation of results
- Communication (patient/family)
- Follow-up care
- Family care
- Helping patients coping with uncertainty
- Reclassification updates of VUS -

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www.cancer.gov **www.cancer.gov/espanol**