Genetics for Cancer Risk

Presenters:

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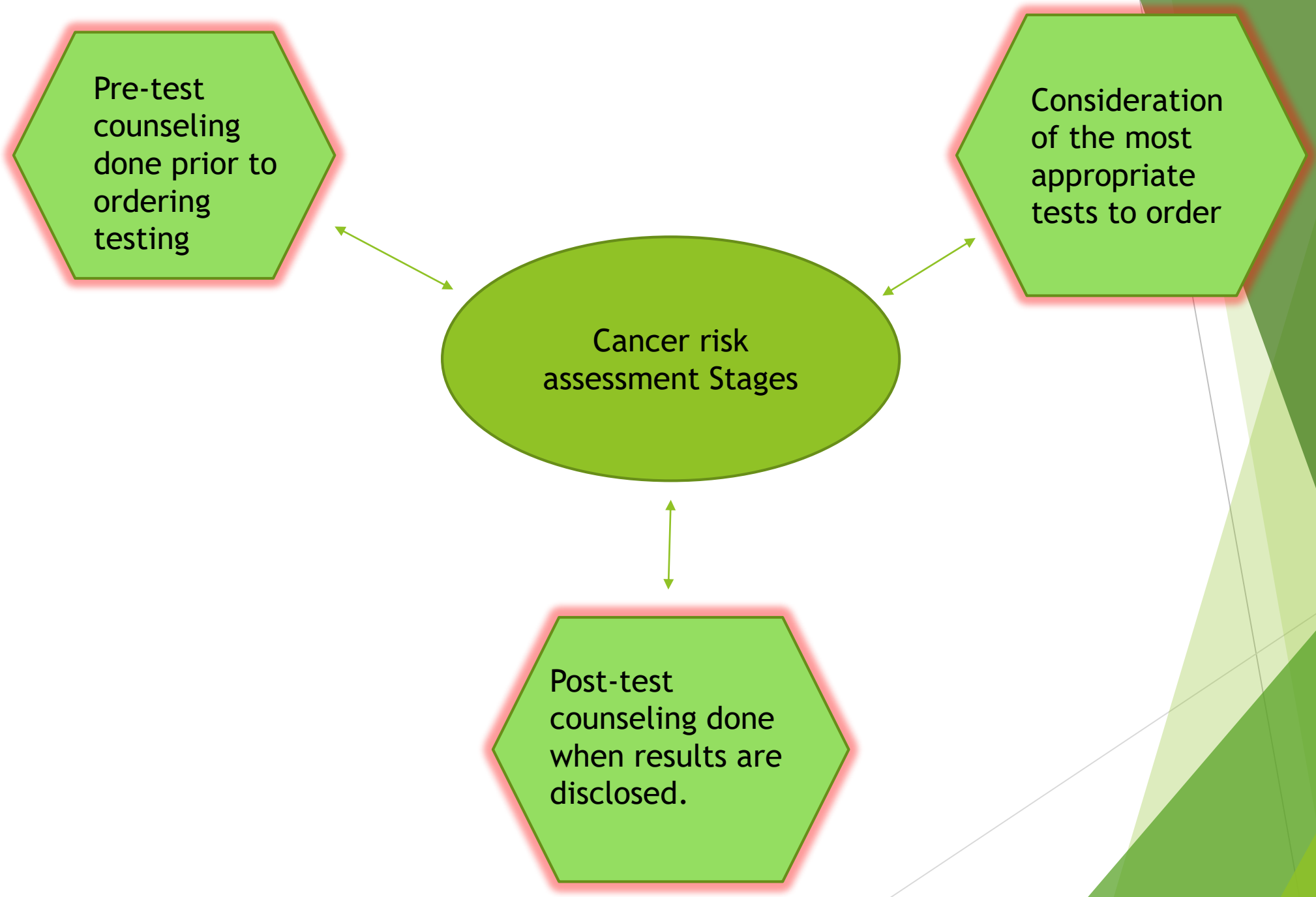
Objectives

- Overview of Cancer Genetics
- Somatic vs Germline mutations
- Cancer risk assessment stages
- NCCN guidelines for Genetic risk assessment for common malignancies like Breast, Ovarian, Colorectal/Pancreatic and Prostate.
- Approaching a patient for Genetic counselling
- Defining a positive result on genetic test and its implications for the patient.

Overview of Cancer Genetics

- Cancers arise due to pathogenic variants in certain genes, such as those involved in the regulation of cell growth and/or DNA repair.
- Not all of these pathogenic variants are inherited from a parent.
- However, family studies have documented an increased risk for several forms of cancer among first-degree relatives and second-degree relatives of affected individuals. These individuals may have an increased susceptibility to cancer as the result of one or more pathogenic variants present in parental germline cells. cancers developing in these individuals may be classified as hereditary or familial cancers.

- Variants associated with Hereditary cancers increase the risk for certain cancers and transmission to offspring through either parent. They often have an early age of onset and exhibit an autosomal dominant inheritance pattern.
- Familial cancers vs Hereditary cancers: The former share some but not all features of hereditary cancers. familial breast cancers occur in a given family more frequently than in the general population, they generally do not exhibit the inheritance patterns or onset age consistent with hereditary cancers. Familial cancers may be associated with chance clustering of sporadic cancer cases within families, genetic variation in lower penetrance genes, a shared environment, or combinations of these factors.
- *An individual suspected of being at risk for hereditary cancer should be offered genetic counseling. This is consistent with recommendations from the USPSTF and NCCN.*
- Assessment of an individual's risk for familial or hereditary cancer is based on a thorough evaluation of the personal and family history.
- advances in molecular genetics have identified a number of genes associated with inherited susceptibility to multiple cancers and have provided a means of characterizing the specific pathogenic variant present in certain individuals and families exhibiting an increased risk for cancer.
- cancer genetics has implications in prevention, screening, and treatment of individuals


Pre-test counseling done prior to ordering testing
Consideration of the most appropriate tests to order
Cancer risk assessment Stages
Post-test counseling done when results are disclosed.

General testing criteria

- Who to test?
- Individuals with any blood relative with a known pathogenic gene implicated in cancer pathogenesis.
- Individuals who tested negative with previous limited testing (eg, single gene analysis) and are interested in pursuing multi-gene testing and : have a pathogenic variant identified on tumor genomic testing that has clinical implications if also identified in the germline (e.g BRCA)
- To aid in systemic therapy and surgical decision-making (e.g testing implication for type of breast surgery)
- Individual who meets Li-Fraumeni syndrome testing criteria, Cowden syndrome/PTEN hamartoma tumor syndrome or Lynch syndrome.
- Testing may be considered in the following scenario (with appropriate pre-test education and access to post-test management): • An individual of Ashkenazi Jewish ancestry without additional risk factors • Personal history of serous endometrial cancer.

Breast and ovarian cancer susceptibility genes

HIGH-PENETRANCE BREAST CANCER SUSCEPTIBILITY GENES (e.g BRCA1, BRCA2, CDH1, PALB2, PTEN, STK11, and TP53).

- *Testing is clinically indicated in the following scenarios:*
- Personal history of breast cancer: ≤50 y
- Any age: Treatment indications – To aid in systemic treatment decisions using PARP inhibitors for breast cancer in the metastatic setting
- Triple-negative breast cancer
- Multiple primary breast cancers (synchronous or metachronous)
- Lobular breast cancer with personal or family history of diffuse gastric cancer
- Male breast cancer
- Ashkenazi Jewish ancestry
- Any age: Family history– ≥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, ≥3 diagnoses of breast and/or prostate cancer (any grade) on the same side of the family including the patient with breast cancer
- Individuals affected or unaffected with breast cancer who otherwise do not meet the criteria above but have a probability >5% of a BRCA1/2 variant based on prior probability models (eg, Tyrer-Cuzick, BRCAPro, CanRisk).

- **HIGH-PENETRANCE OVARIAN CANCER SUSCEPTIBILITY GENES (ATM, BRCA1, BRCA2, BRIP1, Lynch syndrome genes [MLH1, MSH2, MSH6, EPCAM], PALB2, RAD51C, and RAD51D)**
- *Testing is clinically indicated in the following scenarios:*
- Personal history of epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
- Family history of cancer only An individual unaffected with ovarian cancer (with a first- or second-degree blood relative with epithelial ovarian cancer (including fallopian tube cancer or peritoneal cancer) at any age
- An individual unaffected with ovarian cancer who otherwise does not meet the criteria above but has a probability >5% of a BRCA1/2 variant based on prior probability models (eg, TyrerCuzick, BRCAPro, CanRisk).

BRCA1/2 management as per NCCN guidelines

- Absolute Breast cancer risk: >60% lifetime risk
- Contralateral Breast cancer risk: 20-year cumulative risk is 30%–40%
- Male breast cancer: Absolute risk is 0.2%–1.2% by age 70
- Ovarian Cancer Absolute risk: 39%–58%
- Pancreatic cancer: Absolute risk: ≤5%
- Prostate cancer: Absolute risk: 7%–26%
- BRCA2 Primary Breast Cancer: Absolute risk: >60%
- Contralateral Breast Cancer 20-year cumulative risk: 25%
- Male breast cancer: Absolute risk: 1.8%–7.1% by age 70
- Ovarian Cancer Absolute risk: 13%–29%
- Pancreatic cancer: Absolute risk: 5%–10%
- Prostate cancer:Absolute risk: 19%–61%

- *Breast Cancer screening/preventative strategies in BRCA1/2 positive Individuals*:
- Breast awareness starting at age 18 years.
- Clinical breast exam, every 6–12 months, starting at age 25 years.
- Breast screening, Age 25–29 years: annual breast MRI screening with and without contrast(or mammogram, only if MRI is unavailable) or individualized based on family history if a breast cancer diagnosis before age 30 is present.
- Age 30–75 years: annual mammogram and breast MRI screening with and without contrast.
- Age >75 years: management should be considered on an individual basis.
- For individuals with a BRCA pathogenic variant who are treated for breast cancer and have not had a bilateral mastectomy, screening with annual mammogram and breast MRI should continue.
- Discuss option of Risk reducing prophylactic mastectomy.
- Consider risk reduction agents as options for breast cancer, including discussion of risks and benefits.

- *Ovarian/ Fallopian Tube/ Peritoneal/ Uterine Cancers screening/preventative strategies in BRCA1/2 positive Individuals:*
- Non-surgical risk reduction: Consultation with gynecologic oncologist or gynecologist with expertise/experience in genetic susceptibility to gynecologic cancer recommended. Consideration of combination estrogen/progestin contraception (such as oral contraceptive pills) for ovulation suppression.
- Surgical risk reduction with bilateral salpingoophorectomy
- BRCA1: Recommend RRSO between 35 and 40 years. BRCA2: can delay RRSO until age 40–45 years in patients with BRCA2 variants unless age at diagnosis in the family warrants earlier age for consideration of prophylactic surgery.
- CA-125 and pelvic ultrasound are recommended for preoperative planning.
- Hormone replacement therapy is generally not contraindicated and thus should be discussed with premenopausal patients who do not have a personal history of breast cancer.
- RRSO likely reduces incidence of Breast Cancer but data is not strong and Breast Cancer management should be dependent on pathogenic Gene identified.

The Genetic Counseling Process

Referral

- Receive referral from provider/patient
- Review indication and request records

Initial Consult

- Collect Patient Information (Personal/family history of cancer, medical history, hormone history)
- Discuss genetic testing for cancer – methods, risks/benefits, cost, insurance implications, results, recommendations, etc.
- Obtain consent

Testing

- Coordinate sample collection (blood or saliva) and mailing
- Write clinic note and scan pedigree into EMR
- Place orders

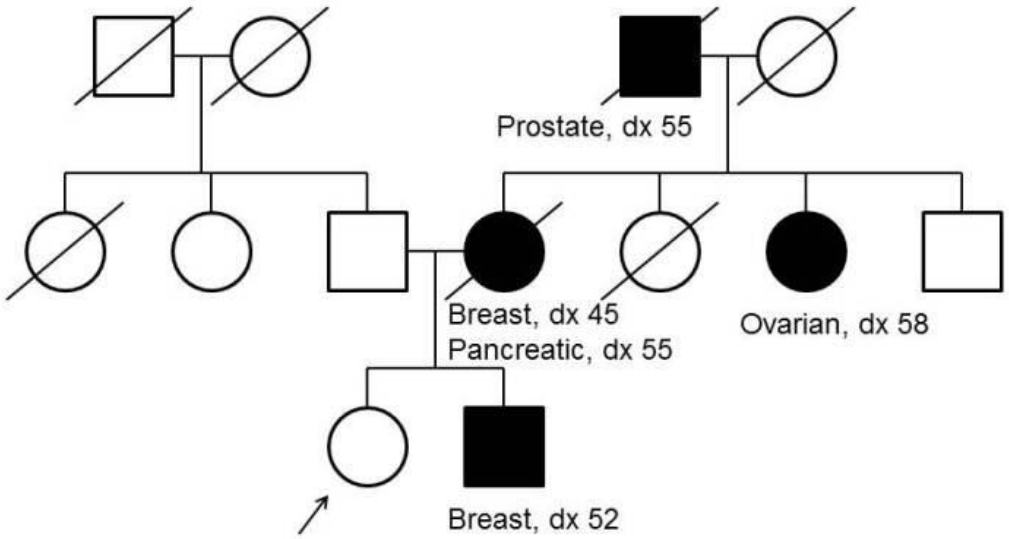
Results

- Write result letters to patient and provider
- Call out results to patient
- Send results and recommendations to referring provider and care team
- Coordinate referrals to other specialties as needed

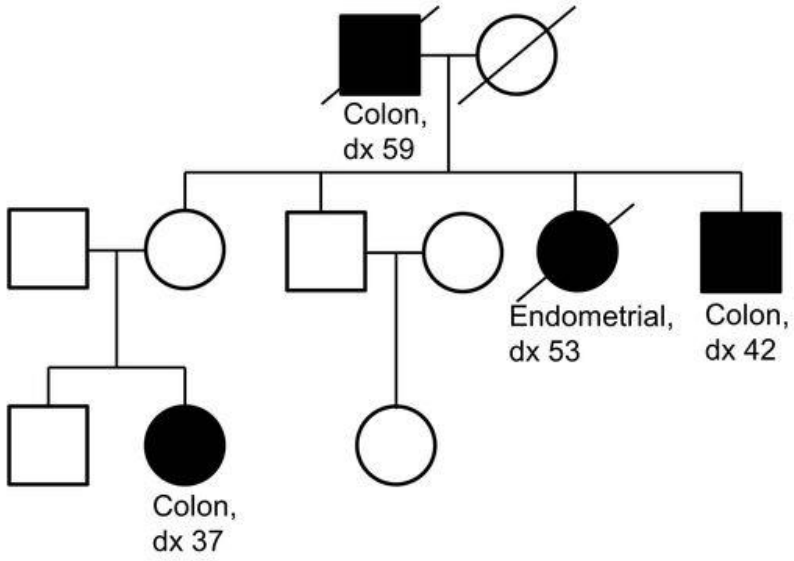
During the appointment

Pedigree

Classic *BRCA2* Pedigree



Lynch Syndrome Pedigree

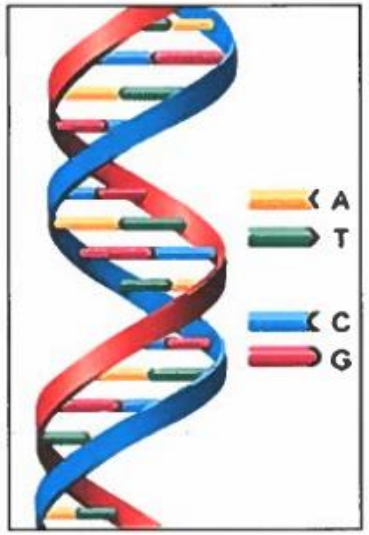


*Pedigree credits to the National Cancer Institute

Red Flags for Hereditary Cancer

- Cancer at early ages (<50)
- Multiple cancers in one person; bilateral cancers
- Multiple cases of the same or related cancers on one side of a family
- Multiple generations with cancer diagnoses
- Rare cancers
- Combination of cancers and benign findings that can be related
  - Ex. ≥ 10 colon polyps in one person

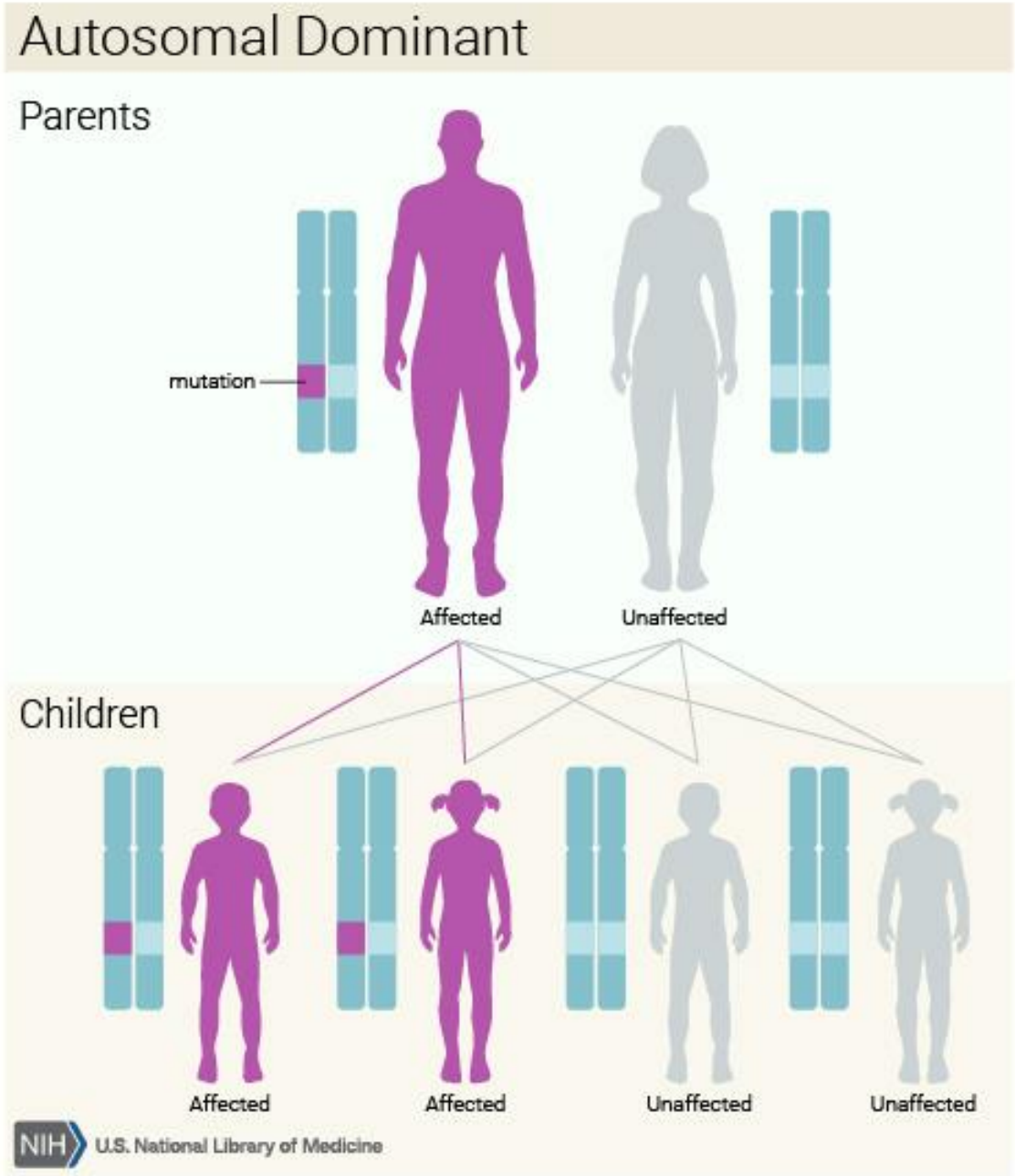
Tumor Suppressor Gene



PROTECTION AGAINST TUMOR DEVELOPMENT

Tumor Suppressor Gene w/ pathogenic variant (mutation)

DECREASED PROTECTION AGAINST TUMOR DEVELOPMENT


Autosomal Dominant
Parents
mutation
Affected
Unaffected
Children
Affected
Affected
Unaffected
Unaffected
NIH
U.S. National Library of Medicine

Genetic Information Non-Discrimination Act (GINA)

- Prevents discrimination based on genetic test results by employers and health insurance companies
  - Exceptions include individuals who work for (or obtain health insurance from) the federal government, military, or a small business of less than 15 employees, or individuals
- GINA does not cover life, long-term care, or disability insurance companies
  - Recommend that unaffected individuals have life, long-term care, or disability policies in place before pursuing genetic testing

Testing and Results

Cancer Genetic Testing

- Somatic vs. Germline
  - Somatic = tumor DNA – Used to target treatments to the patient's tumor
  - Germline = patient's DNA (what they were born with) – Used to identify patient's risk for other cancers and the risk to relatives

- Germline testing is typically done on a blood or saliva sample and is usually covered by insurance
  - Most labs offer a maximum "self-pay" price of $250

- **Panel test** – Many genes tested at one time

- ~4 week turnaround time

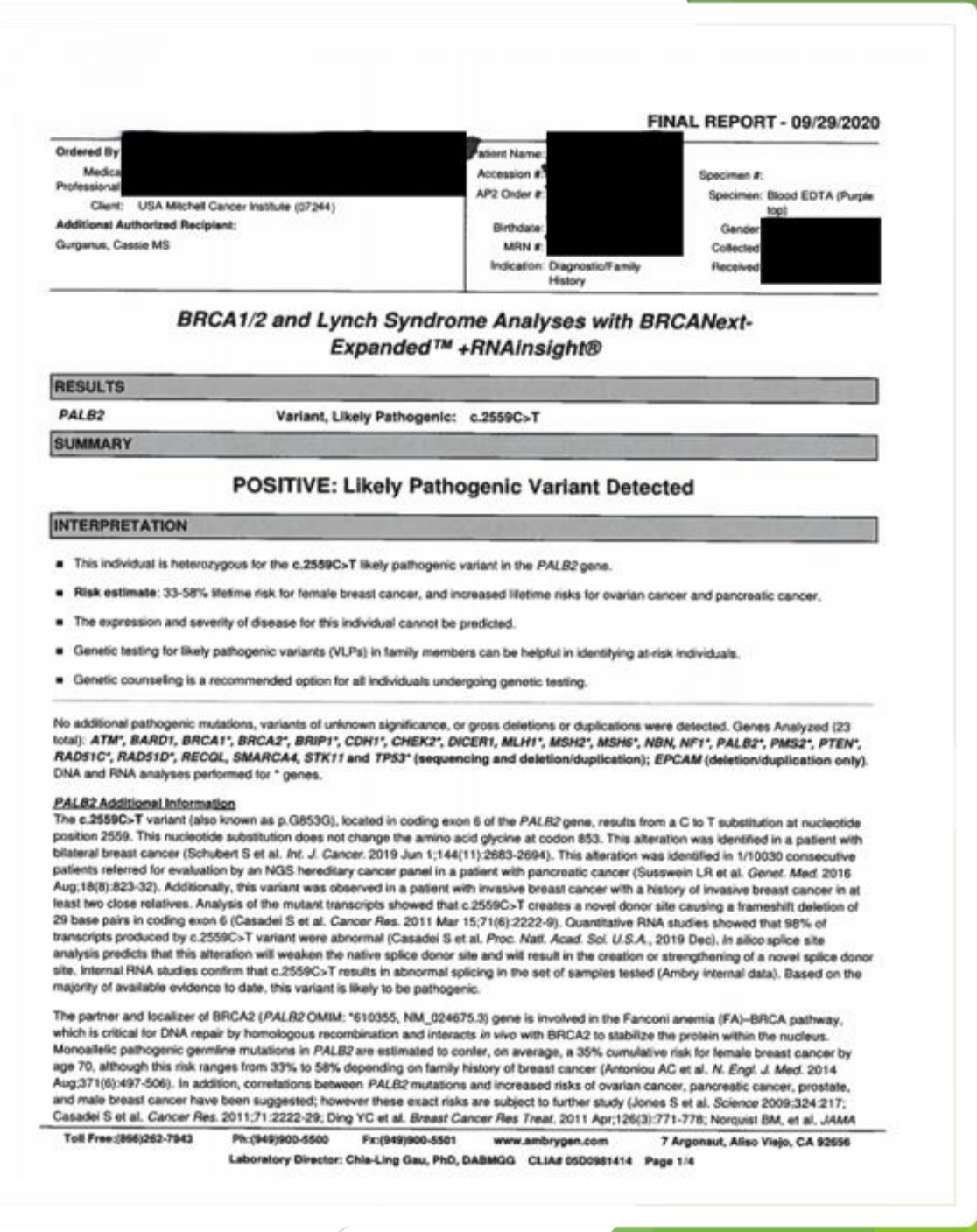
Variant Interpretation

Positive Result

The result report gives information about the cancer risks for that specific variant

Management guidelines for the gene come from the National Comprehensive Cancer Network (NCCN)

Mail the patient a letter explaining the cancer risks and management guidelines, along with a copy of their test results, that way they can share with other family members



FINAL REPORT - 09/29/2020

Ordered By: [redacted]
Medical Professional
Client: USA Mitchell Cancer Institute (07244)
Additional Authorized Recipient:
Gurganus, Cassie MS

Patient Name: [redacted]
Accession #:
AP2 Order #:
Birthdate:
MRN #:
Indication: Diagnostic/Family History

Specimen #:
Specimen: Blood EDTA (Purple top)
Gender:
Collected:
Received: [redacted]

BRCA1/2 and Lynch Syndrome Analyses with BRCANext-Expanded™ +RNAinsight®

RESULTS

PALB2 **Variant, Likely Pathogenic: c.2559C>T**

SUMMARY

POSITIVE: Likely Pathogenic Variant Detected

INTERPRETATION

- This individual is heterozygous for the **c.2559C>T** likely pathogenic variant in the *PALB2* gene.
- **Risk estimate**: 33-58% lifetime risk for female breast cancer, and increased lifetime risks for ovarian cancer and pancreatic cancer.
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for likely pathogenic variants (VLPs) in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

No additional pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected. Genes Analyzed (23 total): ***ATM*, BARD1, BRCA1*, BRCA2*, BRIP1*, CDH1*, CHEK2*, DICER1, MLH1*, MSH2*, MSH6*, NBN, NF1*, PALB2*, PMS2*, PTEN*, RAD51C*, RAD51D*, RECQL, SMARCA4, STK11*** **and** ***TP53**** **(sequencing and deletion/duplication);** ***EPCAM*** **(deletion/duplication only).** DNA and RNA analyses performed for * genes.

PALB2 **Additional Information**

The **c.2559C>T** variant (also known as p.G853G), located in coding exon 6 of the *PALB2* gene, results from a C to T substitution at nucleotide position 2559. This nucleotide substitution does not change the amino acid glycine at codon 853. This alteration was identified in a patient with bilateral breast cancer (Schubert S et al. *Int. J. Cancer.* 2019 Jun 1;144(11):2683-2694). This alteration was identified in 1/10030 consecutive patients referred for evaluation by an NGS hereditary cancer panel in a patient with pancreatic cancer (Susswein LR et al. *Genet. Med.* 2016 Aug;18(8):823-32). Additionally, this variant was observed in a patient with invasive breast cancer with a history of invasive breast cancer in at least two close relatives. Analysis of the mutant transcripts showed that c.2559C>T creates a novel donor site causing a frameshift deletion of 29 base pairs in coding exon 6 (Casadei S et al. *Cancer Res.* 2011 Mar 15;71(6):2222-9). Quantitative RNA studies showed that 98% of transcripts produced by c.2559C>T variant were abnormal (Casadei S et al. *Proc. Natl. Acad. Sci. U.S.A.*, 2019 Dec). *In silico* splice site analysis predicts that this alteration will weaken the native splice donor site and will result in the creation or strengthening of a novel splice donor site. Internal RNA studies confirm that c.2559C>T results in abnormal splicing in the set of samples tested (Ambry internal data). Based on the majority of available evidence to date, this variant is likely to be pathogenic.

The partner and localizer of BRCA2 (*PALB2* OMIM: *610355, NM_024675.3) gene is involved in the Fanconi anemia (FA)–BRCA pathway, which is critical for DNA repair by homologous recombination and interacts *in vivo* with BRCA2 to stabilize the protein within the nucleus. Monoallelic pathogenic germline mutations in *PALB2* are estimated to confer, on average, a 35% cumulative risk for female breast cancer by age 70, although this risk ranges from 33% to 58% depending on family history of breast cancer (Antoniou AC et al. *N. Engl. J. Med.* 2014 Aug;371(6):497-506). In addition, correlations between *PALB2* mutations and increased risks of ovarian cancer, pancreatic cancer, prostate, and male breast cancer have been suggested; however these exact risks are subject to further study (Jones S et al. *Science* 2009;324:217; Casadei S et al. *Cancer Res.* 2011;71:2222-29; Ding YC et al. *Breast Cancer Res Treat.* 2011 Apr;126(3):771-778; Norquist BM, et al. *JAMA*

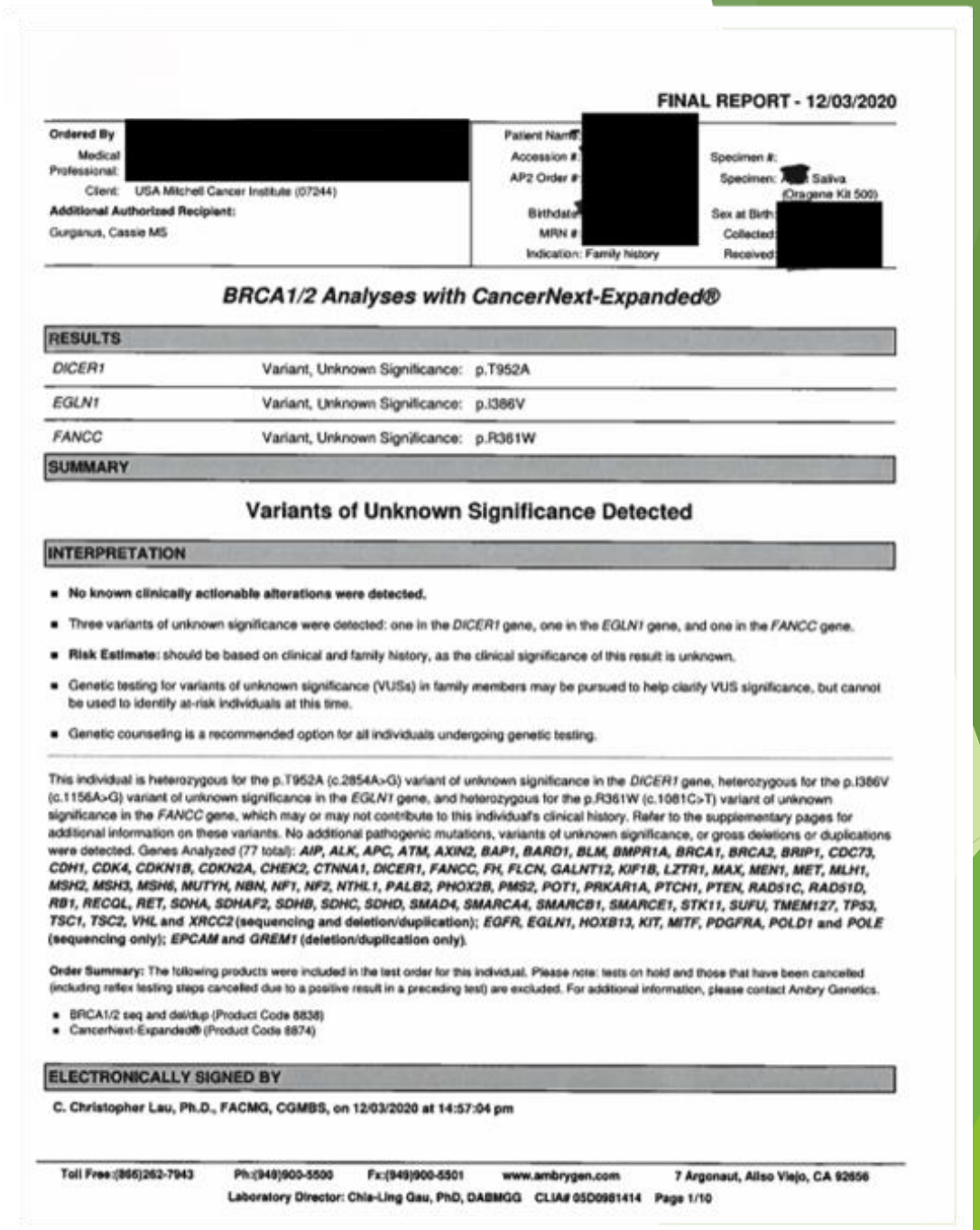
Variant of Uncertain Significance (VUS)

A patient can have multiple VUS or may have a positive result and a VUS

VUS results do not impact medical management!

Unless the patient also has a positive result, make screening recommendations based off the family history of cancer

VUS may be re-classified in the future – recommend that the patient check in every few years for updates



FINAL REPORT - 12/03/2020

Ordered By
Medical Professional: [redacted]
Client: USA Mitchell Cancer Institute (07244)
Additional Authorized Recipient:
Gurganus, Cassie MS

Patient Name: [redacted]
Accession #:
AP2 Order #:
Birthdate:
MRN #:
Indication: Family history

Specimen #:
Specimen: [redacted] Saliva (Oragene Kit 500)
Sex at Birth:
Collected: [redacted]
Received:

BRCA1/2 Analyses with CancerNext-Expanded®

RESULTS

DICER1	Variant, Unknown Significance: p.T952A
EGLN1	Variant, Unknown Significance: p.I386V
FANCC	Variant, Unknown Significance: p.R361W

SUMMARY

Variants of Unknown Significance Detected

INTERPRETATION

- **No known clinically actionable alterations were detected.**
- Three variants of unknown significance were detected: one in the *DICER1* gene, one in the *EGLN1* gene, and one in the *FANCC* gene.
- **Risk Estimate:** should be based on clinical and family history, as the clinical significance of this result is unknown.
- Genetic testing for variants of unknown significance (VUSs) in family members may be pursued to help clarify VUS significance, but cannot be used to identify at-risk individuals at this time.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

This individual is heterozygous for the p.T952A (c.2854A>G) variant of unknown significance in the *DICER1* gene, heterozygous for the p.I386V (c.1156A>G) variant of unknown significance in the *EGLN1* gene, and heterozygous for the p.R361W (c.1081C>T) variant of unknown significance in the *FANCC* gene, which may or may not contribute to this individual's clinical history. Refer to the supplementary pages for additional information on these variants. No additional pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected. Genes Analyzed (77 total): ***AIP, ALK, APC, ATM, AXIN2, BAP1, BARD1, BLM, BMPR1A, BRCA1, BRCA2, BRIP1, CDC73, CDH1, CDK4, CDKN1B, CDKN2A, CHEK2, CTNNA1, DICER1, FANCC, FH, FLCN, GALNT12, KIF1B, LZTR1, MAX, MEN1, MET, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, NF2, NTHL1, PALB2, PHOX2B, PMS2, POT1, PRKAR1A, PTCH1, PTEN, RAD51C, RAD51D, RB1, RECQL, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, SMAD4, SMARCA4, SMARCB1, SMARCE1, STK11, SUFU, TMEM127, TP53, TSC1, TSC2, VHL*** and ***XRCC2*** **(sequencing and deletion/duplication);** ***EGFR, EGLN1, HOXB13, KIT, MITF, PDGFRA, POLD1*** and ***POLE*** **(sequencing only);** ***EPCAM*** and ***GREM1*** **(deletion/duplication only).**

Order Summary: The following products were included in the test order for this individual. Please note: tests on hold and those that have been cancelled (including reflex testing steps cancelled due to a positive result in a preceding test) are excluded. For additional information, please contact Ambry Genetics.

- BRCA1/2 seq and del/dup (Product Code 8838)
- CancerNext-Expanded® (Product Code 8874)

ELECTRONICALLY SIGNED BY

C. Christopher Lau, Ph.D., FACMG, CGMBS, on 12/03/2020 at 14:57:04 pm

Toll Free:(866)262-7943 Ph:(949)900-5500 Fx:(949)900-5501 www.ambrygen.com 7 Argonaut, Aliso Viejo, CA 92656
Laboratory Director: Chia-Ling Gau, PhD, DABMGG CLIA# 05D0981414 Page 1/10

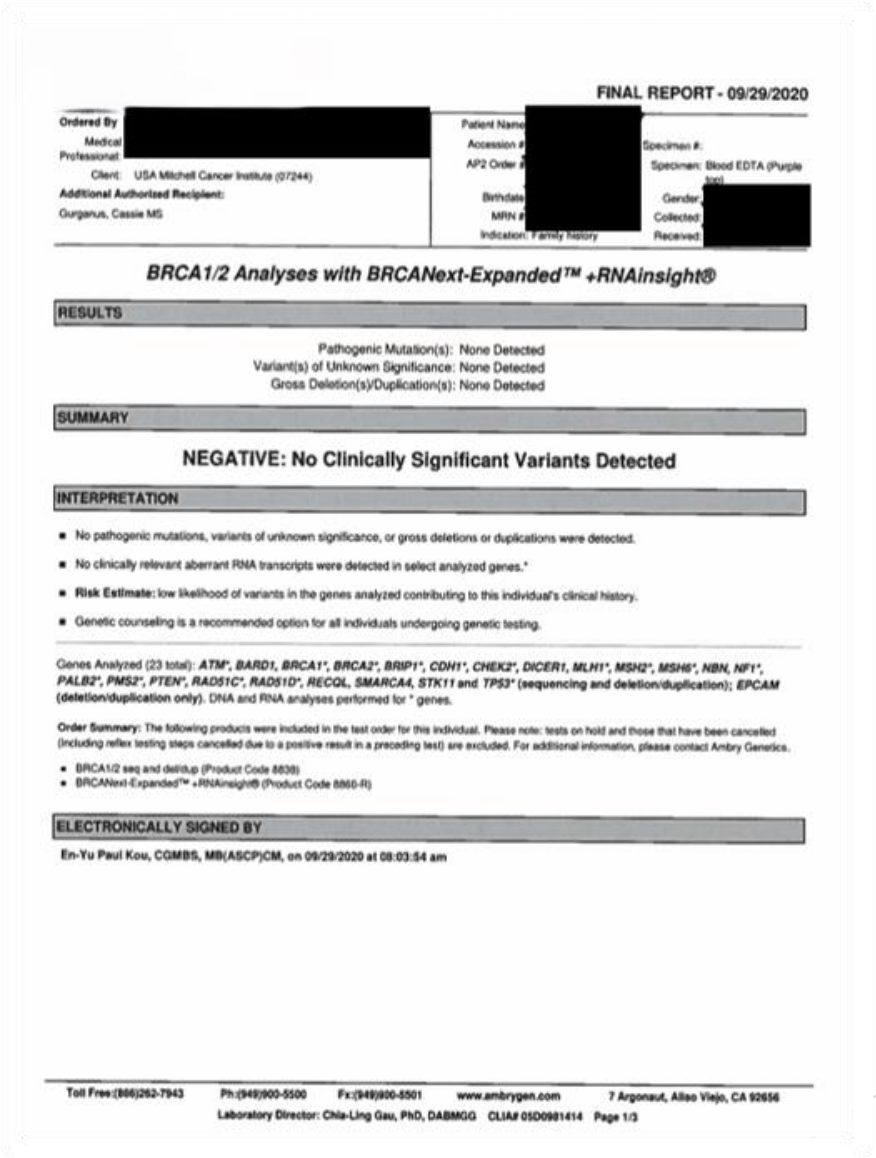
Negative Result

A negative points towards the cancer being due to sporadic or environmental causes.

Depending on the patient's family history, it may be possible that another family member has a pathogenic variant that the patient did not inherit.

A negative may be the result of limited technology*

Make recommendations for cancer screening based on the family history



FINAL REPORT - 09/29/2020

Ordered By
Medical Professional: [redacted]
Client: USA Mitchell Cancer Institute (07244)
Additional Authorized Recipient:
Gurganus, Cassie MS

Patient Name: [redacted]
Accession #:
AP2 Order #:
Birthdate:
MRN #:
Indication: Family history

Specimen #:
Specimen: Blood EDTA (Purple top)
Gender:
Collected: [redacted]
Received:

BRCA1/2 Analyses with BRCANext-Expanded™ +RNAinsight®

RESULTS

Pathogenic Mutation(s): None Detected
Variant(s) of Unknown Significance: None Detected
Gross Deletion(s)/Duplication(s): None Detected

SUMMARY

NEGATIVE: No Clinically Significant Variants Detected

INTERPRETATION

- No pathogenic mutations, variants of unknown significance, or gross deletions or duplications were detected.
- No clinically relevant aberrant RNA transcripts were detected in select analyzed genes.*
- **Risk Estimate:** low likelihood of variants in the genes analyzed contributing to this individual's clinical history.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

Genes Analyzed (23 total): ***ATM**, **BARD1**, **BRCA1***, **BRCA2***, **BRIP1***, **CDH1***, **CHEK2***, **DICER1**, **MLH1***, **MSH2***, **MSH6***, **NBN**, **NF1***, **PALB2***, **PMS2***, **PTEN***, **RAD51C***, **RAD51D***, **RECQL**, **SMARCA4**, **STK11*** and **TP53*** (sequencing and deletion/duplication); **EPCAM** (deletion/duplication only). DNA and RNA analyses performed for * genes.

Order Summary: The following products were included in the test order for this individual. Please note: tests on hold and those that have been cancelled (including reflex testing steps cancelled due to a positive result in a preceding test) are excluded. For additional information, please contact Ambry Genetics.

- BRCA1/2 seq and del/dup (Product Code 8838)
- BRCANext-Expanded™ +RNAinsight® (Product Code 8860-R)

ELECTRONICALLY SIGNED BY

En-Yu Paul Kou, CGMBS, MB(ASCP)CM, on 09/29/2020 at 08:03:54 am

Prostate Cancer

TESTING CRITERIA FOR PROSTATE CANCER SUSCEPTIBILITY GENES
(Specifically *ATM, BRCA1, BRCA2, CHEK2,* and *HOXB13*[z]) (GENE-A)[a,aa,bb]

Testing is clinically indicated in the following scenarios:

- See General Tumor Criteria on CRIT-1.
- Personal history of prostate cancer with specific features:
  - By tumor characteristics (any age)
    - Metastatic[p]
    - Histology
      - high- or very-high-risk group (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer)
  - By family history and ancestry
    - ≥1 close blood relative[o] with:
      - breast cancer at age ≤50 y
      - triple-negative breast cancer at any age
      - male breast cancer at any age
      - ovarian cancer at any age
      - pancreatic cancer at any age
      - metastatic,[p] high-, or very-high-risk group (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer) at any age
    - ≥3 close blood relatives[o] with prostate cancer (any grade) and/or breast cancer on the same side of the family including the patient with prostate cancer
    - Ashkenazi Jewish ancestry
- Family history of cancer
  - An affected (not meeting testing criteria listed above) or unaffected individual with a first-degree blood relative meeting any of the criteria listed above (except unaffected individuals whose relatives meet criteria only for systemic therapy decision-making)[q]

Testing *may be* considered in the following scenario:

- Personal history of prostate cancer with intermediate-risk prostate cancer with intraductal/cribriform histology (see Initial Risk Stratification and Staging Workup in NCCN Guidelines for Prostate Cancer) at any age

Prostate Cancer Genes and Risk

Gene	Risk	Management
ATM	Increased	Consider screening at age 40
BRCA1	7-26%	Consider screening at age 40
BRCA2	19-61%	Recommend screening at age 40
CHEK2	Increased	Consider screening at age 40
HOXB13	Increased	Consider screening at age 40
PALB2	Increased	Consider screening at age 40
TP53	Increased	Recommend screening at age 40

Prostate Cancer Screening = Yearly PSA and Digital Rectal Exam (DRE)

Pancreatic Cancer Screening

PANCREATIC CANCER SCREENING

- Emerging data have examined the efficacy of pancreatic cancer screening in select individuals at increased risk for exocrine pancreatic cancer. To date, most such studies have restricted pancreatic cancer screening to individuals with:
  1. A known P/LP germline variant in a pancreatic cancer susceptibility gene (*ATM, BRCA1, BRCA2, CDKN2A, MLH1, MSH2, MSH6, EPCAM, PALB2, STK11,* and *TP53*; see GENE-A) and a family history of pancreatic cancer (first-degree or second-degree relative) from the same side of the family as the germline P/LP variant; or
  2. A family history of exocrine pancreatic cancer in ≥1 first-degree and ≥1 second-degree relatives from the same side of the family, even in the absence of a known P/LP germline variant (many centers would enroll individuals with one affected first-degree relative and one second-degree relative); or
  3. Some groups have recommended pancreas surveillance for P/LP variant carriers in the absence of a family history.

- For individuals considering pancreatic cancer screening, the panel recommends that screening be performed in experienced high-volume centers. The panel recommends that such screening only take place after an in-depth discussion about the potential limitations to screening, including cost, the high incidence of benign or indeterminate pancreatic abnormalities, and uncertainties about the potential benefits of pancreatic cancer screening.
- Consider screening using annual contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS), with consideration of shorter screening intervals, based on clinical judgment, for individuals found to have potentially concerning abnormalities on screening. Studies have typically started screening with contrast-enhanced MRCP and/or EUS in individuals at increased risk for pancreatic cancer. The panel emphasizes that most small cystic lesions found on screening will not warrant biopsy, surgical resection, or any other intervention.

	Screening
• All individuals with P/LP germline variants in *STK11*	• Consider pancreatic cancer screening beginning at age 30–35 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).
• All individuals with P/LP germline variants in *CDKN2A*	• Consider pancreatic cancer screening beginning at age 40 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier).
• Individuals with P/LP germline variants in one of the other pancreatic cancer susceptibility genes (*ATM, BRCA1, BRCA2, MLH1, MSH2, MSH6, EPCAM, PALB2, TP53*)	• GENE-A ‣ Consider pancreatic cancer screening beginning at age 50 years (or 10 years younger than the earliest exocrine pancreatic cancer diagnosis in the family, whichever is earlier) for individuals with exocrine pancreatic cancer in ≥1 first- or second-degree relatives from the same side of (or presumed to be from the same side of) the family as the identified P/LP germline variant.[a] ‣ The panel does not currently recommend pancreatic cancer screening for carriers of P/LP variants in genes other than *STK11* and *CDKN2A* in the absence of a close family history of exocrine pancreatic cancer.

Colorectal Cancer

CRITERIA FOR THE EVALUATION OF LYNCH SYNDROME BASED ON PERSONAL OR FAMILY HISTORY OF CANCER[a]

- Known LS pathogenic variant in the family

- An individual with a LS-related cancer[b] and any of the following:
  - Diagnosed <50 y
  - A synchronous or metachronous LS-related cancer[b] regardless of age
  - 1 first-degree or second-degree relative with an LS-related cancer[b] diagnosed <50 y
  - ≥2 first-degree or second-degree relatives with an LS-related cancer[b] regardless of age

- Family history[c] of any of the following:
  - ≥1 first-degree relative with a colorectal or endometrial cancer diagnosed <50 y
  - ≥1 first-degree relative with a colorectal or endometrial cancer and a synchronous or metachronous LS-related cancer[b] regardless of age
  - ≥2 first-degree or second-degree relatives with LS-related cancers,[b] including ≥1 diagnosed <50 y
  - ≥3 first-degree or second-degree relatives with LS-related cancers[b] regardless of age

- Increased model-predicted risk for LS
  - An individual with a ≥5% risk of having an MMR gene pathogenic variant based on predictive models (ie, $PREMM_5$, MMRpro, MMRpredict)
    - ◊ Individuals with a personal history of CRC and/or endometrial cancer with a $PREMM_5$ score of ≥2.5% should be considered for MGPT.
    - ◊ For individuals without a personal history of CRC and/or endometrial cancer, some data have suggested using a $PREMM_5$ score threshold of ≥2.5% rather than ≥5% to select individuals for MMR genetic testing. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity.

- Personal history of a tumor with MMR deficiency determined by PCR, NGS, or IHC diagnosed at any age[b,d]

[a] This assumes criteria for evaluation for a polyposis syndrome on hereditary risk assessment has not been met.

[b] LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreatic, urothelial, brain (usually glioblastoma), biliary tract, and small intestine, sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.

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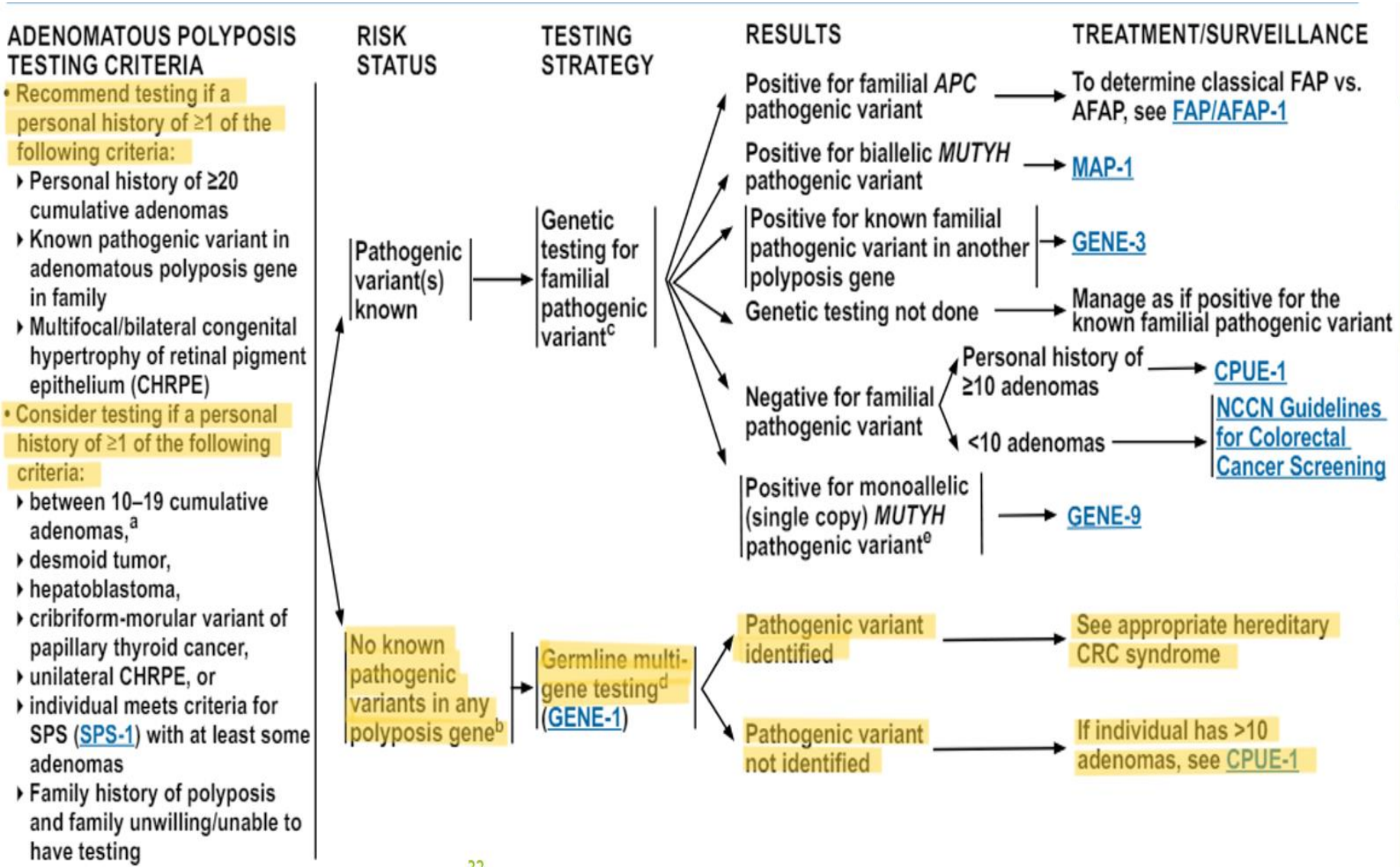
LYNCH SYNDROME CANCER RISKS

Type of Cancer	*General Population Risk*	*MLH1*	*MSH2/EPCAM*	*MSH6*	*PMS2*
Colorectal	4.5%	46-61%	33-52%	10-44%	8.7-20%
Endometrial	2.7%	34-54%	21-57%	16-49%	13-26%
Breast	13%	10-18%	1-12%	11-12%	8-13%
Ovarian	1.3%	4-20%	8-38%	1-13%	1.3-3%
Gastric	<1%	5-7%	0.2-9%	<1-7.9%	NE
Pancreas	1.5%	6.2%	0.5-1.6%	1.4-1.6%	<1-1.6%
Bladder	2.5%	2-7%	4.4-12.8%	1-8.2%	<1-2.4%
Biliary Tract	<1%	1.9-3.7%	0.02-1.7%	<1%	0.2-<1%
Urothelial	<1%	0.2-5%	2-28%	0.7-5.5%	<1-3.7%
Small Bowel	<1%	0.4-11%	1-10%	<1-4%%	0.1-0.3%
Prostate	11.6%	4.4-13.8%	4-16%	2.5-12%	5-12%
Brain/CNS	<1%	0.7-1.7%	2.5-7.7%	0.8-1.8%	0.6-<1%

Lynch Syndrome Screening

Cancer Type	Screening Recommendation
Colorectal Cancer	*MLH1* & *MSH2*: colonoscopy every 1-2 years beginning at age 20-25 (or 2-5 years younger than earliest diagnosis if <25) *MSH6* & *PMS2*: colonoscopy every 1-2 years beginning at age 30-35(or 2-5 years younger than earliest diagnosis if <25)
Gastric and Small Bowel Cancer	Upper GI screening with EGD starting at age 30-40 and repeating every 2-4 years, preferably in conjunction with colonoscopy
Endometrial Cancer	Education regarding symptoms Consideration of hysterectomy after childbearing Can consider endometrial biopsy every 1-2 years beginning at age 30-35
Ovarian Cancer	Education regarding symptoms Consider BSO after childbearing
Pancreatic Cancer	Consider screening with MRCP/EUS beginning at age 50 in patients with close family history of pancreatic cancer
Urothelial Cancer	Consider annual urinalysis beginning at age 30-35 in patients with family history of urothelial cancers or *MSH2* mutations

Hereditary Colon Polyposis



Hereditary Polyposis Genes

- *APC* – Familial Adenomatous Polyposis (FAP), autosomal dominant
- *AXIN2* – autosomal dominant
- *MUTYH* – MUTYH-associated polyposis (MAP), autosomal recessive
- *POLD1* & *POLE* – Polymerase Proofreading-Associated Polyposis (PPAP), autosomal dominant
- *BMPR1A* & *SMAD4* – Juvenile Polyposis Syndrome (JPS), autosomal dominant
- *GREM1* – Hereditary Mixed Polyposis Syndrome, autosomal dominant
- *MLH3* & *MSH3* – autosomal recessive
- *NTHL1* – autosomal recessive
- *PTEN* – Cowden syndrome/PTEN Hamartoma Tumor Syndrome, autosomal dominant
- *STK11* – Peutz-Jeghers Syndrome (PJS), autosomal dominant

Questions?

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References:

1. *NCCN guidelines: Detection, Prevention, and Risk Reduction Version 3.2024 (Slides produced with permission from NCCN)*
2. *ASCO Breast Cancer Guidelines*
3. *National Cancer Institute*