Case Discussions with the Nebraska Medicine Cancer Risk and Prevention Multidisciplinary Clinic

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Agenda

- Overview of Cancer Risk and Prevention Multidisciplinary Clinic
- Case Discussions
  - Updated Genetic Testing
  - Importance of Risk/Benefit Discussion for Screenings

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Cancer Risk and Prevention Multidisciplinary Clinic

Welcome to the Cancer Risk and Prevention Clinic

The first of its kind in Nebraska

This comprehensive clinic is designed to care for individuals who have an increased risk of all types of cancer due to family history, medical and genetic factors, and/or lifestyle influences. Our team – who are specially trained in cancer genetics – includes providers from medical oncology, surgical oncology, gynecology, gastroenterology, endocrinology, urology, dermatology, radiology and genetics.

We are here for you and your loved ones.

Our services include:

- Access to clinical trials in prevention
- Comprehensive risk assessment
- Genetic counseling and testing
- Patient education
- Physician referral services
- Prevention measures
- Psychological services
- Screenings (mammogram, MRI, colonoscopy, blood tests, etc.)

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Multidisciplinary Conference Team

Medical Oncology
Cancer Genetics
Radiology
Breast Surgical Oncology
Gynecologic Oncology
Gastroenterology
Endocrinology
Urology
Dermatology

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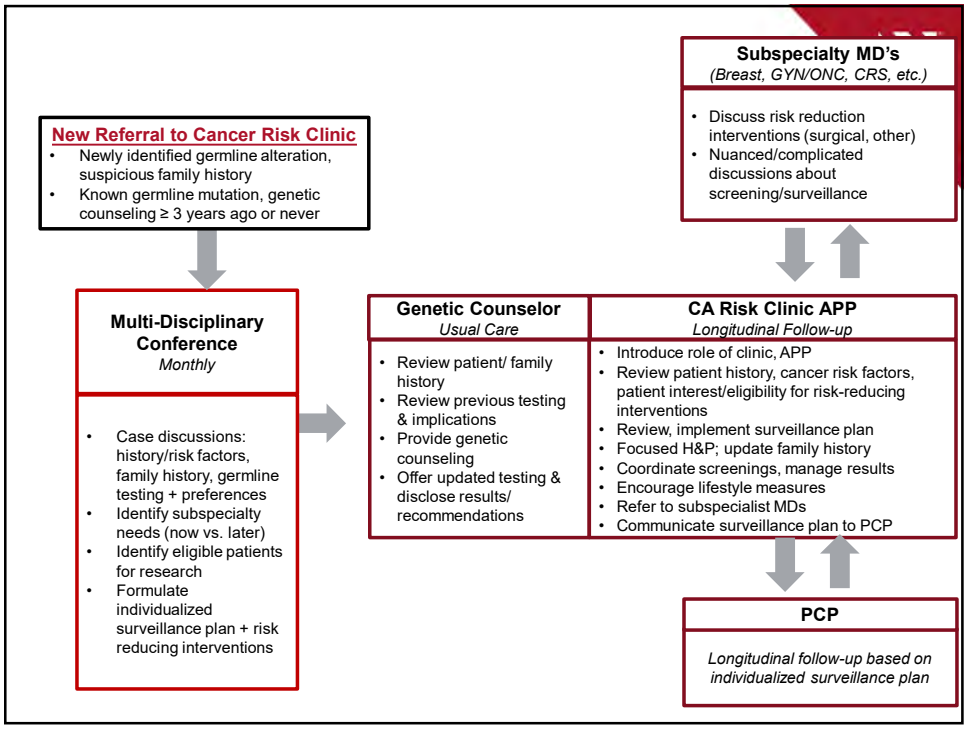
New Referral to Cancer Risk Clinic
Newly identified germline alteration, suspicious family history
Known germline mutation, genetic counseling ≥ 3 years ago or never
Subspecialty MD's
(Breast, GYN/ONC, CRS, etc.)
Discuss risk reduction interventions (surgical, other)
Nuanced/complicated discussions about screening/surveillance
Multi-Disciplinary Conference
Monthly
Case discussions: history/risk factors, family history, germline testing + preferences
Identify subspecialty needs (now vs. later)
Identify eligible patients for research
Formulate individualized surveillance plan + risk reducing interventions
Genetic Counselor
Usual Care
Review patient/ family history
Review previous testing & implications
Provide genetic counseling
Offer updated testing & disclose results/ recommendations
CA Risk Clinic APP
Longitudinal Follow-up
Introduce role of clinic, APP
Review patient history, cancer risk factors, patient interest/eligibility for risk-reducing interventions
Review, implement surveillance plan
Focused H&P; update family history
Coordinate screenings, manage results
Encourage lifestyle measures
Refer to subspecialist MDs
Communicate surveillance plan to PCP
PCP
Longitudinal follow-up based on individualized surveillance plan

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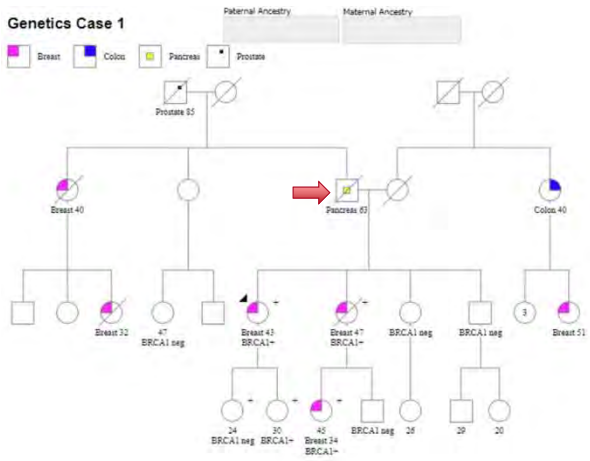
Case 1


Genetics Case 1
Paternal Ancestry
Maternal Ancestry
Breast
Colon
Pancreas
Prostate
Prostate 85
Breast 40
Pancreas 63
Colon 40
Breast 32
47 BRCA1 neg
Breast 43 BRCA1-
Breast 47 BRCA1-
BRCA1 neg
BRCA1 neg
3
Breast 51
24 BRCA1 neg
30 BRCA1-
45 Breast 34 BRCA1-
BRCA1 neg
28
29
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Test Result 2015

Single Site BRCA1

Test Results and Interpretation

POSITIVE FOR A DELETERIOUS MUTATION

Test Performed	Result	Interpretation
3347delAG *BRCA1*	3347delAG	**Deleterious**

This test is designed to detect the specific mutation(s) or variant(s) ind cated above. The classification and interpretation of all variants identified in this assay reflects the current state of scientific understanding at the time this report was issued. In some instances, the classification and interpretation of such variants may change as new scientific information becomes available.

The results of this analysis are consistent with the germline BRCA1 mutation 3347delAG, resulting in premature truncation of the BRCA1 protein at amino acid position 1084. Although the exact risk of breast and ovarian cancer conferred by this specific mutation has not been determined, studies in high-risk families indicate that deleterious mutations in BRCA1 may confer as much as an 87% risk of breast cancer and a 44% risk of ovarian cancer by age 70 in women (Lancet 343 692-695, 1994). Mutations in BRCA1 have been reported to confer a 20% risk of a second breast cancer within five years of the first (Lancet 351:316-321, 1998), as well as a ten-fold increase in the risk of subsequent ovarian cancer (J Clin Oncol 16:2417-2425, 1998). This mutation may also confer an increased (albeit low) risk of male breast cancer (Am J Hum Genet 62 676-689, 1998), as well as some other cancers. Each first degree relative of this individual has a one-in-two chance of having this mutation. Family members can be tested for this specific mutation with a single site analysis.

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Updated Result 2022

Panel Test Result

BRCA1/2 Analyses with CancerNext-Expanded®

RESULTS		
BRCA1	Pathogenic Mutation:	c.3228_3229delAG
BRCA2	Pathogenic Mutation:	p.G1712*

SUMMARY

POSITIVE: Pathogenic Mutations Detected

INTERPRETATION

- This individual is heterozygous for the **c.3228_3229delAG (p.G1077Afs*8)** pathogenic mutation in the *BRCA1* gene.
  - This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome.
  - **Risk estimate**: 57-87% lifetime risk of breast cancer and up to a 40% lifetime risk of ovarian cancer (females only), increased risks of male breast cancer and prostate cancer (males only), and increased lifetime pancreatic cancer risk.
- This individual is heterozygous for the **p.G1712* (c.5134G>T)** pathogenic mutation in the *BRCA2* gene.
  - This result is consistent with a diagnosis of hereditary breast and ovarian cancer (HBOC) syndrome.
  - **Risk estimate**: 45-84% lifetime risk of breast cancer and 11-18% lifetime risk of ovarian cancer (females only), at least a 6% lifetime risk of male breast cancer and 15% risk of prostate cancer by age 65 (males only), and increased lifetime pancreatic cancer risk.
- The expression and severity of disease for this individual cannot be predicted.
- The interactive effect and relative contribution of these alterations on clinical phenotype is unknown at this time.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

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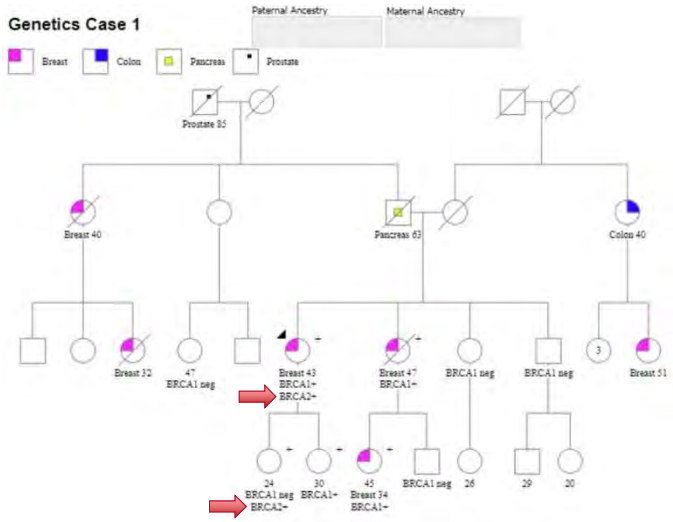
Case 1



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Discussion

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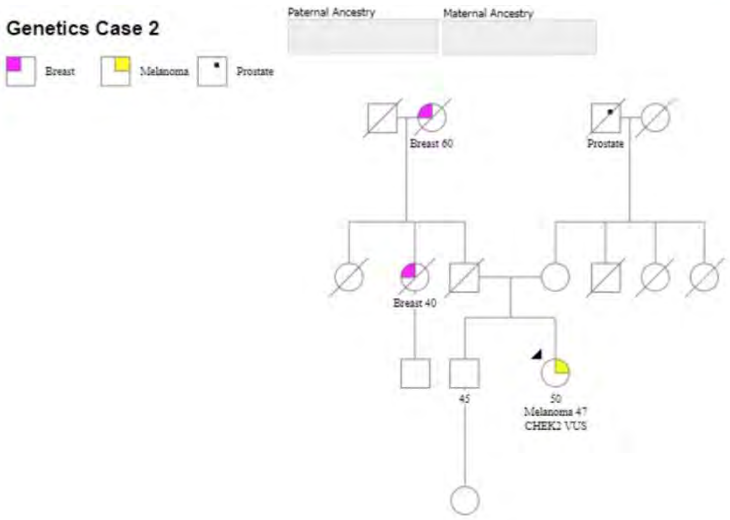
Case 2



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Test Result 2018

CHEK2 VUS

Test Performed
Sequence analysis and deletion/duplication testing of the 46 genes listed in the results section below.
- Invitae Common Hereditary Cancers Panel

Reason for Testing
Family history

Summary

Variant of Uncertain Significance identified in CHEK2.

Clinical Summary

- A Variant of Uncertain Significance, c.846+4_846+7delAGTA (Intronic), was identified in CHEK2.
  - The CHEK2 gene is associated with an increased risk for autosomal dominant breast, colon, thyroid and prostate cancers (PMID: 15492928, 18759107, 21807500, 21876083, 25431674).
  - The clinical significance of this variant is uncertain at this time. Until this uncertainty can be resolved, caution should be exercised before using this result to inform clinical management decisions.
  - This variant is not eligible for complimentary family studies as part of our VUS Resolution Program because the results are unlikely to assist Invitae in reclassifying this particular variant. However, if desired, testing for this variant in other family members can be ordered at a reduced cost through the Family Variant Testing Program. Details on our VUS Resolution and Family Variant Testing Programs can be found at www.invitae.com.
- These results should be interpreted within the context of additional laboratory results, family history, and clinical findings. Genetic counseling is recommended to discuss the implications of this result. For access to a network of genetic providers, please contact Invitae at clientservices@invitae.com, or visit www.nsgc.org or tagc.med.sc.edu/professional_organizations.asp.

Complete Results

Gene	Variant	Zygosity	Variant Classification
CHEK2	c.846+4_846+7delAGTA (Intronic)	heterozygous	Uncertain Significance

The following genes were evaluated for sequence changes and exonic deletions/duplications:
APC, ATM, AXIN2, BARD1, BMPR1A, BRCA1, BRCA2, BRIP1, CDH1, CDKN2A (p14ARF), CDKN2A (p16INK4a), CHEK2, CTNNA1, DICER1, EPCAM*, GREM1*, KIT, MEN1, MLH1, MSH2, MSH3, MSH6, MUTYH, NBN, NF1, PALB2, PDGFRA, PMS2, POLD1, POLE, PTEN, RAD50, RAD51C, RAD51D, SDHB, SDHC, SDHD, SMAD4, SMARCA4, STK11, TP53, TSC1, TSC2, VHL

The following genes were evaluated for sequence changes only:
HOXB13*, NTHL1*, SDHA

Results are negative unless otherwise indicated

Benign and Likely Benign variants are not included in this report but are available upon request. An asterisk (*) indicates that this gene has a limitation. Please see the Limitations section for details.

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Reclassified Test Result

CHEK2 Likely Pathogenic

Reason for testing
Diagnostic test for a personal and family history of disease

Test performed
Sequence analysis and deletion/duplication testing of the 46 genes listed in the Genes Analyzed section.
- Invitae Common Hereditary Cancers Panel

This report supersedes RQ490619 (10.01.2018) and updates the interpretation of the below variant(s).

- The change in variant classification was made as a result of re-review of the evidence in light of new variant interpretation guidelines and/or new information.
- Please note that the design of the report has changed from the original report and some of the content may have moved.

Updated Interpretations

GENE	VARIANT	ZYGOSITY	PRIOR VARIANT CLASSIFICATION	NEW VARIANT CLASSIFICATION
CHEK2	c.846+4_846+7del (Intronic)	heterozygous	Uncertain Significance	Likely Pathogenic

RESULT: POSITIVE

One Likely Pathogenic variant identified in CHEK2. CHEK2 is associated with autosomal dominant predisposition to hereditary cancers.

GENE	VARIANT	ZYGOSITY	VARIANT CLASSIFICATION
CHEK2	c.846+4_846+7del (Intronic)	heterozygous	Likely Pathogenic

About this test
This diagnostic test evaluates 46 gene(s) for variants (genetic changes) that are associated with genetic disorders. Diagnostic genetic testing, when combined with family history and other medical results, may provide information to clarify individual risk, support a clinical diagnosis, and assist with the development of a personalized treatment and management strategy.

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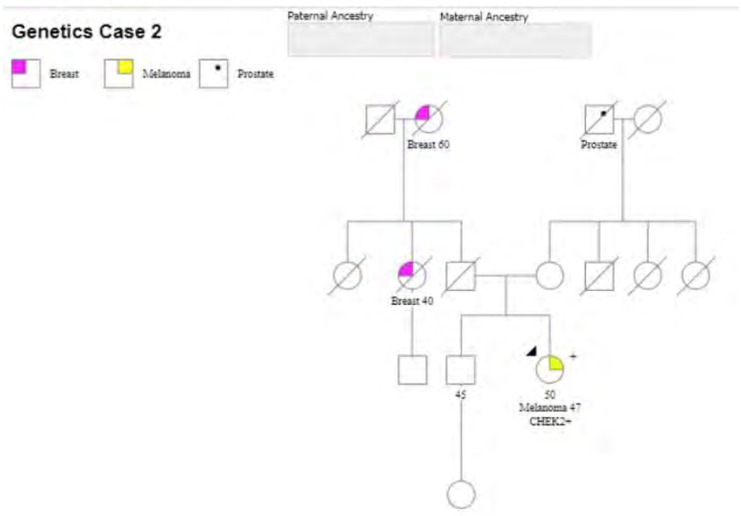
Case 2



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Discussion

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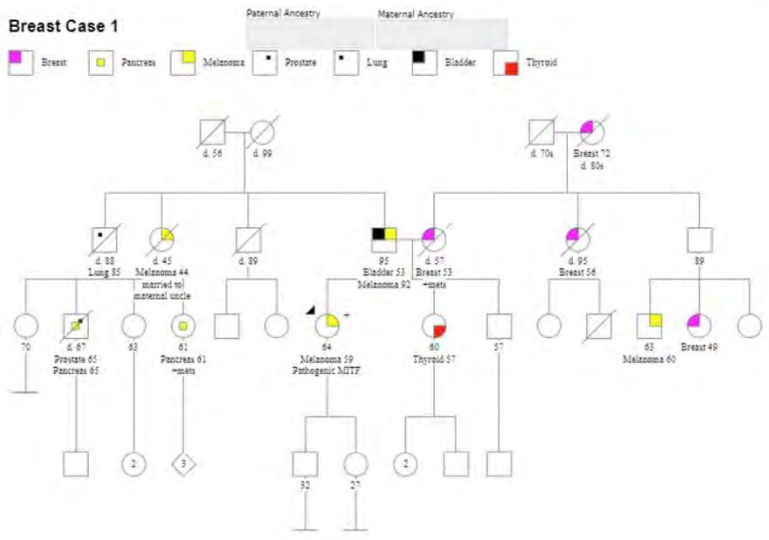
Case 3



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Test Result

MITF Pathogenic

CancerNext-Expanded® +RNAinsight®: Analyses of 77 Genes Associated with Hereditary Cancer

RESULTS

MITF **Pathogenic Mutation: p.E318K**

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **p.E318K (c.952G>A)** pathogenic mutation in the *MITF* gene.
- **Risk estimate**: up to a 5-fold increased risk for renal cell carcinoma (RCC) and a 2- to 8-fold increased risk for melanoma.
- The expression and severity of disease for this individual cannot be predicted.
- Genetic testing for pathogenic mutations in family members can be helpful in identifying at-risk individuals.
- Genetic counseling is a recommended option for all individuals undergoing genetic testing.

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Breast Cancer Risk Factors:

- Maternal FH of breast cancer (mother, maternal aunt, maternal cousin, maternal grandmother)
- First birth after age 30 (32)
- Menarche before age 12 (11)
- Heterogeneously dense breasts

IBIS Breast Cancer Risk Estimate Results:

Ten Year Risk:
This woman's Risk (at age 64): **15.4%**
Average women (at age 64): **3.3%**
Lifetime Risk:
This woman's Risk (to age 85): **26.7%**
Average woman (to age 85): **6.1%**

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Discussion

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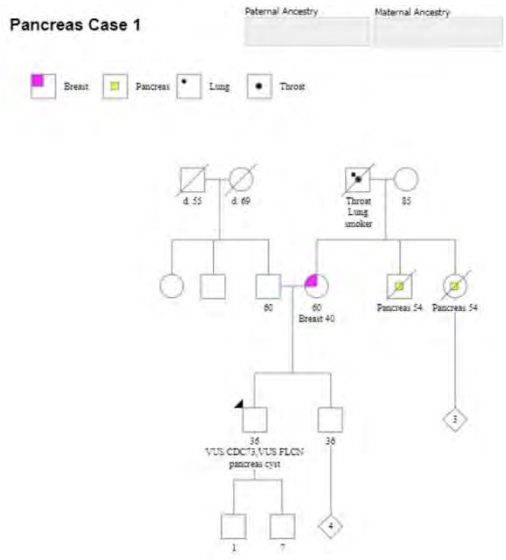
Pancreas Case 1



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Test Result

CDC73 and FLCN VUS

BRCA1/2 Analyses with CancerNext-Expanded® +RNAinsight®

RESULTS		
CDC73	Variant, Unknown Significance:	c.908-5C>T
FLCN	Variant, Unknown Significance:	p.S71P

SUMMARY

Variants of Unknown Significance Detected

INTERPRETATION

- **No known clinically actionable alterations were detected.**
- Two variants of unknown significance were detected: one in the *CDC73* gene and one in the *FLCN* gene.
- No clinically relevant aberrant RNA transcripts were detected in select analyzed genes.*
- **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.

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Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Pancreatic Cancer Screening

NCCN Guidelines Index
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Discussion

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, 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 ≥2 first-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. A family history of exocrine pancreatic cancer in ≥3 first- and/or second-degree relatives from the same side of the family, even in the absence of a known P/LP germline variant.
- These studies have typically started screening with contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS) in such high-risk individuals.

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Radiology and Pathology

- Incidental finding on CT: 3.5 cm cystic lesion in the tail of the pancreas which is indeterminate
- Referred to CRPC and presented at Pancreas Review Board, recommended EUS.
- EUS with biopsy- CEA on FNA was high, diagnostic of mucinous lesion. Fluid signal doesn't indicate any solid components, but can tell it is not simple fluid, likely mucinous.
- Presented at Pancreas Review Board again and panel discussion recommend resection due to family hx, large cyst, pt is young and has a long future of surveillance.
- Proceeded with distal pancreatectomy with splenectomy, pathology showed benign simple cyst (3.7cm)

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Discussion

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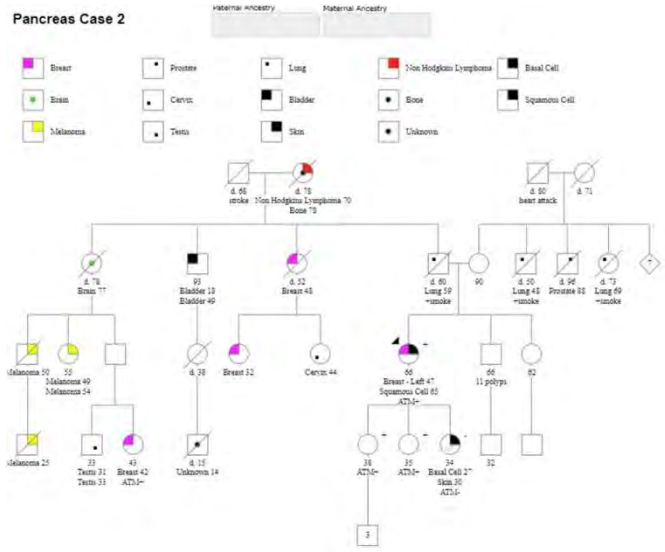
Pancreas Case 2



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Test Result

ATM Pathogenic

RESULT: POSITIVE - 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.

TEST PERFORMED	RESULT	INTERPRETATION
ATM	**Mutation Detected**	**High Cancer Risk**
c.5623C>T (p.Arg1875*)	Heterozygous	This patient has ATM-associated Cancer Risk.

DETAILS ABOUT: ***ATM*** **c.5623C>T (p.Arg1875*): NM_000051.3**

Functional Significance: Deleterious - Abnormal Protein Production and/or Function

The heterozygous germline *ATM* mutation c.5623C>T is predicted to result in the premature truncation of the *ATM* protein at amino acid position 1875 (p.Arg1875*).

Clinical Significance: High Cancer Risk

This mutation is associated with increased cancer risk and should be regarded as clinically significant.

ADDITIONAL FINDINGS: NO VARIANT(S) OF UNCERTAIN SIGNIFICANCE (VUS) IDENTIFIED

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.

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Management Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Gene Summary: Risks and Management

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CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a,1,2]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management (First primary)	Epithelial Ovarian Cancer Risk and Management	Pancreatic Cancer Risk and Management[13-22] and Other Cancer Risks
ATM	• **Absolute risk:** 20%–40%[3,4,5,6] • **Management:**[b] ‣ Screening: Annual mammogram at age 40 y and consider breast MRI with contrast starting at age 30–35 y[c,d,e] ‣ Risk reduction: Evidence insufficient for risk-reducing mastectomy (RRM), manage based on family history • **Strength of evidence of association with cancer:** Strong	• **Absolute risk:** 2%–3%[10-12] • **Management:**[f] ‣ Risk reduction: Evidence insufficient for risk-reducing salpingo oophorectomy (RRSO); manage based on family history • **Strength of evidence of association with cancer:** Strong	**Pancreatic cancer** • **Absolute risk:** ~5%–10%[9,23] • **Management:** Screen P/LP variant carriers with a family history of pancreatic cancer; see PANC-A • **Strength of evidence of association with cancer:** Strong **Prostate cancer** • Emerging evidence for association with increased risk[24]

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2023
Pancreatic Cancer Screening

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  3. A family history of exocrine pancreatic cancer in ≥3 first- and/or second-degree relatives from the same side of the family, even in the absence of a known P/LP germline variant.
- These studies have typically started screening with contrast-enhanced MRI/magnetic resonance cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS) in such high-risk individuals.

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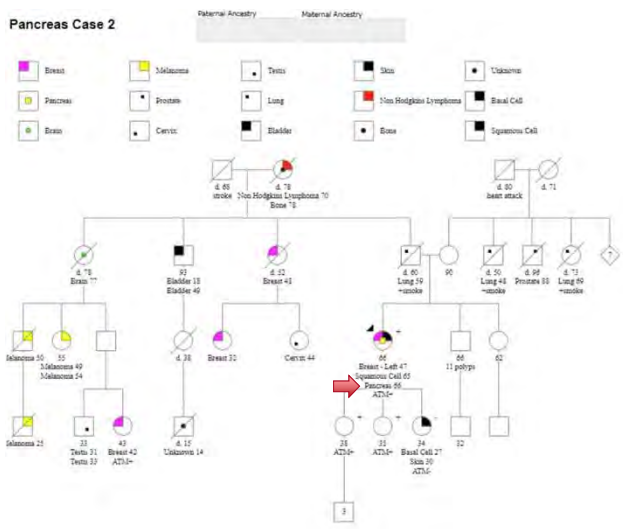
Pancreas Case 2



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Discussion

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Risk/Benefit Discussion

Provide information about:

- The disease
- The screening service

Risks	Benefits
- Overtreatment - Anxiety - False positives (cysts) - Cost	- Downstaging - Improved mortality

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Common Diagnoses

BRCA1/2	PALB2	BRIP1	ATM
Lynch (MLH1/MSH2/ MSH6/PMS2/ EPCAM)	CHEK2	MUTYH	SDHx
CDH1	RET	MEN	TP53
VHL	Fam Hx Breast Cancer >20% TC score	High Risk Breast – ADH/ALH/ LCIS	Fam Hx Pancreas Cancer

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Resources

- Li-Fraumeni Syndrome Association www.lfsassociation.org
- Living Li-Fraumeni Syndrome www.livinglfs.org or 1-844-537-2255
- Hereditary Cancer Foundation www.hereditarycancer.org/
- FORCE (Facing Our Risk of Cancer Empowered), 866-288-7475 or www.facingourrisk.org
- Bright Pink, www.brightpink.org
- Alive and Kickin' www.aliveandkickin.org
- Lynch Syndrome International https://lynchcancers.com/
- No Stomach for Cancer www.nostomachforcancer.org/
- Pheo Para Alliance www.pheopara.org
- VHL Alliance www.vhl.org
- Aim at Melanoma Foundation - www.aimatmelanoma.org
- Melanoma Genetics Consortium - www.genomel.org
- Information about GINA (Genetic Information Non-Discrimination Act) Law: https://www.genome.gov/about-genomics/policy-issues/Genetic-Discrimination
- The National Pancreas Foundation - https://pancreasfoundation.org/
- National Society of Genetic Counselor - www.nsgc.org
- Find a genetic counselor - www.findageneticcouselor.com

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