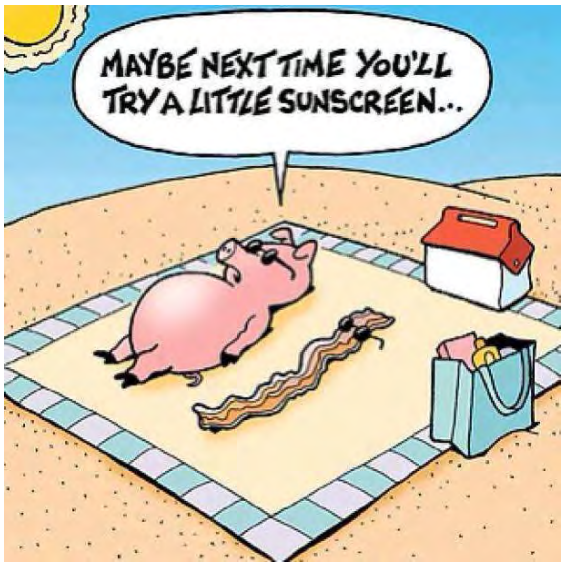
1

DISCLOSURES

I have no disclosures.



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2

LEARNING OBJECTIVES

Objective 1  Recognize genes related to hereditary skin cancer.

Objective 2  Determine the differences between specific hereditary skin cancer syndromes.

Objective 3  Assess clinical scenarios involving skin cancer to determine a differential diagnosis.

3

3

ARE THERE ANY GENETIC CAUSES OF SKIN CANCER?

Yes | No | Maybe?

4

4

DO YOU KNOW OF ANY GENE(S) ASSOCIATED WITH SKIN CANCER?

Yes
(which ones?)

No

Maybe?

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MELANOMA GENES

6

HEREDITARY MELANOMA GENES

Genes
BAP1
BRCA2
CDK4
CDKN2A
MITF
POT1
PTEN
RB1
TP53

Potentially Associated/Preliminary Evidence Genes: ATM, BRCA1, CHEK2, MC1R, TERT

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HEREDITARY MELANOMA GENES

Genes	Melanoma	Breast	Ovarian	Colorectal	Uterine	Pancreatic	Kidney	Others
BAP1	✓						✓	✓ mesothelioma
BRCA2	✓	✓	✓			✓		✓ prostate, male breast
CDK4	✓							
CDKN2A	✓					✓		✓ Brain/CNS tumors (astrocytomas)
MITF	✓						✓	
POT1	✓							✓ gliomas, leukemia, sarcomas
PTEN	✓	✓		✓	✓		✓	✓ thyroid
RB1	✓							✓ Eye tumors (retinoblastomas), brain tumors, and sarcomas
TP53	✓	✓	✓	✓	✓	✓	✓	✓

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HEREDITARY MELANOMA SYNDROMES

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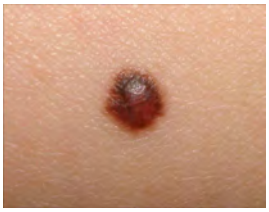
BAP1 TUMOR PREDISPOSITION SYNDROME

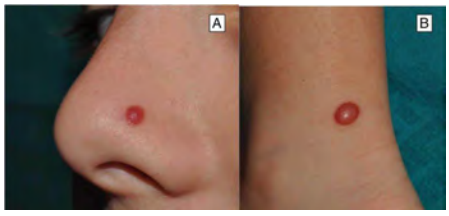
Genes
BAP1
BRCA2
CDK4
CDKN2A
MITF
POT1
PTEN
RB1
TP53

Autosomal dominant

BAP1 gene



Highest risks for melanocytic BAP1 atypical intradermal tumor(MBAIT – formerly known as atypical Spitz tumors), cutaneous and uveal melanoma, BCC, mesothelioma, and RCC



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BRCA2 AND CDK4

Genes
BAP1
BRCA2
CDK4
CDKN2A
MITF
POT1
PTEN
RB1
TP53

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BRCA2

- Autosomal Dominant
- Cancer Risks
  - Breast (AFAB 40-80%)
    - (7-8% AMAB)
  - Ovary (13-29%)
  - Prostate (19-61%)
  - Pancreatic (5-10%)
  - Melanoma (Increased)

CDK4

- Autosomal Dominant
- Cancer Risks
  - Melanoma (Up to 74%)
- Less than 100 families

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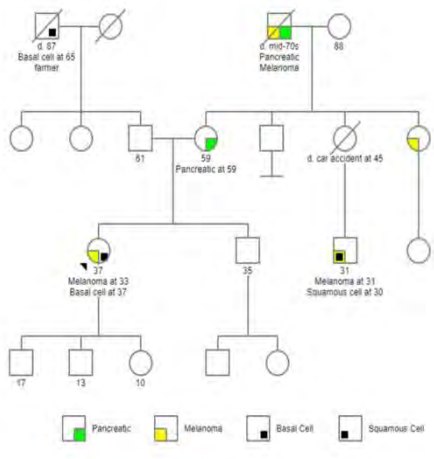
FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (FAMMM)

Genes
BAP1
BRCA2
CDK4
CDKN2A
MITF
POT1
PTEN
RB1
TP53



Autosomal dominant

CDKN2A gene

Highest increased risks for melanoma (28-76%), pancreatic cancer (17-58%), and astrocytoma (increased)

2 proteins – p14 and p16

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MITF-TUMOR PREDISPOSITION SYNDROME

Genes
BAP1
BRCA2
CDK4
CDKN2A
MITF
POT1
PTEN
RB1
TP53

Autosomal dominant

MITF gene

Highest increased risks for cutaneous melanoma and renal cell carcinoma

FUN FACT: Only one specific mutation in this gene is known to be associated with increased risk for melanoma (*MITF* c.952G>A, p.Glu218Lys, or known as E318K).

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POT1-TUMOR PREDISPOSITION SYNDROME

Genes
BAP1
BRCA2
CDK4
CDKN2A
MITF
POT1
PTEN
RB1
TP53

Autosomal dominant

POT1 gene

Highest increased risks multiple cutaneous melanomas, CLL, cardiac angiosarcomas, and gliomas

FUN FACT: Age of onset of melanoma is 15-80 years – so if family history has a young age of onset, testing of teenagers may be considered

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PTEN AND RB1 AND TP53

Genes
BAP1
BRCA2
CDK4
CDKN2A
MITF
POT1
PTEN
RB1
TP53

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PTEN

- Cowden syndrome (*PTEN* hamartoma tumor syndrome)
- Autosomal Dominant
- Cancer Risks
  - Breast
  - Uterine
  - Thyroid
  - Renal
  - Colon
  - Melanoma

RB1

- Autosomal Dominant
- Cancer Risks
  - Retinoblastoma
  - Melanoma
  - Pineoblastoma
  - Sarcomas

TP53

- Li-Fraumeni Syndrome
- Autosomal Dominant
- Cancer Risks
  - Sarcoma
  - Breast
  - Ovarian
  - Colon
  - Uterine
  - Prostate
  - Melanoma

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BESIDES MELANOMA, WHAT OTHER CANCER RISK IS INCREASED IN FAMMM SYNDROME?

- #1 Kidney
- #2 Breast
- #3 Pancreatic
- #4 Colon
- #5 Uterine

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BESIDES MELANOMA, WHAT OTHER CANCER RISK IS INCREASED WHEN THE MITF GENE IS ALTERED?

#1	#2	#3	#4	#5
Kidney	Breast	Pancreatic	Colon	Uterine

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OTHER HEREDITARY SKIN CANCER SYNDROMES

AND CANCER SYNDROMES WITH SKIN FINDINGS

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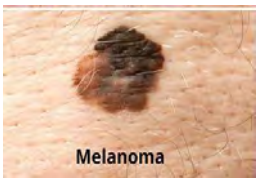
NEVOID BASAL CELL CARCINOMA (GORLIN) SYNDROME

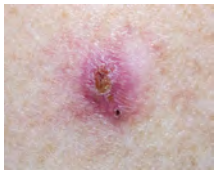
Autosomal dominant

PTCH1 and *SUFU* genes



Highest risks for BCC, medulloblastomas, jaw keratocyts, ovarian and cardiac fibromas

Have you had more than 5 BCCs in your life, or had one before age 30?



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Syndrome	Gene(s)	Skin findings	Cancer and/or Tumor Risks	Other features
Neurofibromatosis type I	*NF1*	Café-au-lait macules (CALMs), neurofibromas, and axillary freckling	Brain (astrocytoma), Eye (optic glioma), Breast, Stomach (GIST), Pheochromocytomas	Scoliosis, Lisch nodules
Tuberous Sclerosis	*TSC1* and *TSC2*	Hypopigmented macules, Shagreen patch, confetti skin lesions, facial angiofibromas, and ungual fibromas	Brain (astrocytoma), Eye (retinal hamartomas), Heart (cardiac rhabdomyoma), Lung (lymphangioleiomoymatosis – LAM), Kidney (RCC, renal angiomyolipomas – RAM, renal cysts)	Cortical tubers, dental enamel pits, neuropsychiatric (LD, ASD, ADHD), Seizures
Cowden (*PTEN* Hamartoma Tumor Syndrome)	*PTEN*	Papillomatous papules, acral keratoses, trichilemmomas, and mucosal lesions, Melanoma	Breast, Thyroid (follicular and/or papillary), Endometrial, Kidney, Colon (hamartomatous polyps), lipomas	Macrocephaly, ID
Gorlin (Nevoid Basal Cell Carcinoma Syndrome)	*PTCH1* and *SUFU*	Multiple basal cell carcinomas, palmo-plantar pits	Brain (medulloblastoma), Jaw keratocysts, cardiac fibroma, ovarian fibroma	Macrocephaly, calcification of falx, vertebral/rib anomalies, polydactyly, CL/P, ocular anomalies
Birt-Hogg-Dube	*FLCN*	Multiple fibrofolliculomas, trichodiscomas, and/or acrochordons	Kidney cancer (RCC)	Pulmonary cysts and spontaneous pneumothorax
HLRCC	*FH*	Cutaneous leiomyomas	Uterine leiomyomas (fibroids), Kidney cancer (papillary type 2), Breast, Bladder	N/A
Muir-Torre	*MLH1* and *MSH2*	Multiple sebaceous tumors (adenoma, epithelioma, carcinoma) and keratocanthomas	Colon, Endometrial, Small Bowel, Pancreas, Hepato-biliary tract, Brain, and Ovarian	N/A
FAP	*APC*	Epidermoid cysts and fibromas	Colon (Adenomatous polyps), Thyroid (papillary), desmoid tumors, Liver (hepatoblastoma), Brain (medulloblastoma), Pancreas, Stomach (fundic gland polyps), osteomas	CHRPE, dental anomalies
Peutz-Jehgers syndrome	*STK11*	Mucocutaneous pigmentation	Colon (hamartomatous polys), Gonadal (ovarian sex cord or Sertoli cell), Breast, Stomach, Pancreas	Gynecomastia

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ARE THERE GUIDELINES FOR GENETIC TESTING FOR MELANOMA?

Yes

No

Maybe?

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GUIDELINES

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NCCN GUIDELINES

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2023
Melanoma: Cutaneous

NCCN Guidelines Index
Table of Contents
Discussion

COMMON FOLLOW-UP RECOMMENDATIONS FOR ALL PATIENTS

- **Clinical and family history can identify patients in whom multigene testing might indicate an increased genetic risk for cutaneous and uveal melanoma, astrocytoma, mesothelioma, and cancers of the breast, pancreas, and kidney. This information can guide recommendations for surveillance and early detection in appropriate patients and their relatives.**
  - **Consider genetic counseling referral for *p16/CDKN2A* mutation testing in the presence of 3 or more invasive cutaneous melanomas, or a mix of invasive melanoma, pancreatic cancer, and/or astrocytoma diagnoses in an individual or family.**
  - **Multigene panel testing that includes *CDKN2A* is recommended for patients with invasive cutaneous melanoma who have a first-degree relative diagnosed with pancreatic cancer (see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic).**
  - **Testing for other genes that can harbor melanoma-predisposing mutations (see Risk Factors for Development of Single or Multiple Primary Melanomas ME-A 1 of 2) may be warranted.**

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Melanoma: Uveal

In conclusion, the NCCN Panel recommends evaluation for evidence of hereditary syndrome and referral for genetic counseling and testing in case of: early age of diagnosis (<30 years of age), history of other primary cancers in the patient, or family or personal history of other cancers known to be associated with a hereditary syndrome.

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AMERICAN ACADEMY OF DERMATOLOGY

J Am Acad Dermatol
Volume 80, Number 1

Table XX. Recommendations for genetic counseling of patients with CM

Cancer risk counseling by a qualified genetic counselor is recommended for patients with CM who have

- A family history of invasive CM or pancreatic cancer (≥3 affected members on 1 side of the family)
- Multiple primary invasive CM (≥3), including 1 early-onset tumor (at age <45 y)
- ≥1 MBAIT and a family history of mesothelioma, meningioma, and/or uveal melanoma
- ≥2 MBAITs

CM, Cutaneous melanoma, *MBAIT*, melanocytic BAP1-mutated atypical intradermal tumor.

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DO MOST INSURANCE PAYORS COVER GENETIC TESTING FOR HEREDITARY SKIN CANCER?

Yes

No

It depends

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CASE EXAMPLE #1

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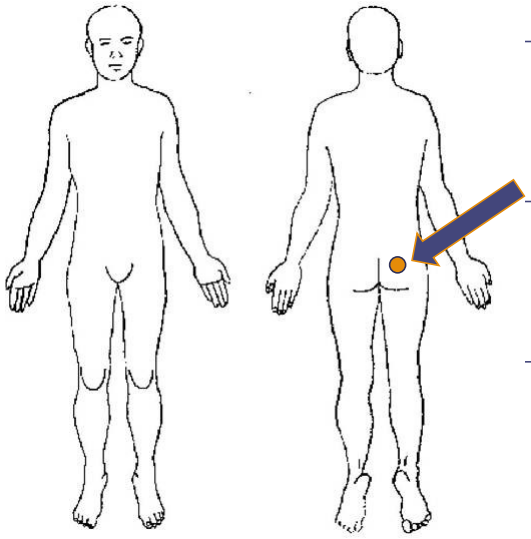
Case Example #1 - Patient Info



PATIENT: 65-year-old male; fair skin, blonde hair, blue eyes

INDICATION: Melanoma on right flank at 44; Reports 6 other melanomas in lifetime between ages 44-64

LIFESTYLE: Works as a lawyer, enjoys golfing outside and traveling

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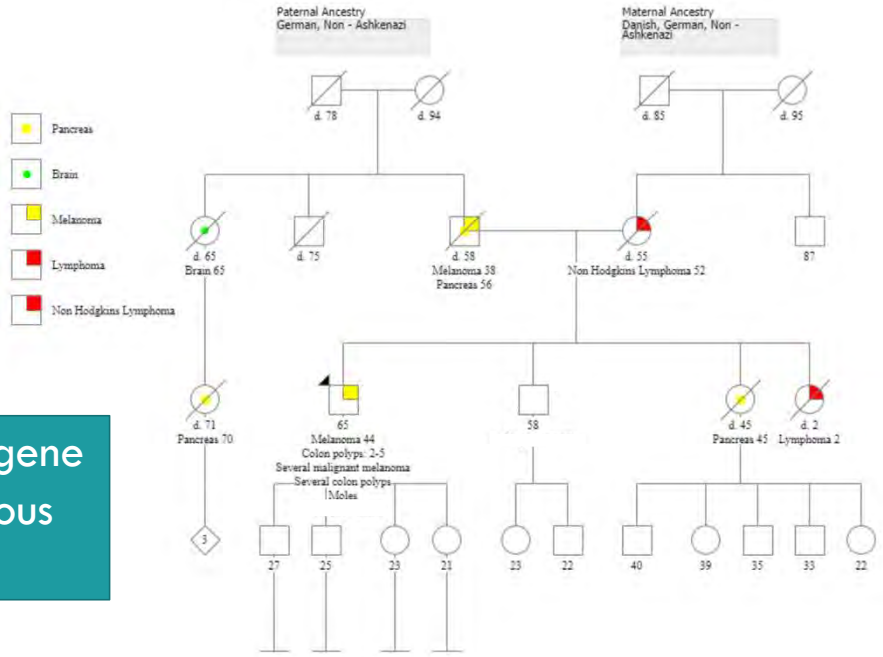
CASE EXAMPLE #1



What syndrome/gene is this most suspicious for?

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CASE EXAMPLE #1 - RESULTS

RESULTS

CDKN2A **c.457G>T Pathogenic Mutation: Detected**

SUMMARY

POSITIVE: Pathogenic Mutation Detected

INTERPRETATION

- This individual is heterozygous for the **c.457G>T** pathogenic mutation in the *CDKN2A* gene.
- This result is consistent with a diagnosis of familial atypical multiple mole melanoma (FAMMM) syndrome.
- **Risk estimate**: lifetime risks of 28-67% for melanoma and 17-58% for pancreatic cancer.
- 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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CDKN2A

General Population Risk

Risk with *CDKN2A* variant

CANCER RISK		MANAGEMENT
MELANOMA	28-76% 2-3%	Monthly self exams Clinical total body exam very 3-12 months (including scalp, mouth, genital area, and nails) Wear/reapply sunscreen and wear protective clothing Avoid tanning beds and excessive sun burns/exposures
PANCREATIC	17-58% 2%	Consider annual MRI/MRCP or endoscopic ultrasound starting at age 40 or 10 years before earliest known pancreatic cancer Reduce or eliminate alcohol and tobacco use

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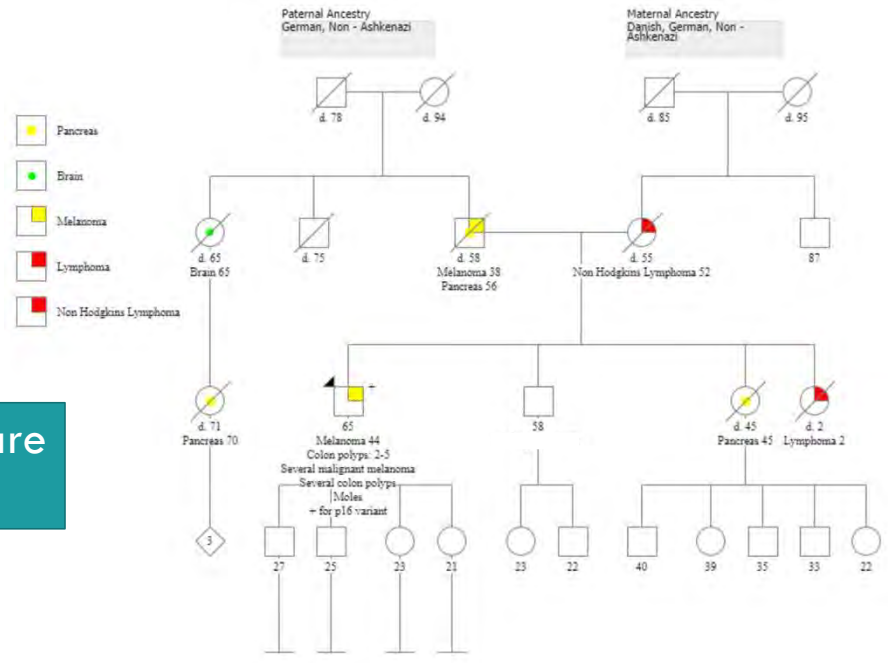
CASE EXAMPLE #1



What relatives are at risk?

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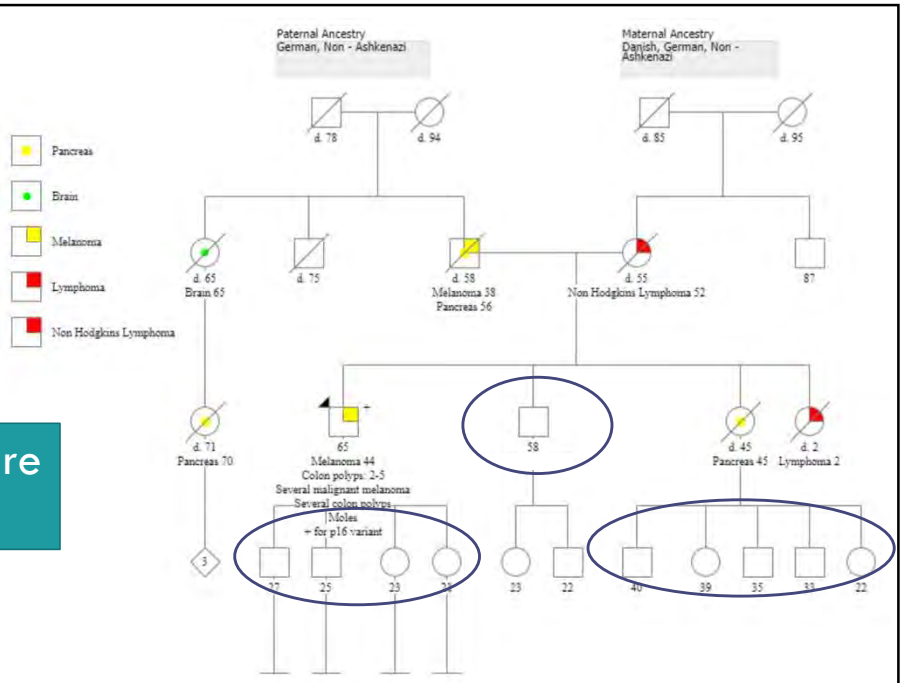
CASE EXAMPLE #1

What relatives are at risk?



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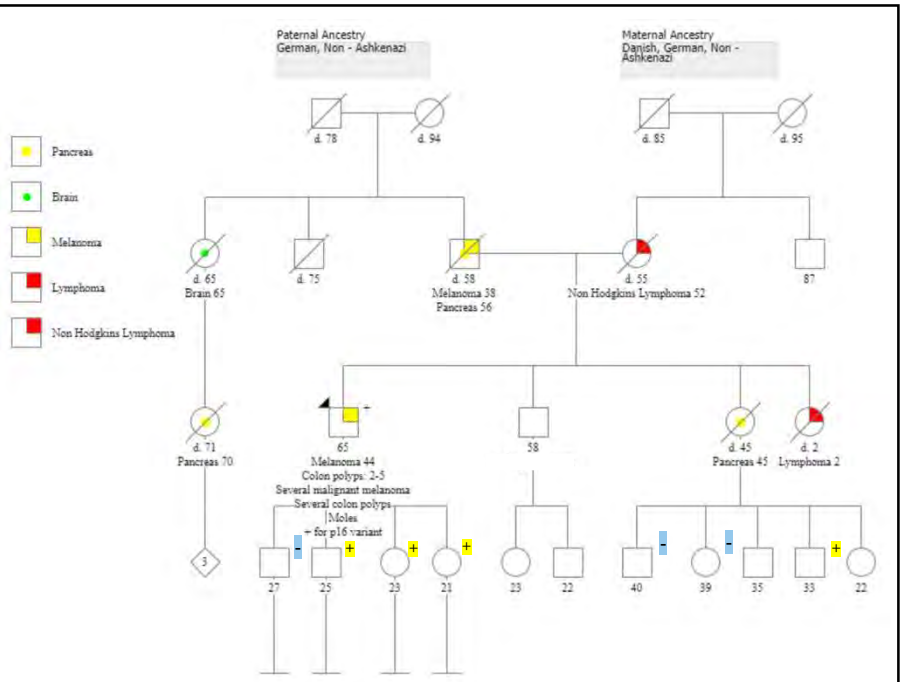
CASE EXAMPLE #1



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CASE EXAMPLE #2

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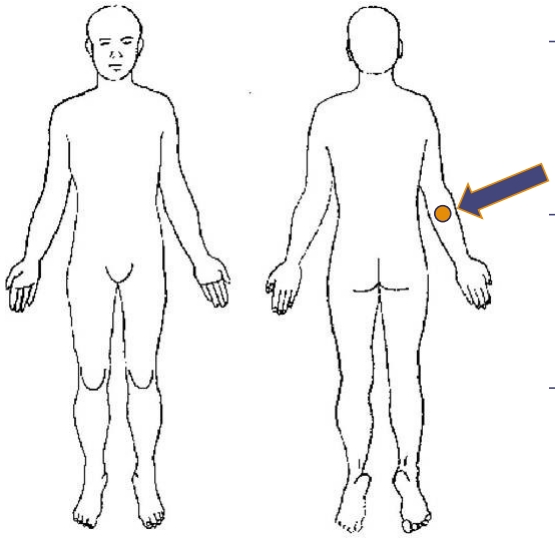
Case Example #2 - Patient Info



PATIENT: 63-year-old male; fair skin, red hair, blue eyes

INDICATION: Melanoma on right arm at 59

LIFESTYLE: Non-smoker; 1 drink of alcohol a week; Works as a farmer in the Midwest and limited sunscreen use

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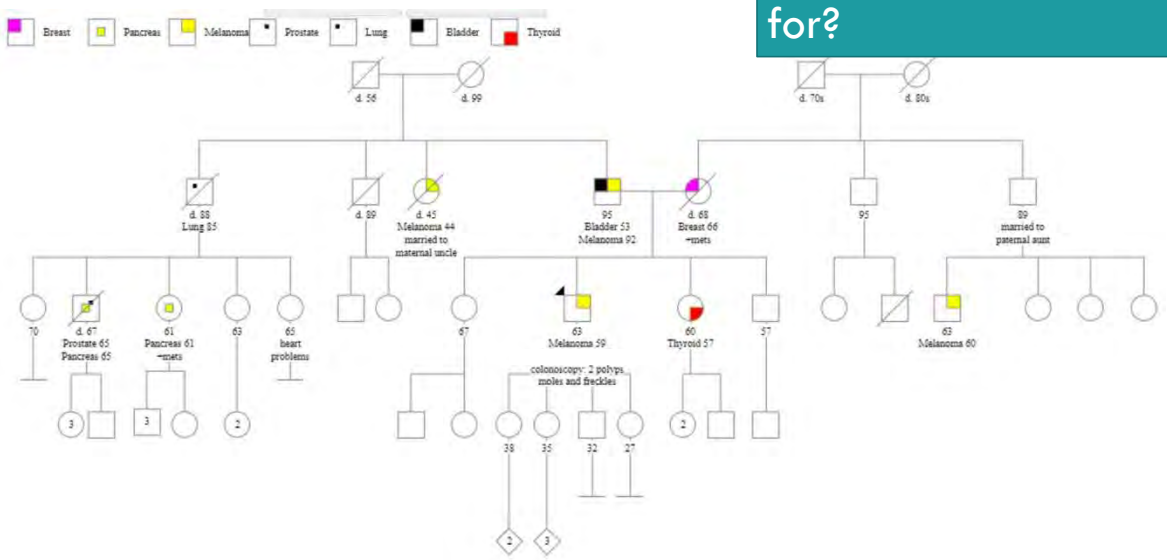
CASE #2 - PEDIGREE

What syndrome(s) is this most suspicious for?



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CASE #2 – GENETIC TEST RESULTS

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.

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).** RNA data is routinely analyzed for use in variant interpretation for all genes.

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MITF

General Population Risk

Risk with *MITF* variant

CANCER RISK		MANAGEMENT
MELANOMA	Up to 24% 2-3%	Monthly self exams Clinical total body exam very 3-12 months (including scalp, mouth, genital area, and nails) Wear/reapply sunscreen and wear protective clothing Avoid tanning beds and excessive sun burns/exposures
KIDNEY	Up to 10% 1-2%	Consider renal ultrasounds every 2-4 years.

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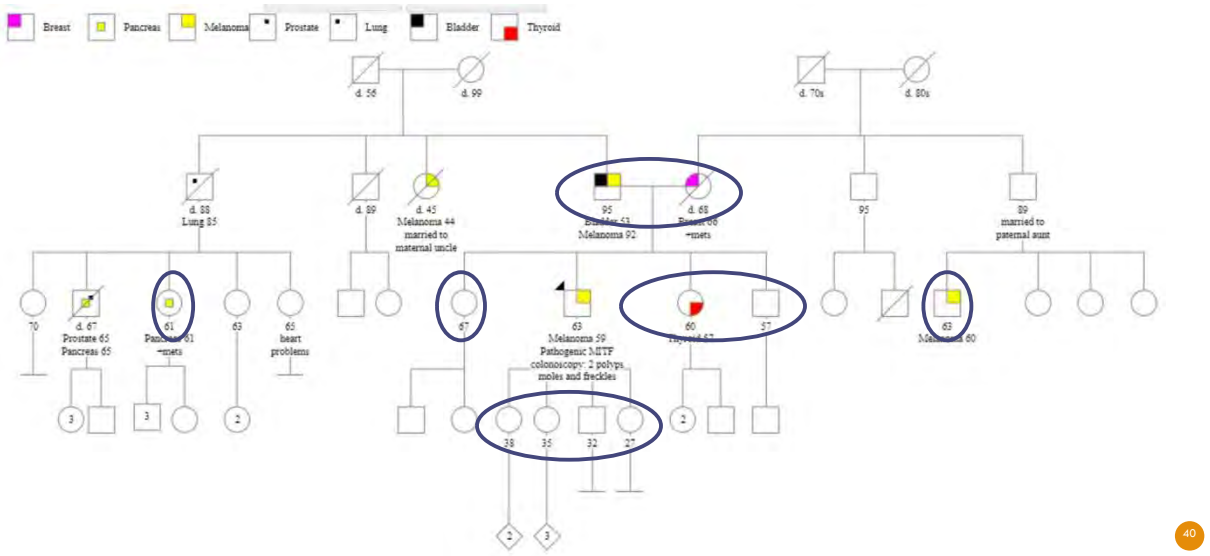
Who else should we test?



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DID YOU LEARN SOMETHING TODAY?

Yes

No

Maybe?

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https://www.treatcancer.com/skin-cancer/

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QUESTIONS?

THANK YOU!

Jessie.Poskochil@unmc.edu

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