KENTUCKY CANCER REGISTRY'S ADVANCED CANCER REGISTRARS' WORKSHOP

NOVEMBER 2022

MICHAEL GOSKY, MS, GC

OBJECTIVES

1. DISCUSS THE ROLE OF GENETIC COUNSELING IN THE PEDIATRIC CANCERS SETTING
2. UNDERSTAND AN OVERVIEW OF COMMON HEREDITARY CANCER SYNDROMES WITH CHILDHOOD CANCER RISKS
3. DISCUSS THE PROJECT INHERITED CANCER RISK (PICR) STUDY
4. ANALYZE CASE EXAMPLES

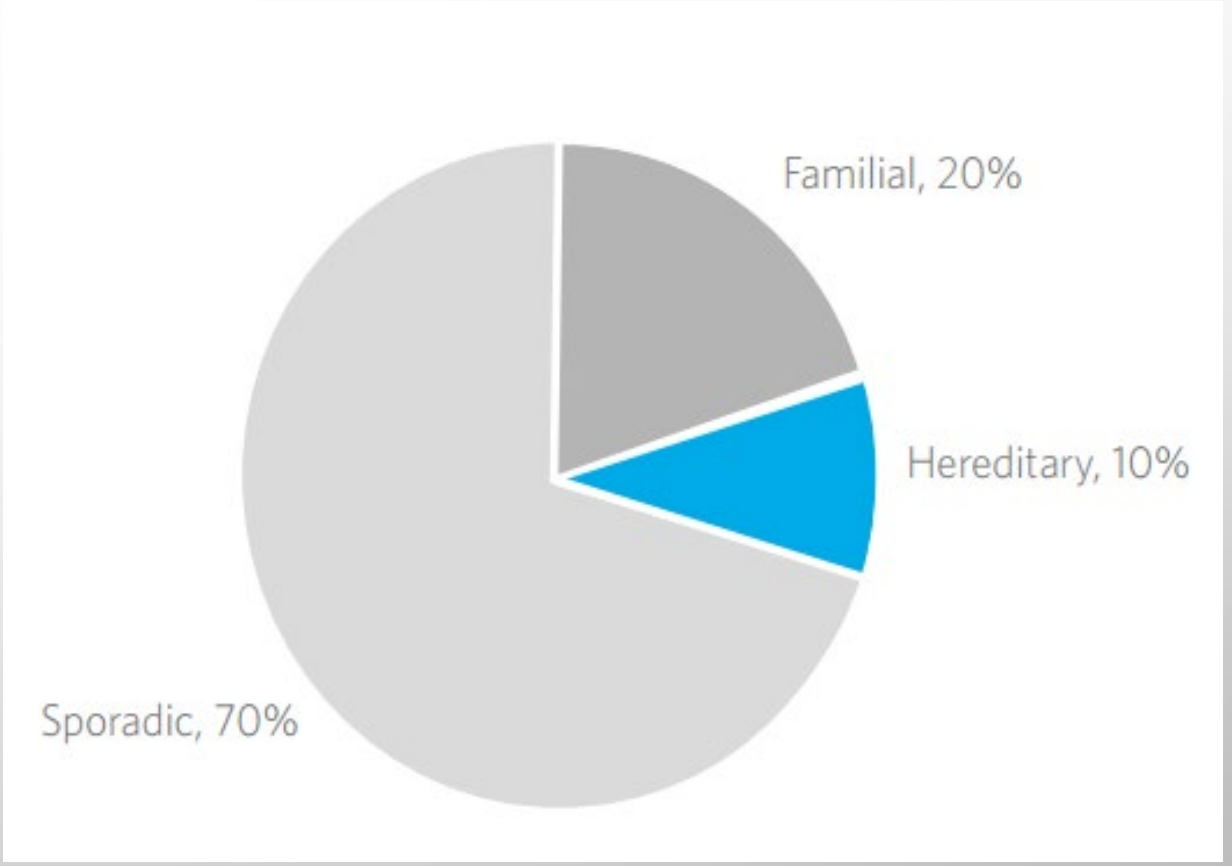
WHAT IS GENETIC COUNSELING?

- GENETIC COUNSELORS HAVE SPECIALTY TRAINING IN GENETICS AND IN ADVANCED COUNSELING
- 4 MAIN CATEGORIES OF GENETIC COUNSELORS:
  - PRENATAL
  - PEDIATRIC
  - CANCER
  - LAB
- MANY SUBSECTIONS, OFTEN OVERLAPPING

CANCER GENETIC COUNSELING

- TYPICALLY, CANCER IS THOUGHT OF AS AN ADULT-ONSET CONDITION

- NUMEROUS HEREDITARY CANCER PREDISPOSITION SYNDROMES HAVE CHILDHOOD-ONSET RISKS



CANCER GENETIC COUNSELING

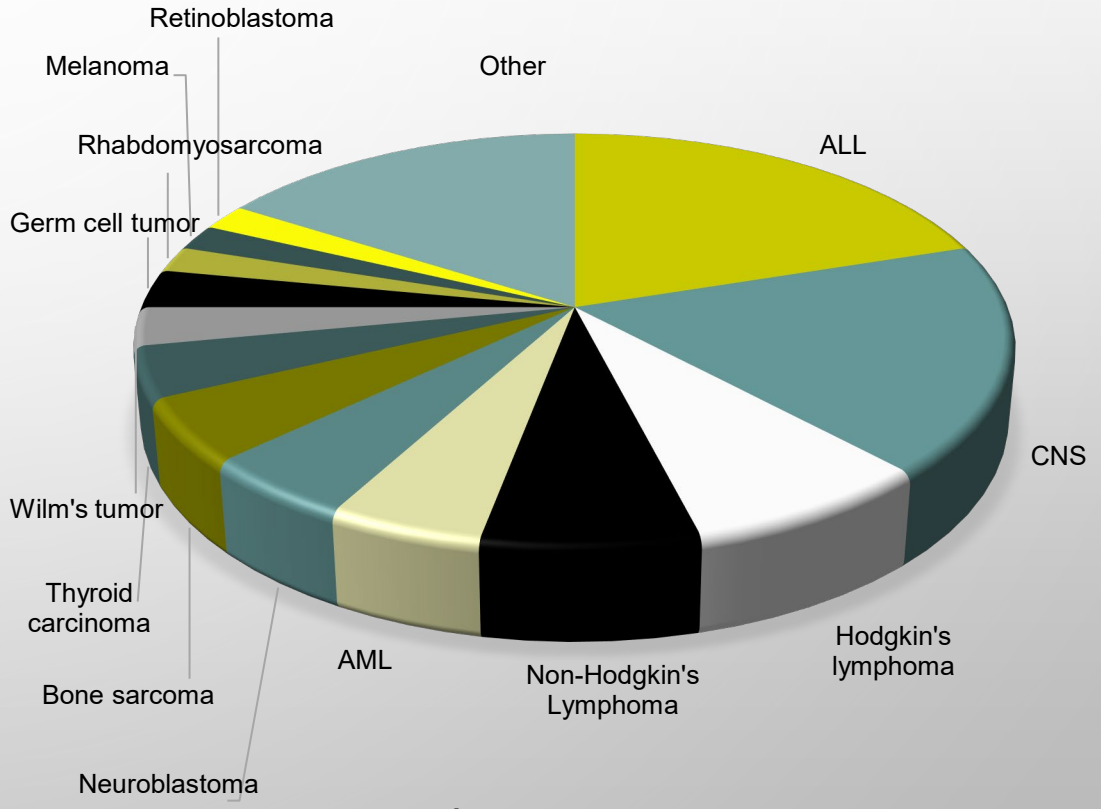
WHAT WE DO:

1. PRETEST COUNSELING
   - SPEAK WITH INDIVIDUALS/FAMILIES ABOUT THEIR PERSONAL/FAMILY HISTORY OF CANCER
   - DISCUSS TESTING OPTIONS – INCLUDING BENEFITS/LIMITATIONS
   - ORDER GENETIC TESTING
2. RECEIVE RESULTS
   - LAB SENDS US RESULTS
   - WE INTERPRET THESE RESULTS
   - INFORM/EDUCATE THE PATIENT OF RESULTS
3. POST-TEST COUNSELING
   - REVIEW RESULTS
   - DISCUSS SCREENING/MANAGEMENT
   - PROVIDE SUPPORT

*This can all be done in the pediatric setting with special attention given to the fact that the patient is typically <18 years old

PEDIATRIC CANCERS

- IN THE U.S., ~15,000 CHILDREN ARE DIAGNOSED WITH CANCER EACH YEAR
- ~8% OF THESE HAVE AN INHERITED CANCER SYNDROME (~1,200 CHILDREN)
  - ZHANG, J. ET. AL., 2015, *NEJM*.
  - GROBNER, S. ET. AL., 2018, *NATURE*.



Curesearch.org; American Cancer Society Facts and Figures (2014)

HEREDITARY CANCER SYNDROMES WITH CHILDHOOD CANCER RISKS

Autosomal Dominant

- BIRT-HOGG-DUBE - *FLCN*
- FAMILIAL ADENOMATOUS POLYPOSIS (FAP) - *APC*
- FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (FAMMM) – *CDKN2A*
- LI-FRAUMENI SYNDROME – *TP53*
- MULTIPLE ENDOCRINE NEOPLASIA TYPE 2 (MEN2) - *RET*
- DICER1 SYNDROME – *DICER1*
- VON HIPPEL-LINDAU - *VHL*

Autosomal Recessive

- CONSTITUTIONAL MISMATCH REPAIR DEFICIENCY (CMMRD) – *MLH1, MSH2, MSH6, PMS2*
- MUTYH-ASSOCIATED POLYPOSIS - *MUTYH*
- FANCONI ANEMIA – *FANC FAMILY*
- ATAXIA TELANGIECTASIA - *ATM*
- BLOOM SYNDROME - *BLM*
- NIJMEGEN BREAKAGE SYNDROME - *NBN*
- XERODERMA PIGMENTOSUM – *XP FAMILY*

PROJECT INHERITED CANCER RISK (PICR)

- LEAD BY DR. JOHN D'ORAZIO – BEGAN IN AUGUST 2021
- A CLINICAL TRIAL TO IDENTIFY AND MANAGE CHILDREN AND YOUNG ADULTS WITH GENETIC PREDISPOSITION TO MALIGNANCY
- GOAL: TO PROVIDE MULTIDISCIPLINARY COMPREHENSIVE CARE TO PATIENTS AND FAMILIES AFFECTED BY INHERITED CANCER PREDISPOSITION SYNDROMES

CANCER GENES ANALYZED IN PICR STUDY

- *AIP, ALK, APC, ATM, AXIN2, BAP1, BLM, BMPR1A, CDC73, CDKN1C, CEBPA, DICER1, DIS3L2, DKC1, EPCAM, ETV6, EXT1, EXT2, FANCA, FANCB, FANCC, FANCD2, FANCE, FANCF, FANCG, FANCI, FANCL, FANCM, FH, GATA1, GATA2, GPC3, HRAS, IKZF1, MAX, MEN1, MLH1, MSH2, MSH6, NBN, NF1, NF2, PAX5, PHOX2B, PMS2, PRKAR1A, PTCH1, PTEN, RB1, RECQL4, RET, RPS19, RUNX1, SAMD9, SBDS, SDHA, SDHAF2, SDHB, SDHC, SDHD, SH2B3, SMAD4, SMARCA4, SMARCB1, SMARCE1, SRP72, STK11, SUFU, TERC, TERT, TMEM127, TP53, TSC1, TSC2, VHL, WRN, WT1*

- CAN OPTIONALLY ADD IN *APC, BMPR1A, BRCA1, BRCA2, MAX, MEN1, MLH1, MSH2, MSH6, MUTYH, NF2, PALB2, PMS2, PTEN, RB1, RET, SDHAF2, SDHB, SDHC, SDHD, SMAD4, STK11, TMEM127, TP53, TSC1, TSC2, VHL, WT1*

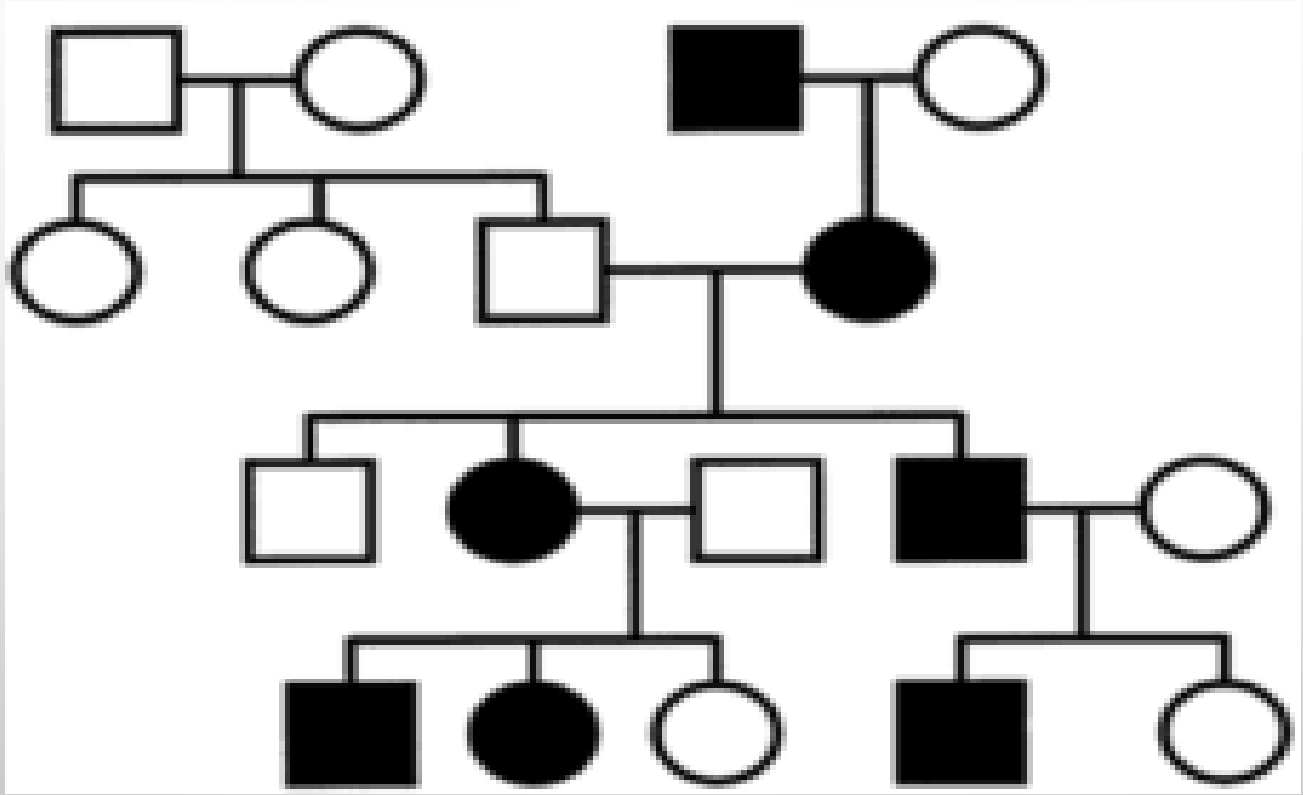
- CAN ALSO ADD IN CARDIOVASCULAR CONDITIONS, INBORN ERRORS OF METABOLISM, MISCELLANEOUS PHENOTYPE, AND SELECT PHARMACOGENOMIC GENES

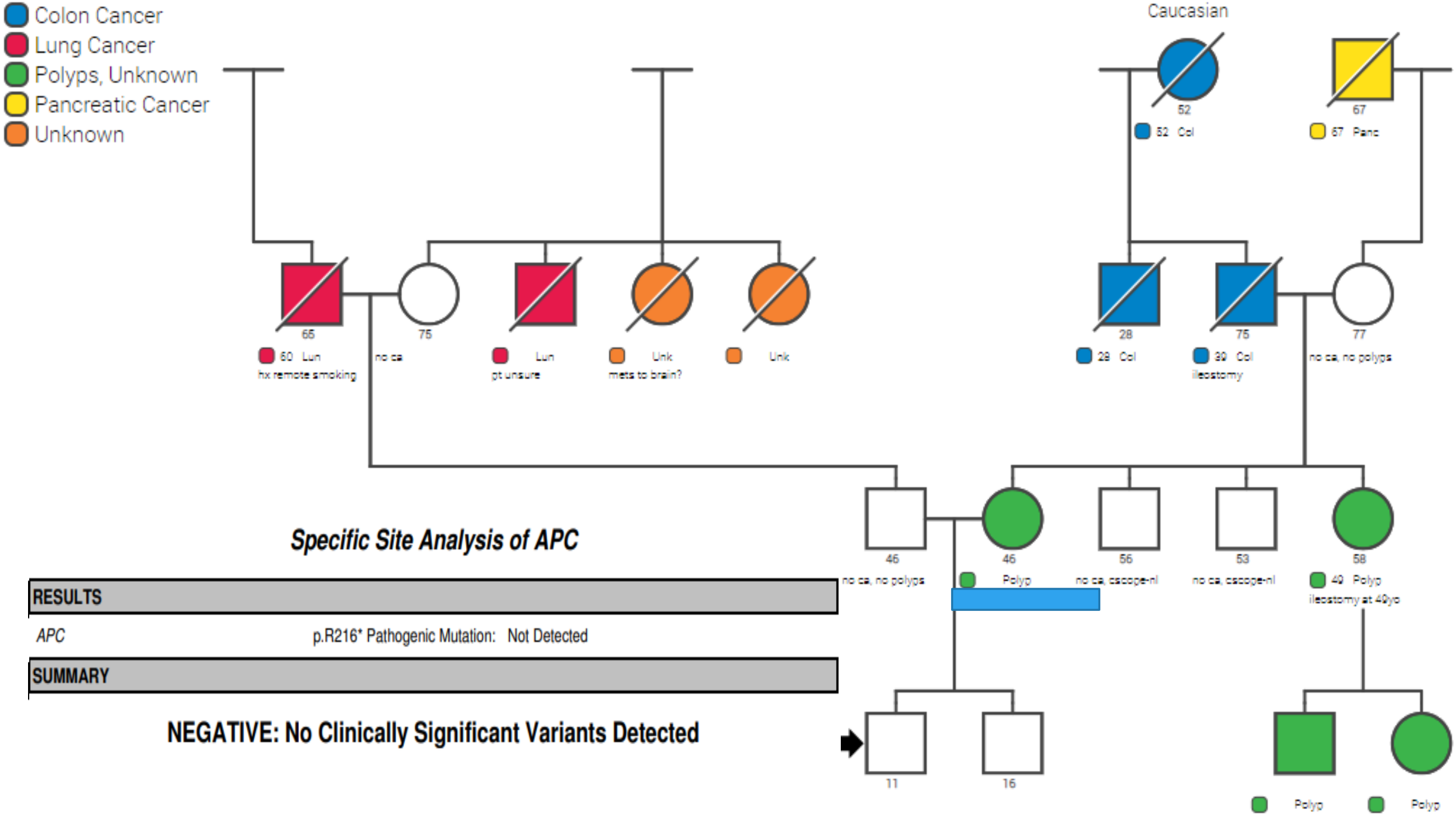
PICR AS OF MARCH 2022

- OFFERED TO 34 PATIENTS, ACCRUED 30 PATIENTS
  - 88.2% OF PATIENTS AGREED TO PARTICIPATE
  - 93.3% AGREED TO ALL PARTS OF THE STUDY
- RESULTS AS OF MARCH 2022:
  - 5.6% POSITIVE FOR PEDIATRIC INHERITED CANCER PANEL GENES
  - 11.1% POSITIVE FOR OPTIONAL ADDITIONAL GENES

- INITIALLY ONLY OFFERED TO NEWLY DIAGNOSED PATIENTS
  - NOW ALL CURRENT AND FORMER PEDIATRIC ONCOLOGY PATIENTS CAN PARTICIPATE

CASE EXAMPLES





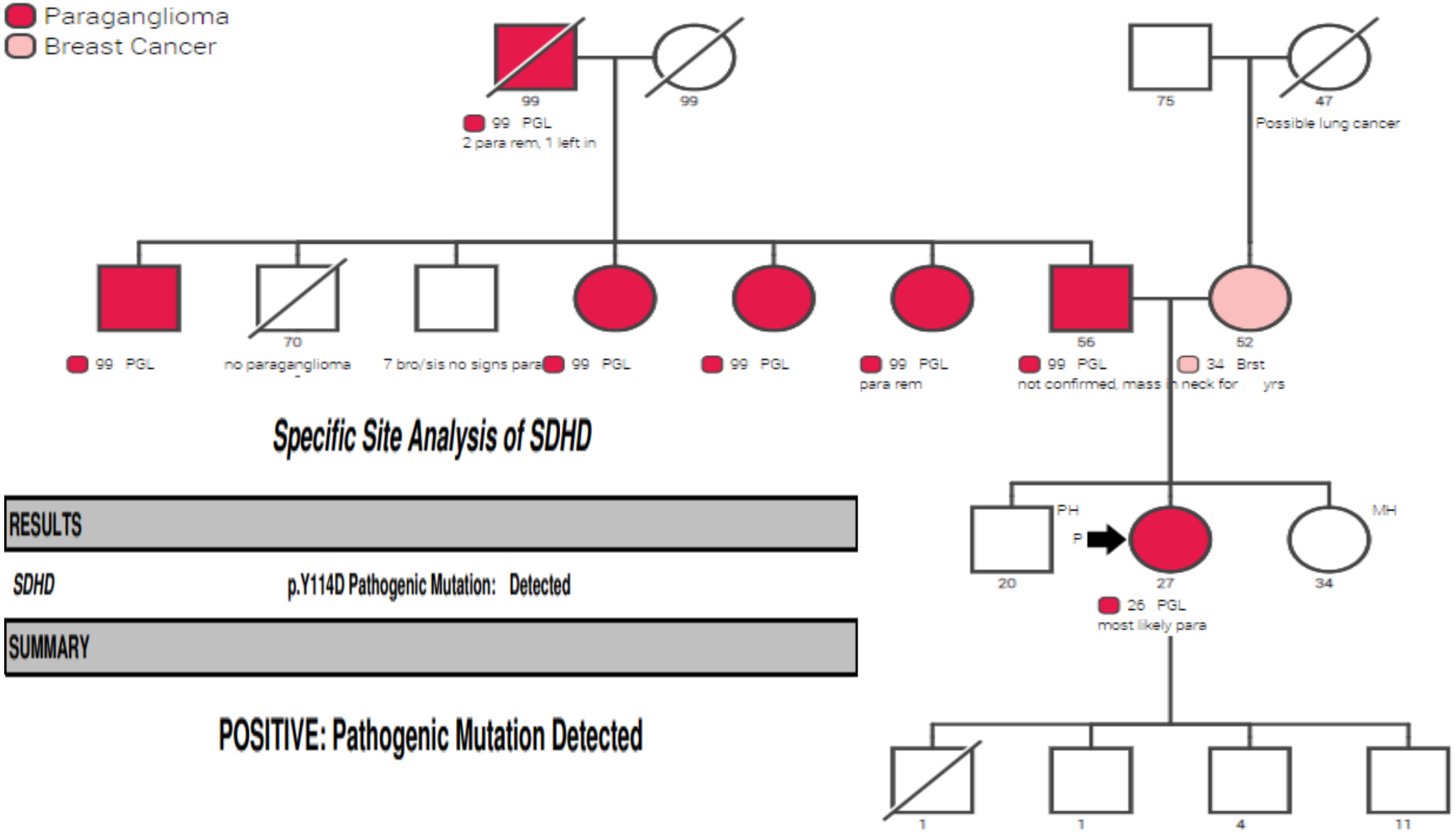
Specific Site Analysis of APC

RESULTS

APC p.R216* Pathogenic Mutation: Not Detected

SUMMARY

NEGATIVE: No Clinically Significant Variants Detected



Specific Site Analysis of SDHD

RESULTS	
SDHD	p.Y114D Pathogenic Mutation: Detected

SUMMARY

POSITIVE: Pathogenic Mutation Detected

- Polyps, Unknown
- Colon Cancer
- Lung Cancer
- Basal Cell Carcinoma
- Melanoma
- Prostate Cancer
- Skin Cancer
- Polyps, Adenomataous
- Uterine Cancer
- Polyps, Hamartomatous

Lynch Syndrome Analyses with CustomNext-Cancer®

RESULTS

BMPR1A **Variant, Likely Pathogenic: p.M470R**

SUMMARY

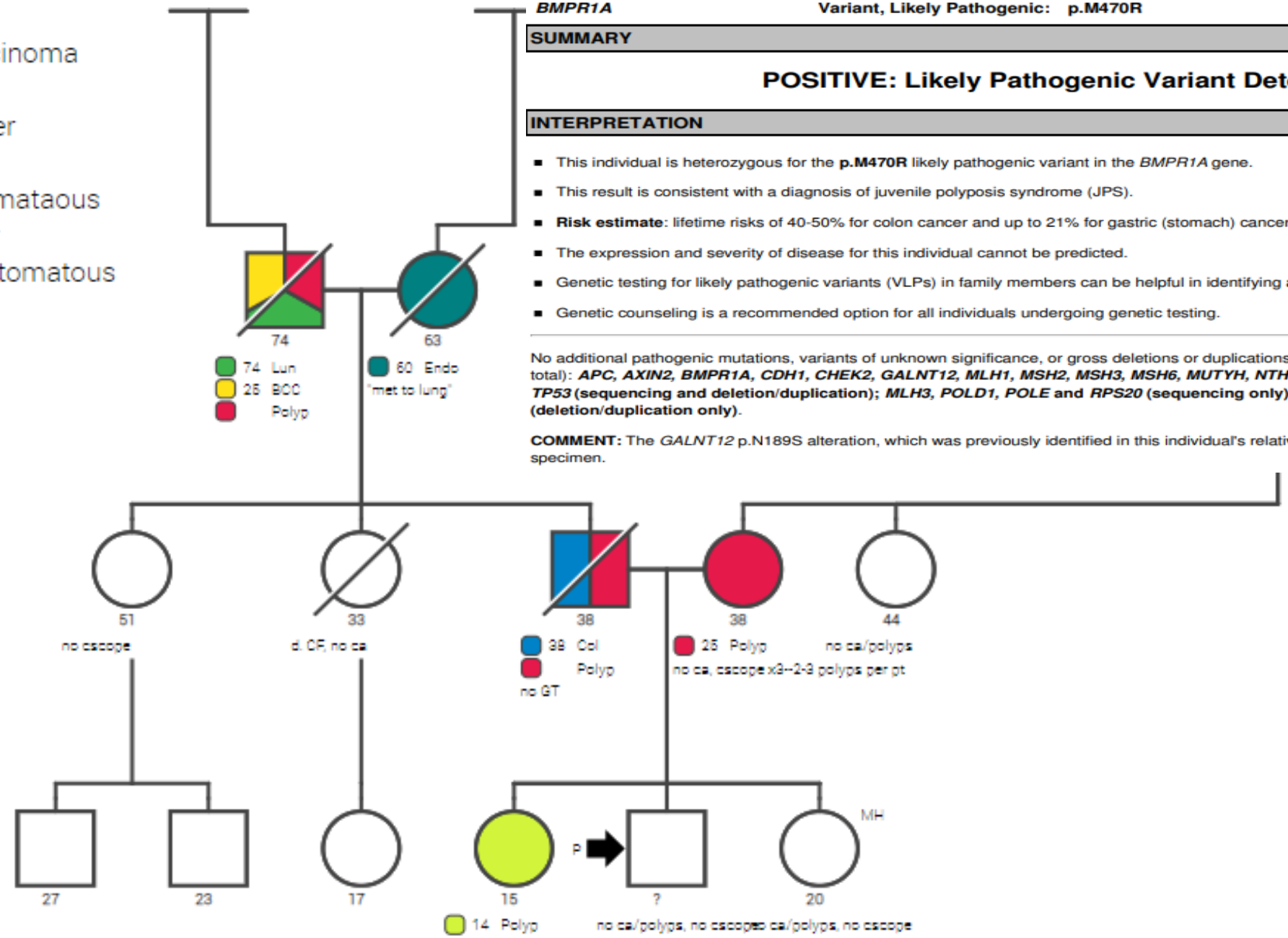
POSITIVE: Likely Pathogenic Variant Detected

INTERPRETATION

- This individual is heterozygous for the **p.M470R** likely pathogenic variant in the *BMPR1A* gene.
- This result is consistent with a diagnosis of juvenile polyposis syndrome (JPS).
- **Risk estimate**: lifetime risks of 40-50% for colon cancer and up to 21% for gastric (stomach) 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): ***APC, AXIN2, BMPR1A, CDH1, CHEK2, GALNT12, MLH1, MSH2, MSH3, MSH6, MUTYH, NTHL1, PMS2, PTEN, SMAD4, STK11*** **and** ***TP53*** **(sequencing and deletion/duplication);** ***MLH3, POLD1, POLE*** **and** ***RPS20*** **(sequencing only);** ***EPCAM*** **and** ***GREM1*** **(deletion/duplication only).**

COMMENT: The *GALNT12* p.N189S alteration, which was previously identified in this individual's relative(s), was not detected in this individual's specimen.



QUESTIONS?

MICHAEL GOSKY, MS, GC

MICHAEL.GOSKY@UKY.EDU

859-562-2455

JUSTINE PICKARSKI, MS, LGC

JUSTINE.COOPER@UKY.EDU

859-323-3083

Terra Lucas, MS, LGC

Terra.lucas@uky.edu

859-323-2825