Cancer Genetics: Common Hereditary Cancer Syndromes

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June 1, 2019

Learning Goals

- Understanding sporadic v. familial v. hereditary cancers
- Patterns of inheritance of hereditary cancer risk
- Characteristics of inherited cancer syndromes
- Goals of genetic counseling and testing for hereditary cancer
- Diagnosis and management of cancer syndromes
  - Hereditary Breast (Ovarian) Cancer
  - HNPCC – Lynch syndrome/ FAP- Familial Polyposis
  - Gene Panels
- Cancer Genomics – profiling tumors; personalized oncology

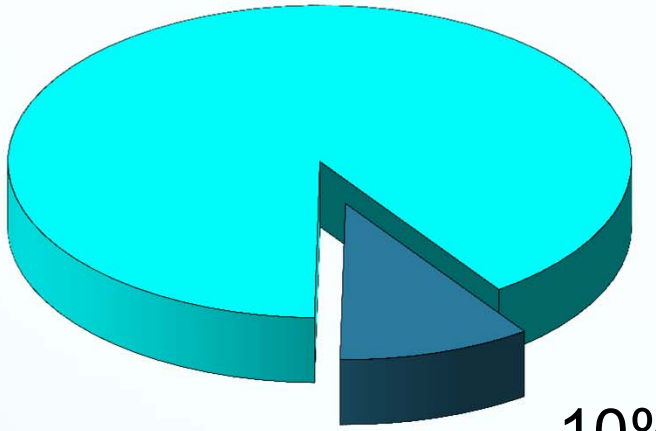
Precision Medicine in Cancer: Risk Assessment and Prevention

- **HEREDITARY CANCER GENETICS**
- Identification of germline and familial genetic alterations that increase **risk** of cancer
- Development of targeted **screening and early detection** techniques prevent development of advanced cancers
- Incorporation of moderate and low-penetrant, common genetic variants in risk prediction and modification
- Germline mutations may direct targeted treatments

Precision Medicine in Cancer: Tumor Profiling and Therapeutics

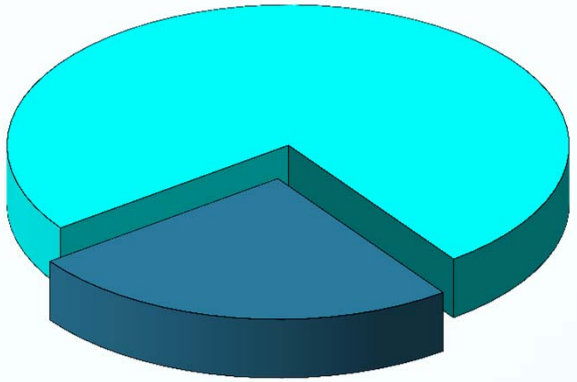
- **TUMOR CANCER GENOMICS**
- Identification of tumor **genetic** alterations that drive carcinogenesis
- Development of **drugs** that can effectively inhibit the function of these genetic alterations
- Molecularly **targeted** therapies to be used consistently and effectively in patients with cancer
- Assessment and prediction of drug **response** and **resistance** mechanisms
- **Germline** genetic testing and risk assessment based on tumor genomic profiles

Incidence of Hereditary Breast and Ovarian Cancer



10%

Breast Cancer



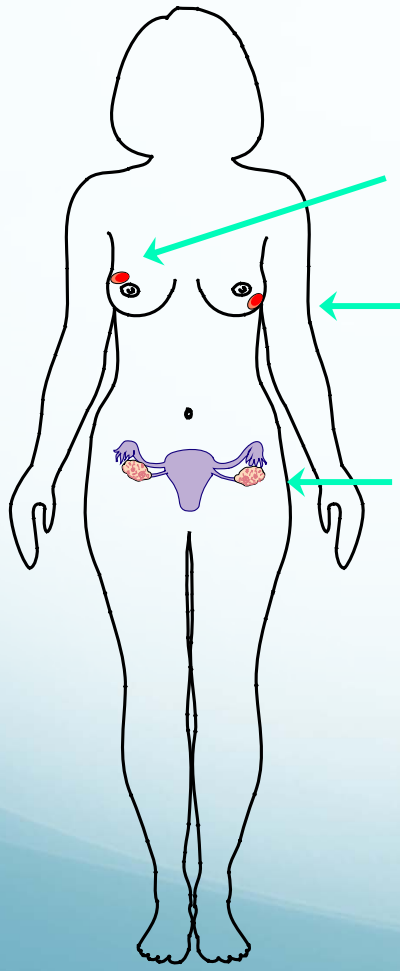
25%

Ovarian Cancer

Sporadic

Hereditary

BRCA1-Associated Cancers Lifetime Risks



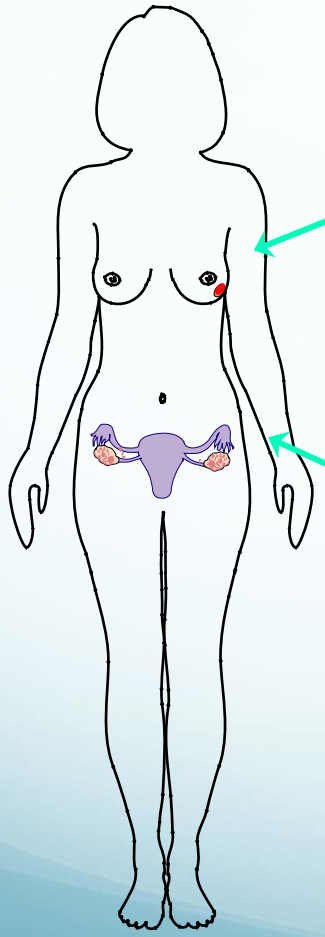
Breast cancer ~65% by age 70 (51- 75%)

Second primary breast cancer ~50-60%

Ovarian cancer: ~39% (22 – 51%)

Smaller increased risk of other cancers (i.e. prostate, pancreas)

BRCA2-Associated Cancers Lifetime Risks

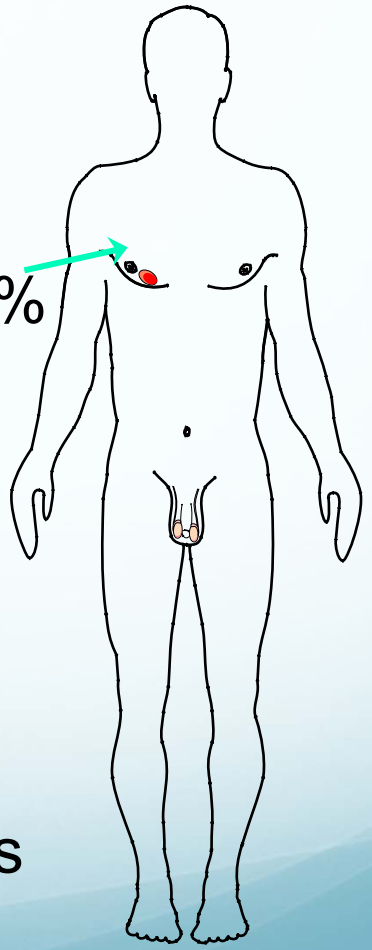


Breast cancer:
45%
40% 2nd –primary

Male breast cancer: 6%
Prostate cancer: 25%

Ovarian cancer
11-20%

Increased risk of prostate, laryngeal, bile duct, stomach, melanoma and pancreatic cancers (~1.5 – 3 fold risk)



Age-Specific Cancer Risks

BRCA1 Mutation Carriers:

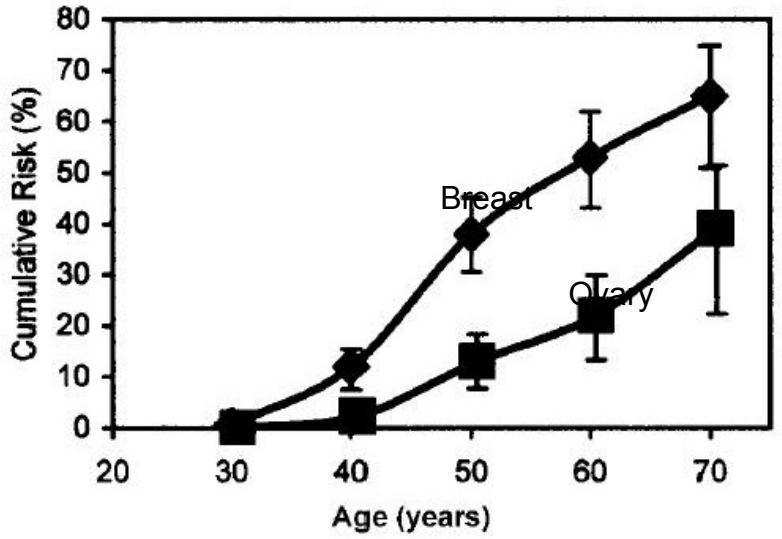


Figure 3 Cumulative risk of breast (♦) and ovarian (■) cancer in *BRCA1*-mutation carriers.

BRCA2 Mutation Carriers:

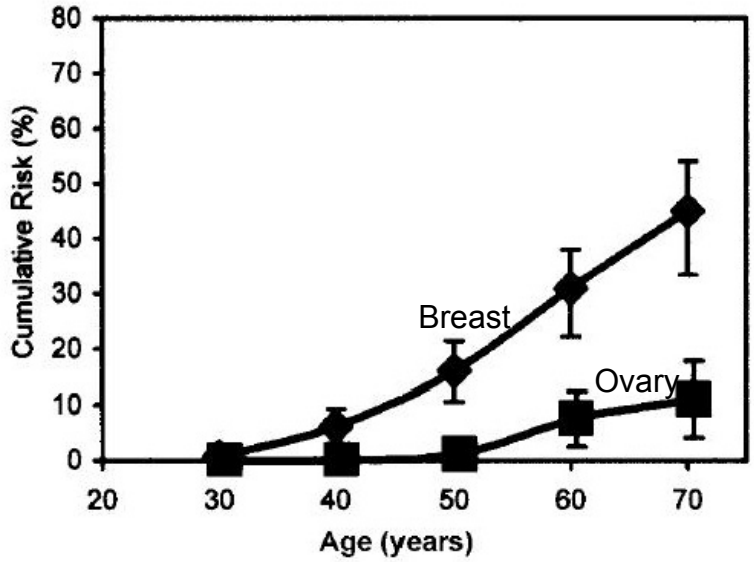


Figure 4 Cumulative risk of breast (♦) and ovarian (■) cancer in *BRCA2*-mutation carriers.

Antoniou Am J Hum Genet 2003

How common are hereditary BRCA mutations?

- 1/400 in the general population
  - (Early population studies suggesting 1/200)
- 1/40 in the Ashkenazi (Eastern European) Jewish population
- 5% of breast cancer diagnoses

How much does testing cost?

- $4000 BRCA1 and BRCA2 gene testing due to patent until Supreme Court overturned 6/2013
- 6/2013: Multigene NGS panels (now up to 100 genes)
- Now $900-$4000 insurance contracts
- **$250** (out of pocket at 2 labs)

Angelina Jolie: I had double mastectomy

May 15, 2013, 1:24 am
AFP

Next Generation Sequencing

U.S. Supreme Court Strikes Down Human Gene Patents
13 June 2013

2019 Breast CA Genetic Testing Guidelines

- National Comprehensive Cancer Network (NCCN)
  Expert consensus revised yearly; http://www.nccn.org
- Family member with known BRCA1/2 mutation
- Personal history of breast cancer, with:
  - Onset age ≤45 (7% prevalence)
  - Onset < 50 and one close relative with breast, ovarian
  - Two primary breast cancers; first <50
  - Onset any age, if ≥ 2 close relatives with breast /ovarian/ pancreatic/ prostate (Gleason >7)
  - Triple negative (ER/ PR/ Her2 neu negative) <60 (5-10%)
  - High-risk ethnicity, such as Ashkenazi (20-25% prevalence) with any above cancer history
- Personal history of ovarian cancer (10% prevalence)
- Male breast cancer (12-16% prevalence)
- Stage IV prostate or Gleason ≥ 7 (10-12% prevalence)
- Pancreatic cancer (10% prevalence)
- Close family member meeting above criteria (**if most informative unavailable**)

High Breast Cancer Risk Syndromes

- P53 (Li-Fraumeni Syndrome)
  - Mutation prevalence 1/5,000-20,000; 7-20% de novo
  - Sarcoma, brain, leukemia, colon, childhood cancers
  - 30-50% breast cancer, age [31]: prevalence 7% in breast cancers <35
- PTEN (Cowden's Syndrome)
  - Mutation prevalence 1/200,000; >75% de novo
  - Uterine cancers, thyroid dysfunction, mucosal lesions, OFC>98%
  - 40-50% lifetime breast cancer risk; 10% thyroid, increased uterine & colon
- STK11 (Peutz Jeghers Syndrome)
  - Mutation prevalence 1/60,000 - 300,000; 50% de novo
  - High risk for breast (50%), colon (40%), ovarian (20%) and other cancers
  - Lip freckles in childhood
- CDH1 (Hereditary Diffuse Gastric Cancer Syndrome)
  - Mutation prevalence 1/100,000-300,000? De novo?
  - 60-80% develop gastric cancer
  - 40-50% lifetime risk of lobular breast cancer

Mascari ASCO 2005; Eng J Med Genet 2000; Pharoah Gastroenterology 2001; www.geneclinics.org

Moderate Breast Cancer Risk Syndromes

- ATM
  - Mutation prevalence **1/100**
  - OR =**2-4** for breast cancer risk; OR =2 for colon cancer
  - Possible pancreatic risk
- CHEK2
  - Mutation prevalence up to **1/66** (Dutch); others **1/200-1/500**
  - Breast (OR=**2.6-4.8**), colon (OR=2) cancer risks
  - Possible prostate and thyroid cancer risk
- PALB2
  - Mutation prevalence **~1/1000**
  - OR =**3-5** for breast cancer risk
  - Suggestion of increased ovarian and pancreatic cancer risks

Mascari ASCO 2005; Eng J Med Genet 2000; Pharoah Gastroenterology 2001; www.geneclinics.org

Low Breast Cancer Risk Syndromes

- BRIP1, BARD1, RAD51C, RAD51D
  - Prevalence uncertain
  - OR= **2-3** for breast cancer
  - OR 3-6 for ovarian cancer with BRIP1, RAD51D
- RAD 50, MRE11A, NBN
  - Prevalence uncertain
  - **1.5-2.0** OR breast cancer risk
  - Possibly ovarian cancer risk
- NF1, Lynch, MUTYH
  - Traditionally not breast cancer genes; other defining symptoms
  - Prevalence much more common; 1/ 3000, 1/300, 1/50
  - Breast cancer risk varies (OR= **2** fold; **5** fold <50 for NF1)

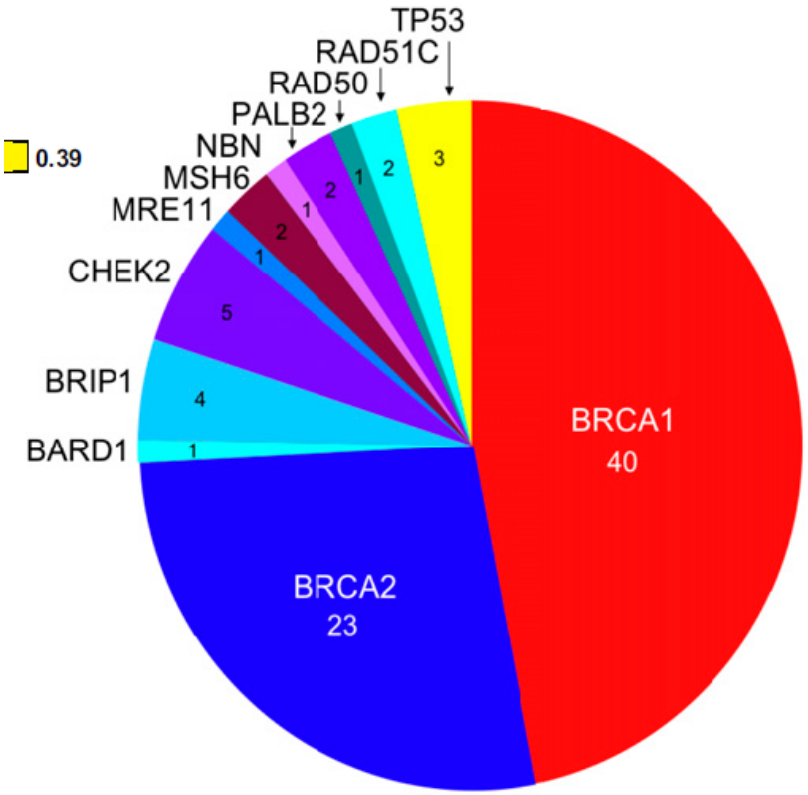
Mascari ASCO 2005; Eng J Med Genet 2000; Pharoah Gastroenterology 2001; www.geneclinics.org

Table 2. Clinical studies of next-generation sequencing panels, reporting prevalence of deleterious mutations and variants of uncertain s

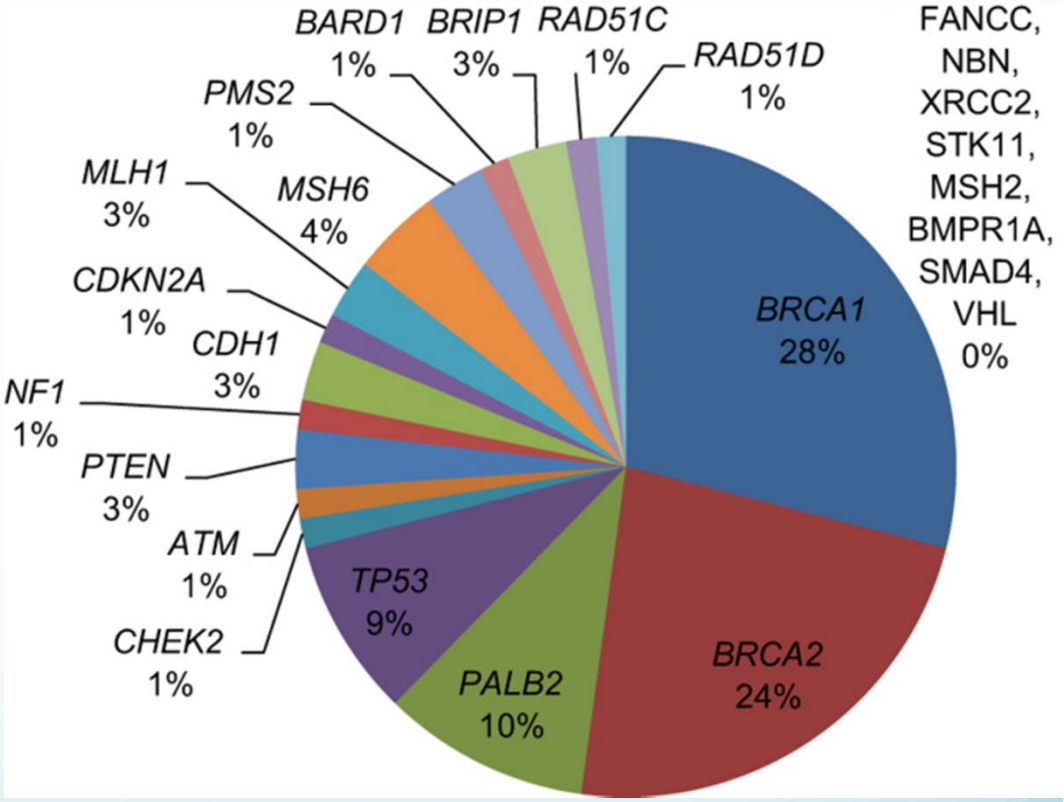
Study	N	Population	Race/Ethnicity	Testing Panel	Deleterious Mutations	Variants Uncertai Significan
Walsh et al, Proc Natl Acad Sci 2011	360	Ovarian cancers, unselected	Not reported	BROCA (University of Washington, WA; 21 genes)	6.1% (non-*BRCA1/2*)	Not reporte
Harrell et al, American Society of Human Genetics Annual Meeting, 2013	1412	Ovarian cancers, unselected (extension of above study)	Not reported	BROCA (University of WA; 41 genes)	5.5% (non-*BRCA1/2*)	Not reporte
Walsh et al, American Society of Human Genetics Annual Meeting, 2013	800	*BRCA1/2*-negative, personal or family history of ≥3 breast or ovarian cancers	Not reported	BROCA (University of WA; 41 genes)	15.8% (non-*BRCA1/2*)	Not reporte
Olopade et al, American Society of Human Genetics Annual Meeting, 2013	395	Cancer genetics clinic testing sample	100% African American	BROCA (University of WA; 41 genes)	4.1% (non-*BRCA1/2*)	Not reporte
Tung et al, Cancer 2014	2158	Testing laboratory database (Myriad Genetics, for *BRCA1/2*)	Mostly Non-Hispanic (NH) White	MyRisk (Myriad, 25 genes)	4.3% (non-*BRCA1/2*)	42%
Castera et al, Eur J Hum Genet 2014	708	Met practice guidelines criteria for Hereditary Breast / Ovarian Cancer Syndrome	Not reported	Custom designed (16 genes	5.6% (non-*BRCA1/2*)	Not reporte
Kurian et al, J Clin Oncol 2014	198	Met practice guidelines criteria for *BRCA1/2* testing (most *BRCA1/2*-negative)	70% NH White, 20% Asian American	Custom designed (42 genes)	11.4% (non-*BRCA1/2*)	88%
Ford et al, Montreal Hereditary Breast and Ovarian Cancer Symposium, 2014	380	Met practice guidelines criteria for *BRCA1/2* testing (extension of above study)	70% NH White, 20% Asian American	Hereditary Cancer Panel (Invitae, 29 genes)	9% (non-*BRCA1/2*)	35%
LaDuca et al, Genet Med 2014	2079	Testing laboratory database (Ambry)	72% NH White, 3% African American, 2% Hispanic	BreastNext, CancerNext, ColoNext, OvaNext (Ambry, 13-24 genes)	7-10% (non-*BRCA1/2*)	15-25%
Maxwell et al, American Society of Clinical Oncology Annual Meeting, 2014	278	Breast cancer at age <40, *BRCA1/2*-negative	69% NH White, 24% African American	Custom designed (22 genes)	11% (non-*BRCA1/2*)	19%
Langer et al, American Society of Clinical Oncology	648	Ovarian cancer patients in laboratory database	Not reported	MyRisk (Myriad, 25	6.2% (non-	40.6%

Panel Identified Hereditary Mutations

OVARIAN CANCER MUTATIONS



BREAST CANCER MUTATIONS



Ovarian: 10-18%; *BRCA1/2* 10-18%; 5-9% other genes
Breast: 5% BRCA1/2; 5% other genes

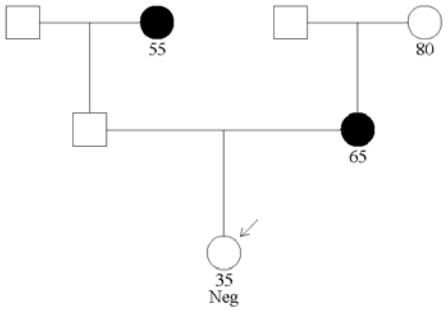
Walsh et al, PNAS 2011

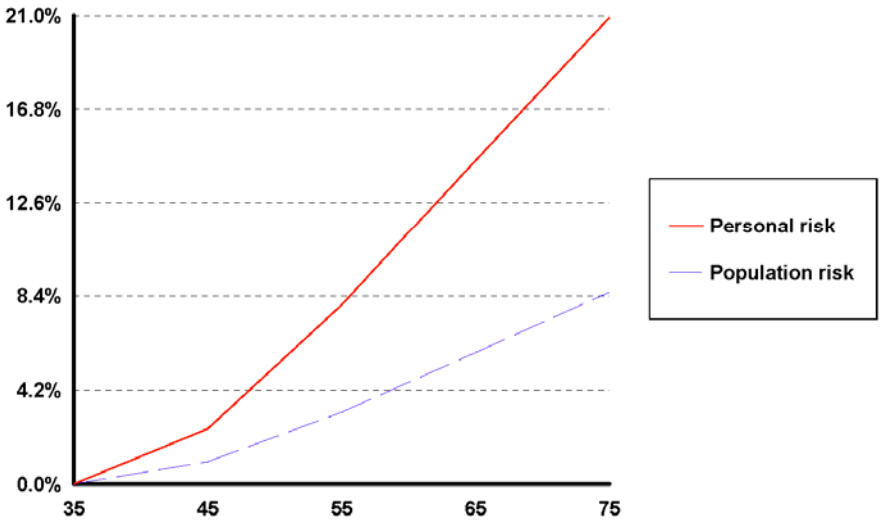
Wong et al, Genomic Med. 2016

IBIS: Tyrer-Cuzick Future Breast Risk

Woman's age is 35 years.
Age at menarche was 12 years.
Person is nulliparous.
Person is premenopausal.
Height is 1.6 m.
Weight is 70 kg.
Woman has never used HRT.

Risk after 10 years is 2.463%.
10 year population risk is 0.988%.
Lifetime risk is 24.4%.
Lifetime population risk is 10.06%.
Probability of a BRCA1 gene is 0%.
Probability of a BRCA2 gene is 0%.





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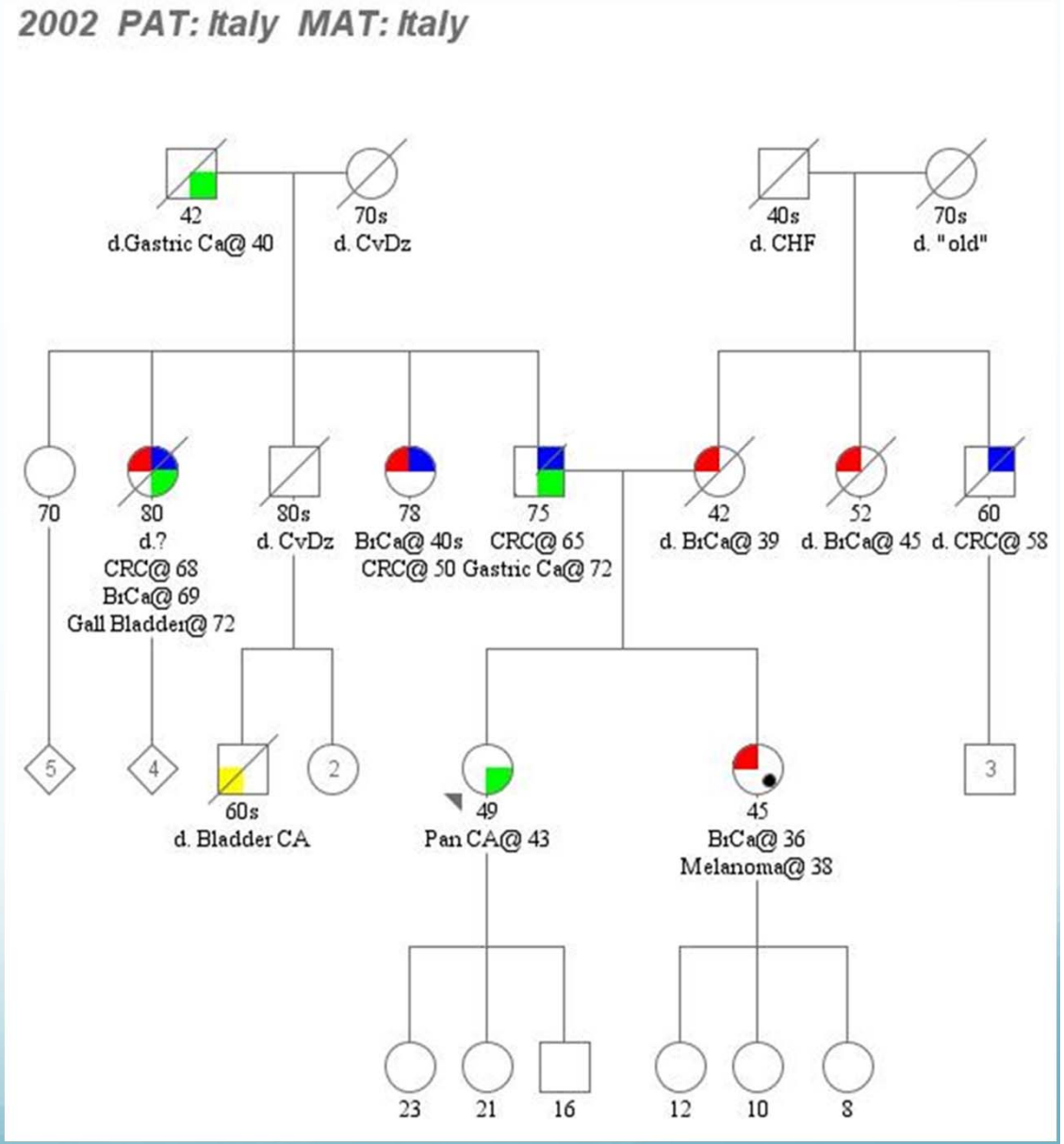
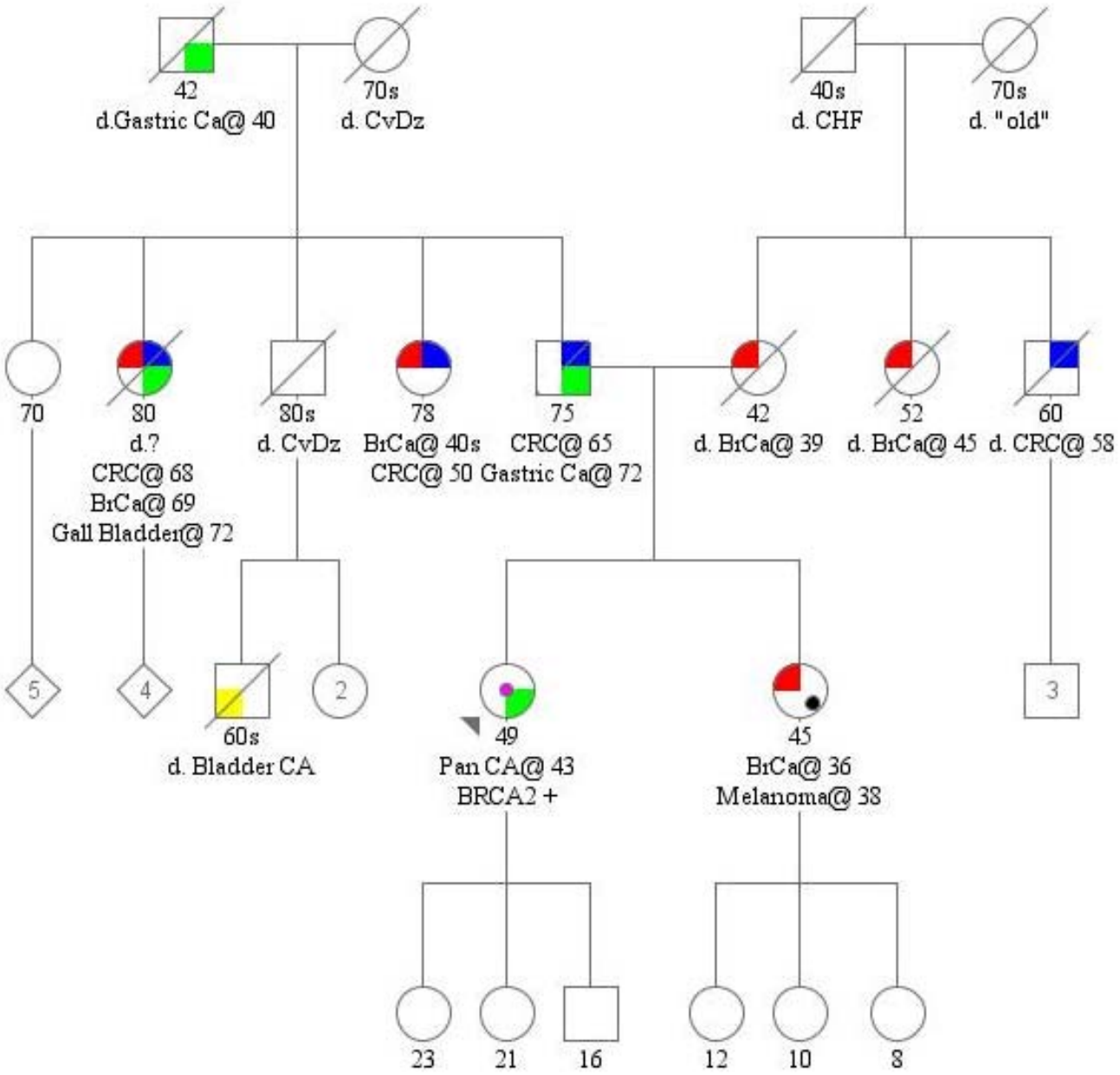
Case 1

- 49 yo female NED after pancreas cancer at 43
- Striking family hx; many cancers on both sides
- Relatives refused GT
- Which is parent of origin?
- What about the other parent?
- What do you test first?
- Remember GT <u>was</u> single gene and costly

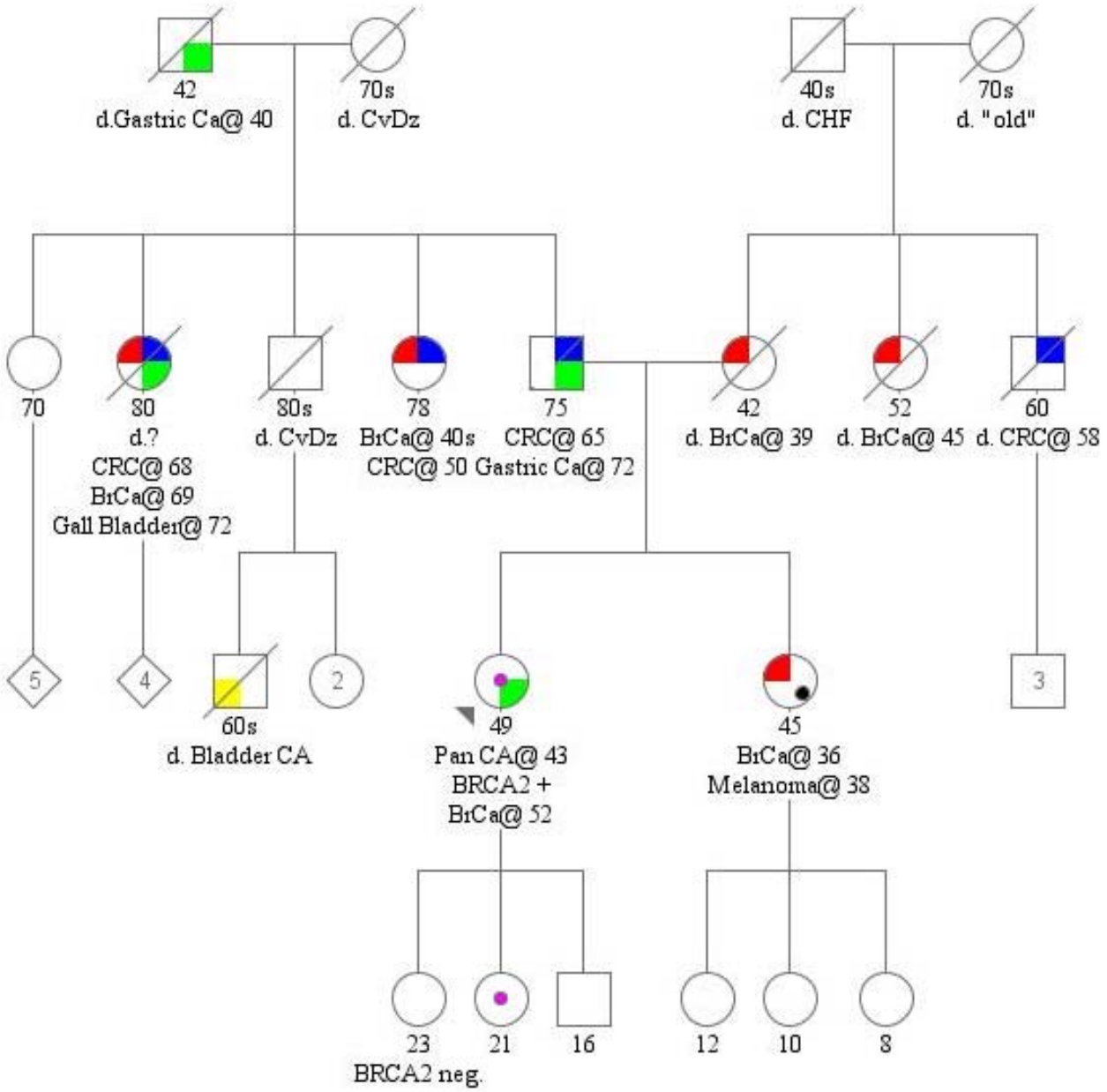


2002 PAT: Italy MAT: Italy

24-1



2002 PAT: Italy MAT: Italy

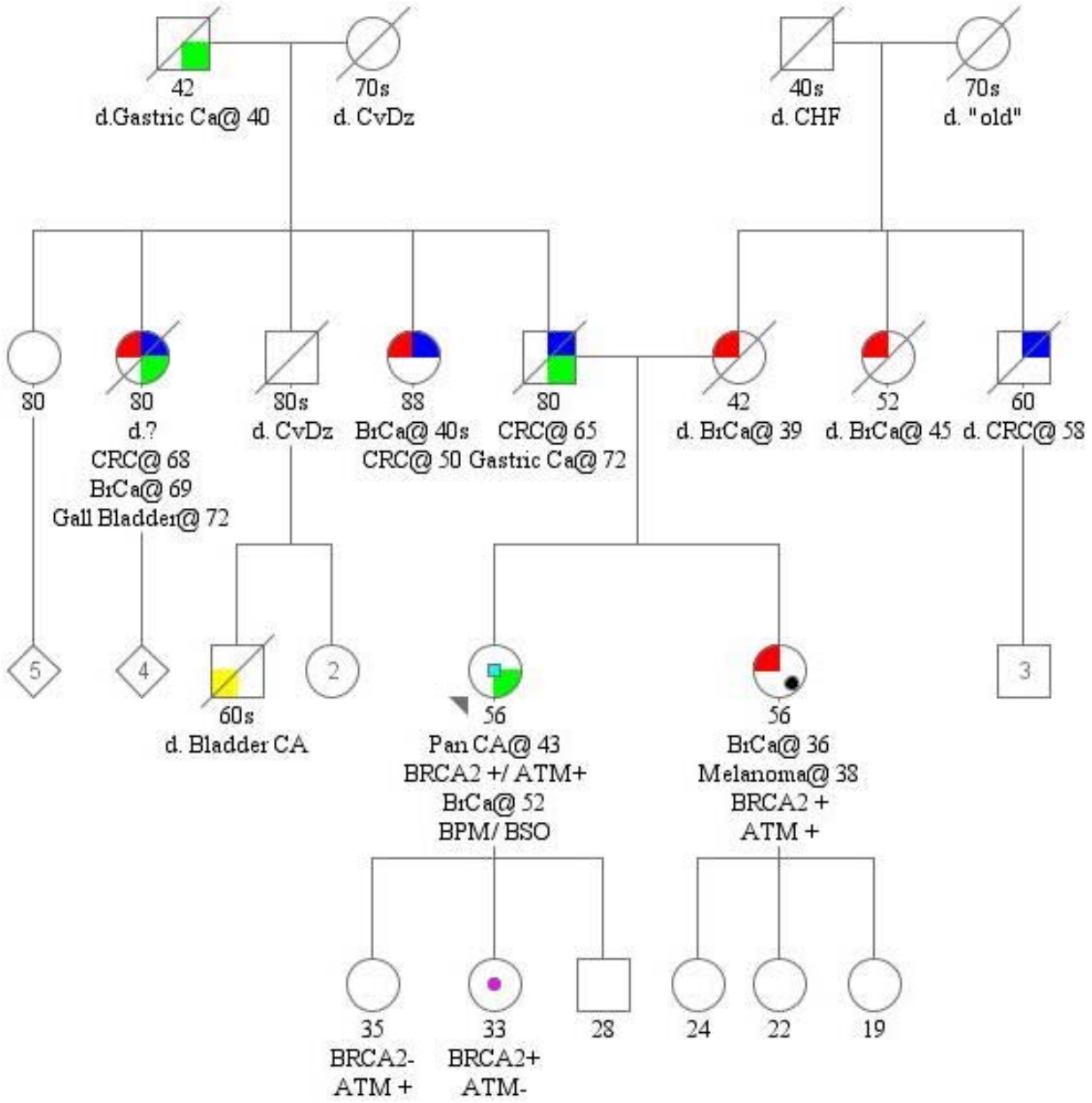


12 year later-late 2013

Niece turns 24; sister comes in for genetic testing

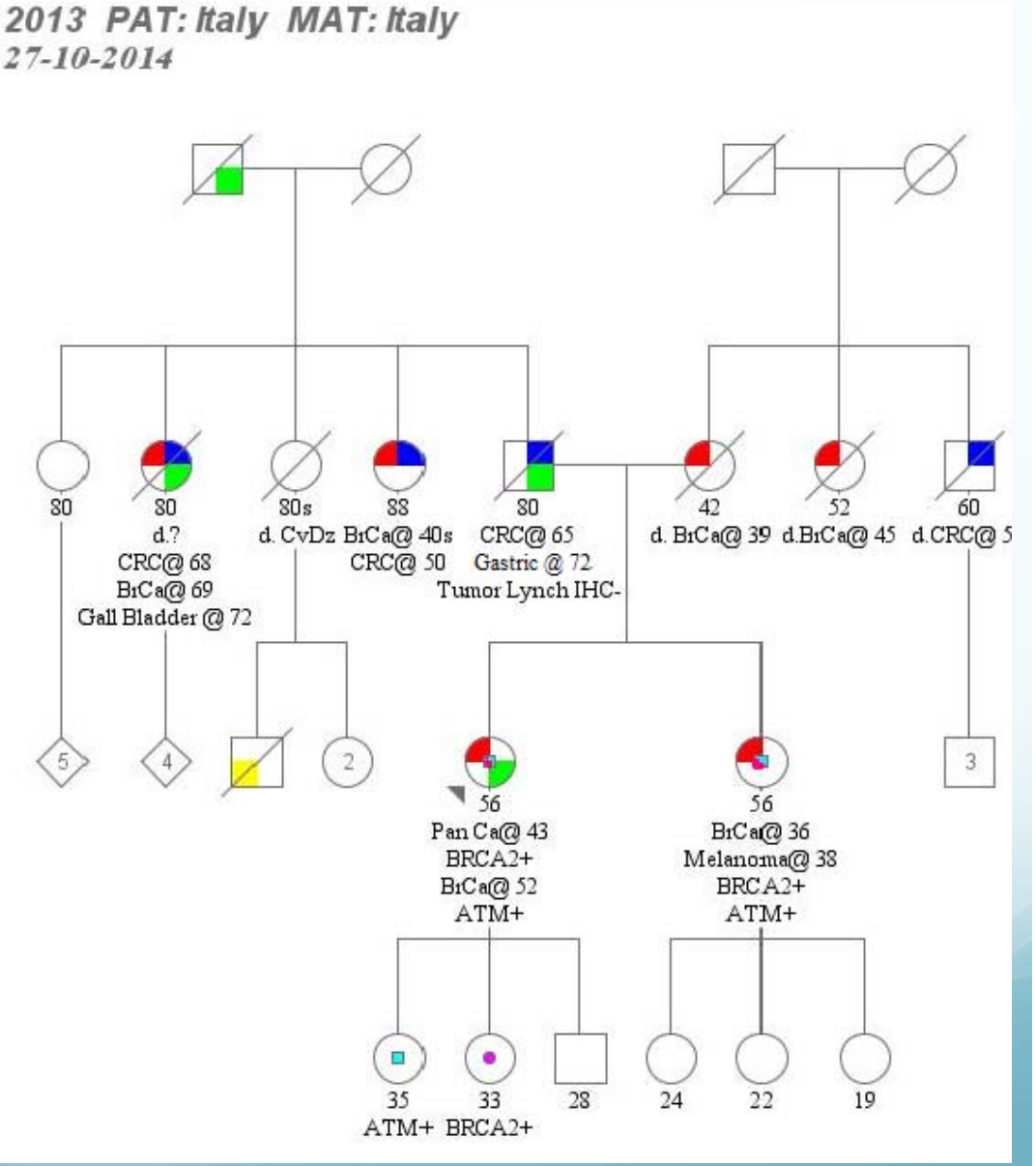
2002 PAT: Italy MAT: Italy

24-10-2014



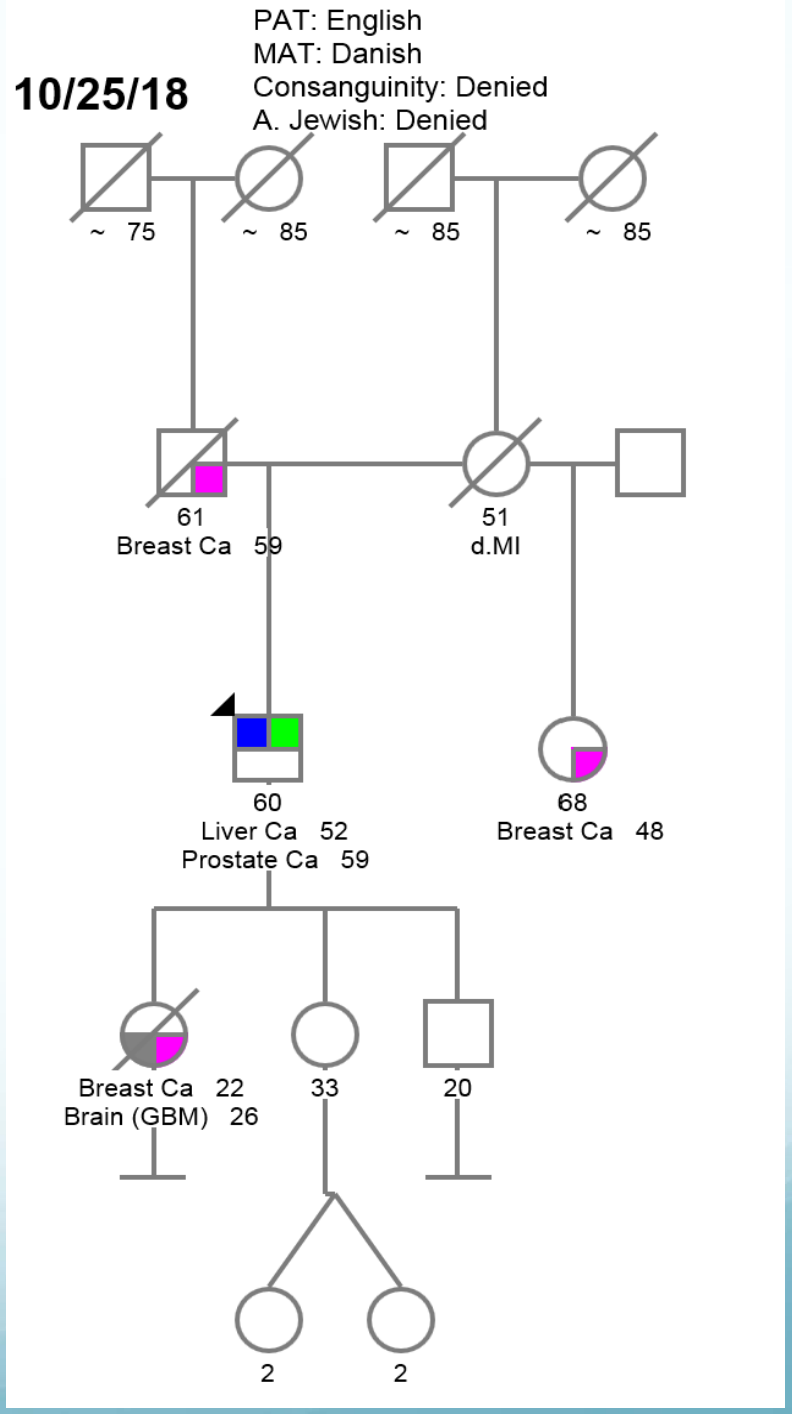
Case 1: Cascade Testing

- Patient returned and tested positive for the ATM
- Her daughter who had positive BRCA2 test did NOT have ATM
- Her daughter who had tested negative for BRCA2 was positive for ATM
- Paternal aunt finally had GT and was positive for ATM



Case 2

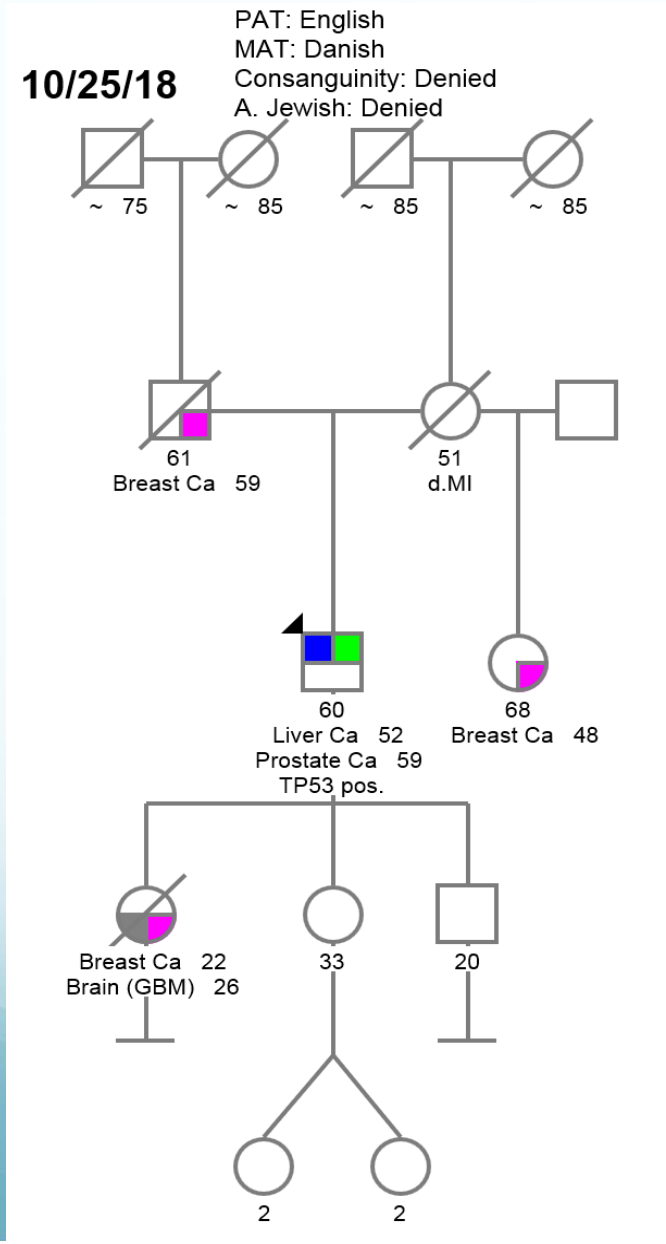
- 60 yo male referred to evaluate newly found colon oligopolyposis
- History of IVDA/ ETOH and liver cancer; s/p transplant
- History of aggressive prostate cancer at 59
- Family history of breast cancer in 3 close relatives including **Dad**,1/2 sister and Daughter at **age 22**
- Daughter then died of Glio at 26

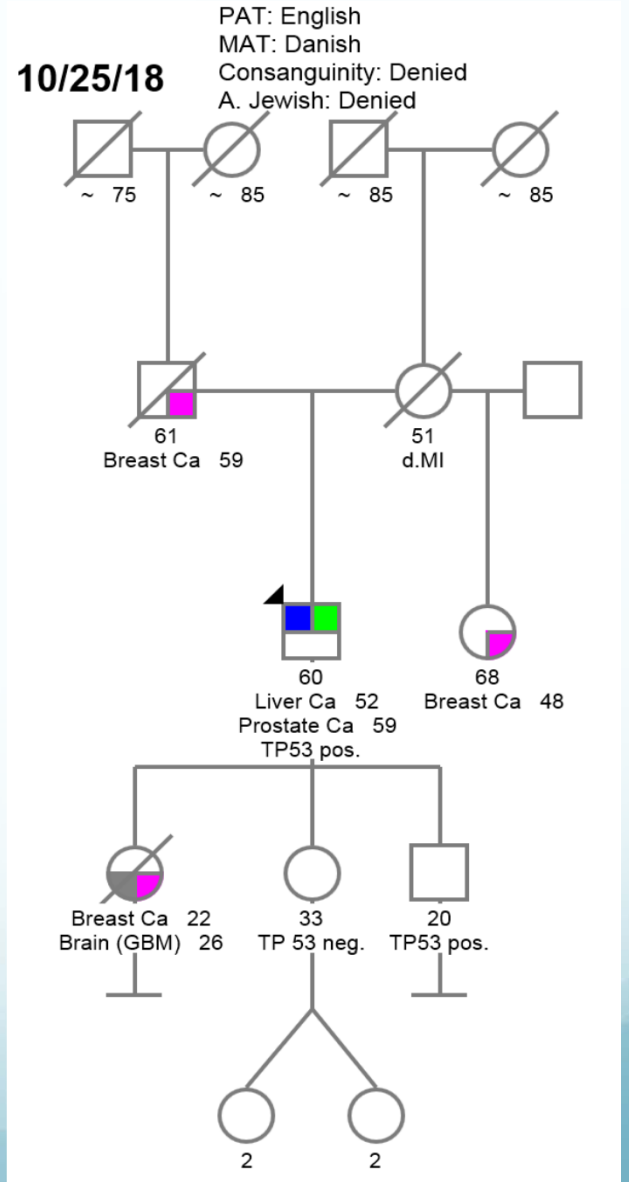


Differential Diagnosis

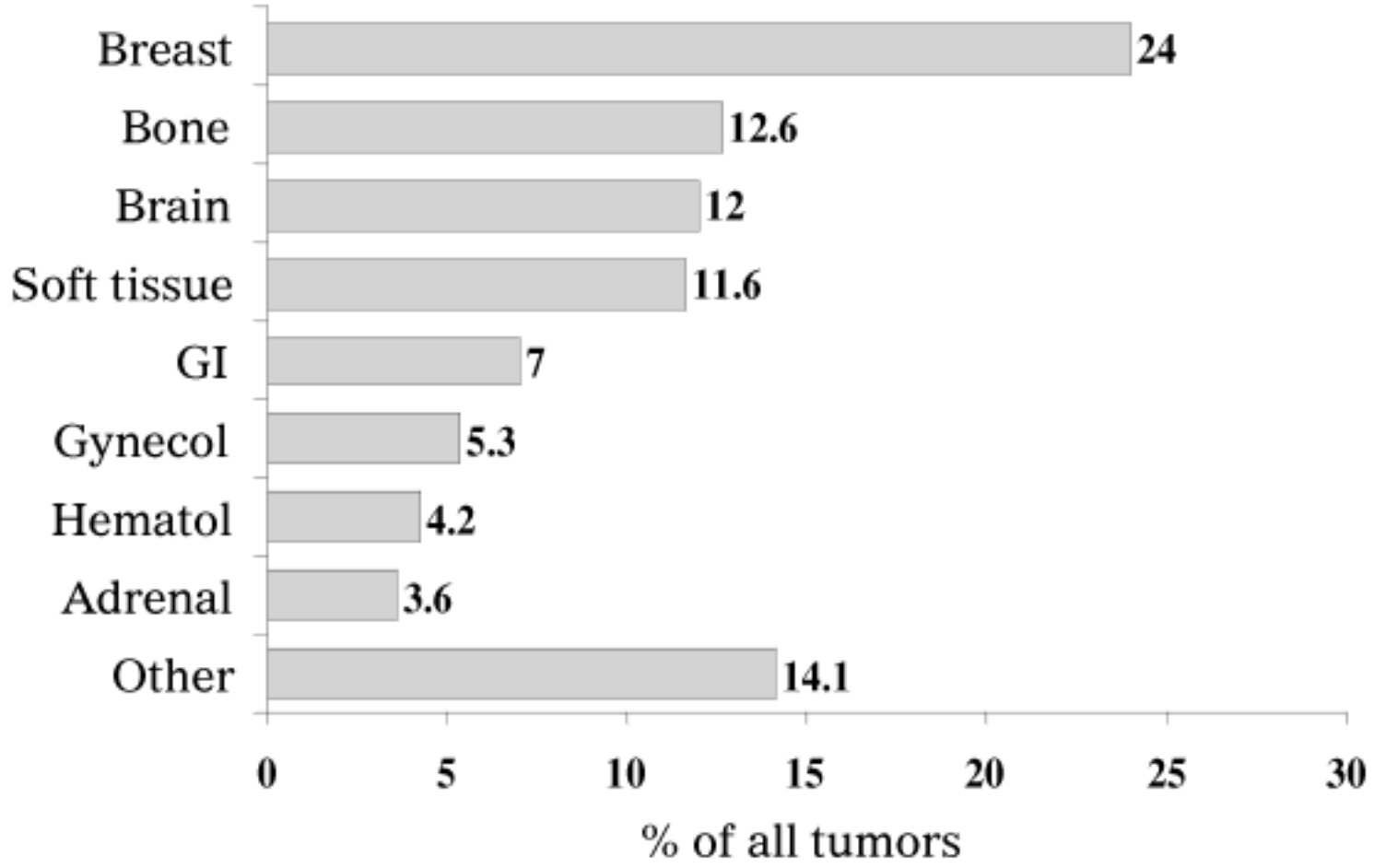
- BRCA1/2 and other breast cancer syndromes
- Polyposis cancer syndromes
- Li Fraumeni/ multiple cancer syndrome
- Other undefined cancer syndrome

Case 2: Results





Tumor Sites in Families with *TP53* Germline Mutations



Hisada M et al. *J Natl Cancer Inst*. 1998;90:606-611.

Kleihues P et al. *Amer J Pathol*. 1997;50:1-13.

TP53 Carrier Cancer Age Penetrance

Age	Male	Female	All	Population
20	10%	18%	12%	0.7%
30	21%	49%	35%	1.0%
40	33%	77%	52%	2.2%
50	68%	93%	80%	5.1%

Wu CC, Shete S, Amos CI, *et al. Joint effects of* germ-line p53 mutation and sex on cancer risk in Li-Fraumeni syndrome. Cancer Res. 2006; 66:8287-92.

Hwang SJ, Lozano G, Amos CI, *et al. Germline* p53 mutations in a cohort with childhood sarcoma: sex differences in cancer risk. Am J Hum Genet. 2003;72:975-83.

2019 NCCN Guidelines

Li Fraumeni Testing Criteria

- Individual from a family with known P53 mutation
- Classic Li-Fraumei Syndrome (LFS) (70%+):
  - Proband with sarcoma <45 AND
  - First-degree relative with cancer <45 AND
  - 1st or 2nd relatives with cancer <45 or sarcoma at any age; same side of family
- Chompret criteria (25-35%+):
  - Proband with LFS tumor <46 (sarcoma, brain, breast, ACC, leukemia, lung) AND 1st or 2nd degree relative with LFS tumor <56

    OR multiple primary tumor at any age
  - OR proband with multiple tumors; 1st <46 AND 2 in LFS spectrum
  - OR Adrenal Cortical Carcinoma or Choroid Plexus Carcinoma, rhabdosarcoma or embryonal anaplastic at any age
- Proband with breast cancer <35 AND BRCA ½ negative (7%+)

Managing Hereditary Risk

High Risk Breast/ Ovarian CA Carriers

- **Female Breast Risk**
  - Monthly SBE starting at 18
  - CBE q 6-12 months start at 20-25 (or 5 yr < 1st dx)
  - Annual breast MRI starting at 25 (tailor to fm)
  - Annual MRI and mammogram starting at 30-75
  - Discuss prophylactic bilateral mastectomies
- **Ovarian Risk**
  - Risk reducing salpingo-oophrectomy (RRSO)
    - 35-40 in BRCA1 carriers
    - 40-45 in BRCA2 carriers
- **Males**
  - Monthly self breast exams and annual CBE start at 35
  - Prostate screening starting at 40

NCCN LFS Screening Guidelines

- Breast Risk
  - Monthly SBE starting at 18
  - CBE q 6-12 months start at 20-25 (or 5 yr < 1st dx)
  - Annual breast MRI starting at 20-29 (tailor to fm)
  - Annual MRI and mammogram starting at 30-75
  - Discuss prophylactic bilateral mastectomies

NCCN LFS Screening Guidelines

- Other Cancer Risks
  - Discuss limits of screening options
  - Annual physical exam with skin and neuro exam
  - Use XRT for treatment with caution
  - Colonoscopy q 2-5 years starting at 25
  - Investigate options for novel technologies
    - Whole body MRI, ultrasounds, brain MRI
  - Target screenings based on family history
  - Educate patient on early symptoms

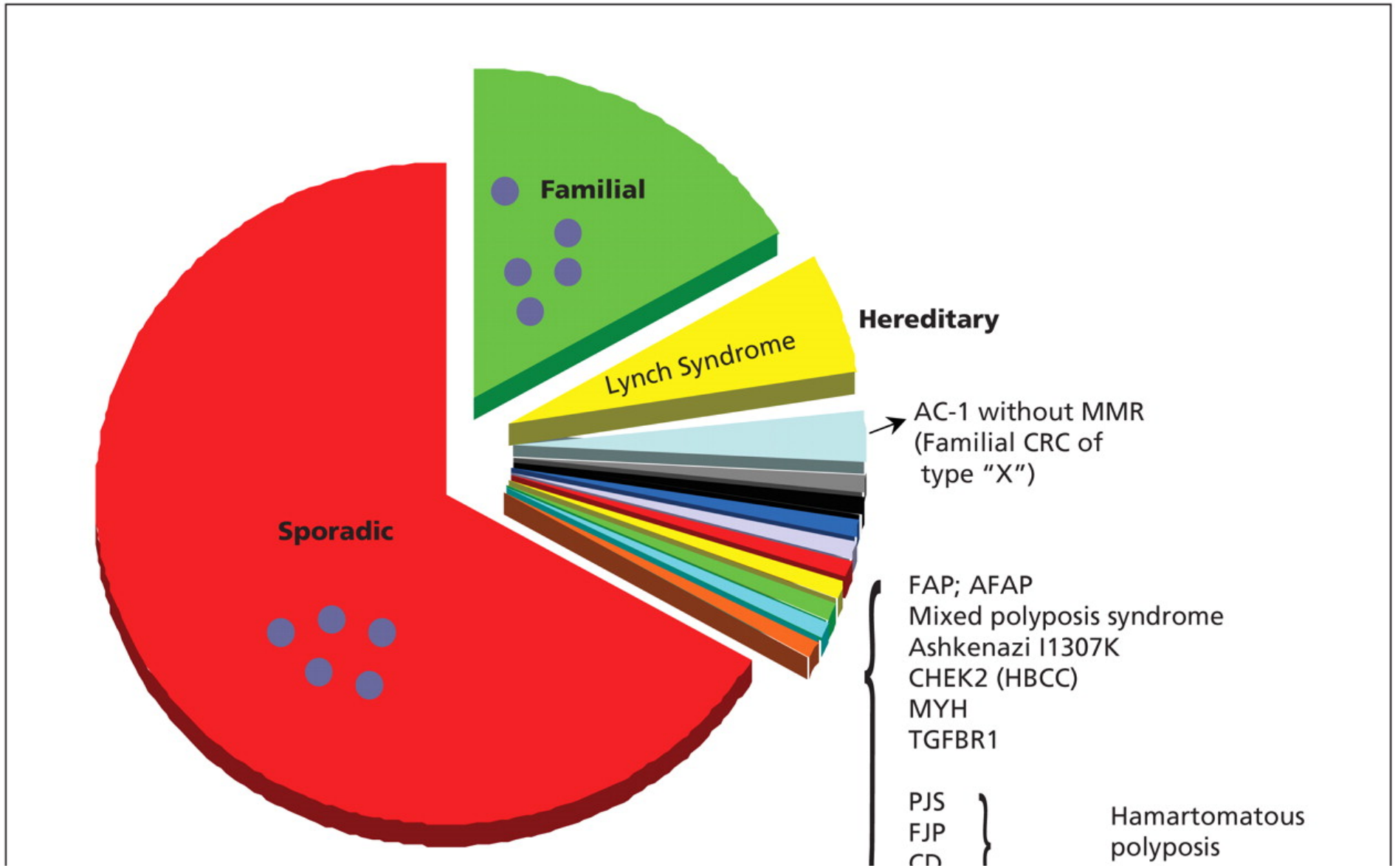
Psychological Issues

- Proband proceeded with total colectomy despite our recommendations against it
- Recent contact with his wife; she reports he never recovered from surgery and died within 2 years
- Son has been episodically MIA; has completed 1 cycles of screening in 3 years
- Son did attend LFS meeting in 2010/ connected with peer support at that time

Psychological Interventions

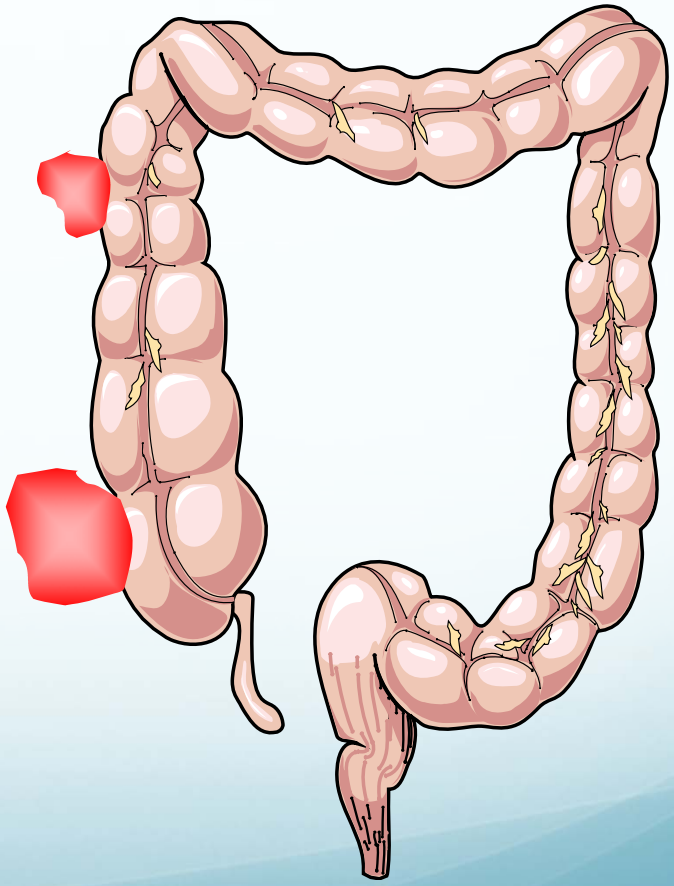
- Specialized mental health professionals
- On-line support groups
- Genetic counselor network/ assistance with family communication and referrals
- Peer referrals
- LFS Consortium/ Family Network

Causes of Hereditary Susceptibility to Colorectal Cancer

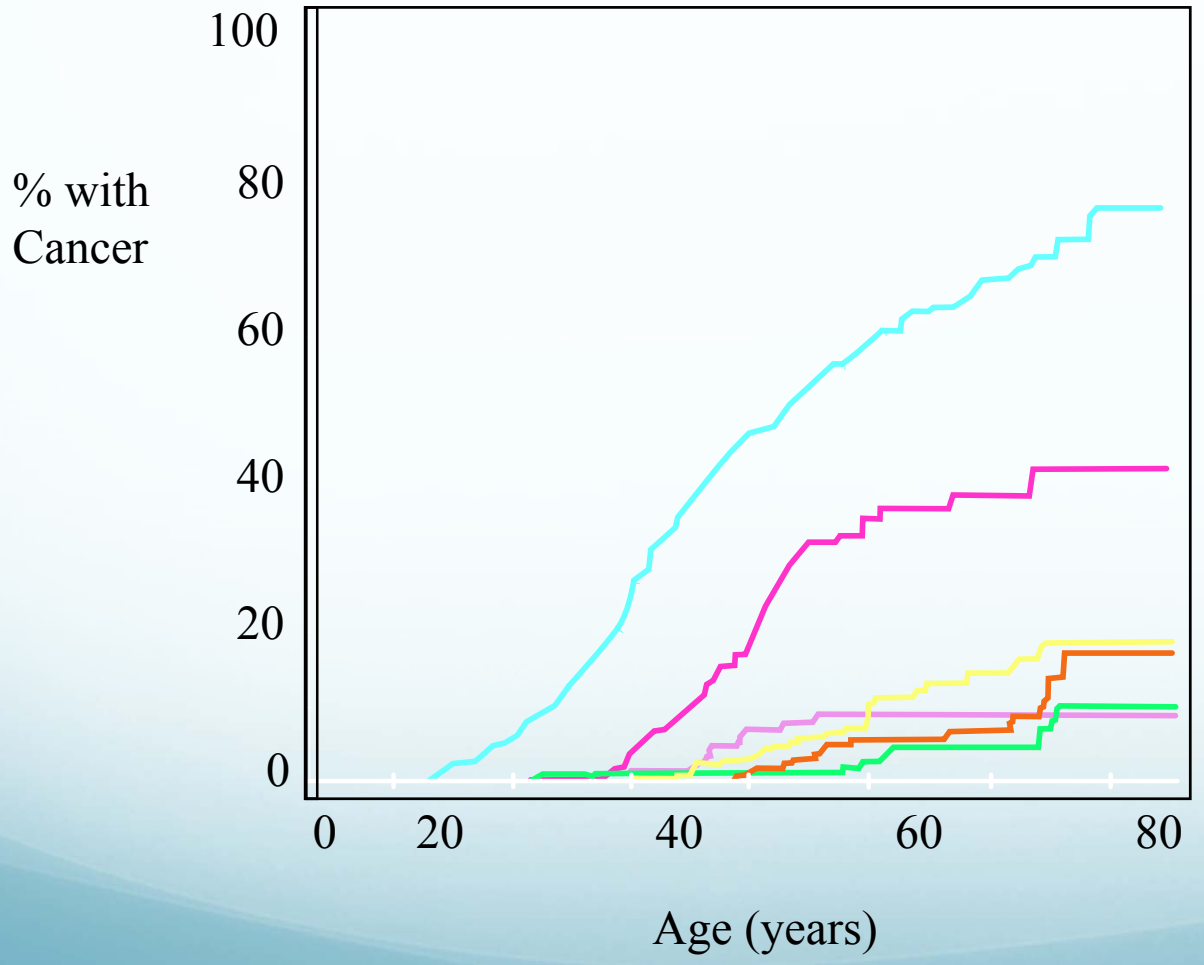


Clinical Features of HNPCC (Lynch Syndrome)

- Early but variable age at CRC diagnosis (~45 years)
- Tumor site in proximal colon predominates (2/3rds)
- Extracolonic cancers: endometrium, ovary, stomach, urinary tract, small bowel, bile ducts, sebaceous skin tumors
- Autosomal pattern of inheritance
- 1/400 (recent population studies suggest 1/250)



Cancer Risks in Lynch Syndrome



Colorectal 78%

Endometrial 43%

Stomach 10%
Urinary tract 10%
Biliary tract 15%
Ovarian 9%

Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population

Cancer	General Population Risk[1]	*MLH1* or *MSH2*[1,2,3]		*MSH6*[4,5,6]		*PMS2*[7,8]	
		Risk	Mean Age of Onset	Risk	Mean Age of Onset	Risk	Mean Age of Onset
Colon	4.5%	52%–82%	44–61 years	10%–22%	54 years	15%–20%	61–66 years
Endometrium	2.7%	25%–60%	48–62 years	16%–26%	55 years	15%	49 years
Prostate[9]	11.6%	~30%	59–69 years	~30%	59–69 years	Not reported	Not reported
Ovary	1.3%	MLH1 - 11%–20% by age 70 y[2,12] MSH2 - 15%–24% by age 70 y[2,12] See additional age-specific risks on LS-B 2 of 2	45y - MLH1[12] 43 y - MSH2[12]	*MSH6*: There are limited data on ovarian cancer risk, with some studies suggesting average risk,[2,12] and some suggesting increased risk[5,6] *PMS2*: There are limited data on ovarian cancer risk[5,8] See additional age-specific risks on LS-B 2 of 2			
Stomach	<1%	6%–13%	56 years	≤3%	63 years	†	70–78 years
Hepatobiliary tract	<1%	1%–4%	50–57 years	Not reported	Not reported	†	Not reported
Urinary tract	<1%	1%–7%[10]	54–60 years	<1%	65 years	†	Not reported
Small bowel	<1%	3%–6%	47–49 years	Not reported	54 years	†	59 years
Brain/CNS	<1%	1%–3%	~50 years	Not reported	Not reported	†	45 years
Sebaceous neoplams	<1%	1%–9%	Not reported	Not reported	Not reported	Not reported	Not reported
Pancreas[11]	<1%	1%–6%	Not reported	Not reported	Not reported	Not reported	Not reported

†The combined risk for renal pelvic, stomach, ovary, small bowel, ureter, and brain is 6% to age 70 (Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 2008;135:419-428).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued
Footnotes

Universal Tumor Screening

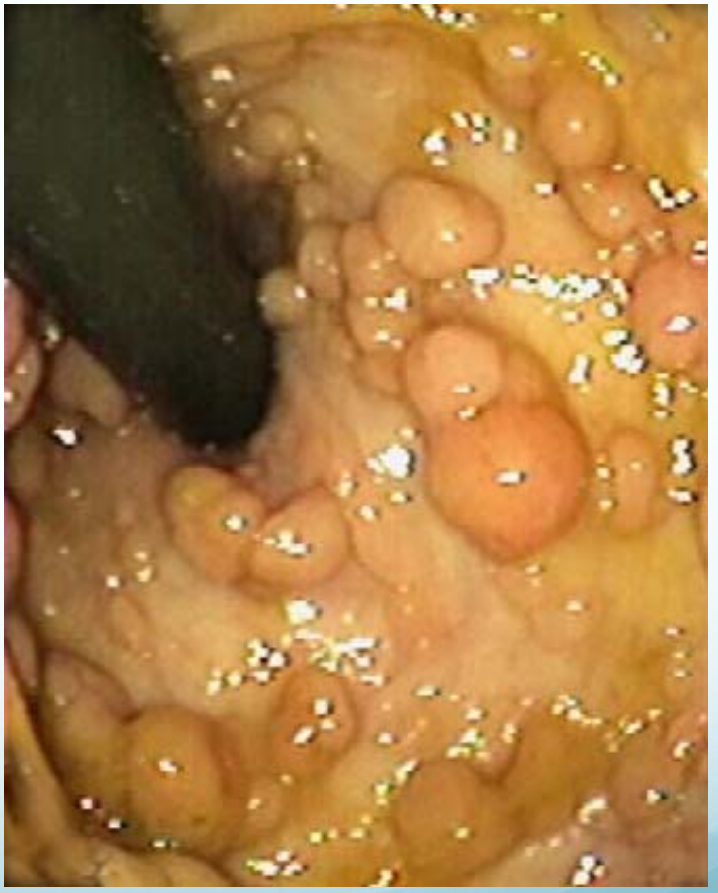
- All colon, uterine, ovarian tumors screened for Lynch protein loss
  - Occurs in 15% of colon tumors
  - If loss of MSH2, MSH6 or PMS2- germline test
  - If loss of MLH1, check for methylation or BRAF mutation first
  - Refer positive screen cases for tumor/ germline testing
  - Half of Lynch IHC loss is due to double somatic tumor/ not hereditary mutations so parallel testing is needed

  - Recently started Lynch IHC screening for all solid tumors
    - Based on PD1 blockade therapy

- This is likely to be replaced by direct germline testing as the costs continue to drop and tumor screening becomes more common

Clinical Features of FAP

- Estimated penetrance for adenomas >90%
- Risk of extracolonic tumors (upper GI, **desmoid**, osteoma, thyroid, brain, other)
- CHRPE may be present
- Untreated polyposis leads to 100% risk of cancer



Genetics of FAP

- Autosomal dominant inheritance; 1/10,000
- Caused by mutations in *APC* tumor suppressor gene on chromosome 5q
- Up to **30%** of patients have *de novo* germline mutations
- Attenuated FAP associated with terminal mutations
- 1-2% risk of childhood hepatoblastoma (10%cases); slight increased thyroid risk

Indications for *APC/ MUTYH* Gene Testing

- polyposis (>100 adenomas)
- attenuated FAP (**10** or **20**-99 adenomas)
- Bilateral CHRPE
- Childhood hepatoblastoma
- Childhood desmoids

Giardiello FM et al. *N Engl J Med*, 336:823, 1997

MAP syndrome/MUTYH gene

- **Multiple adenomatous polyposis (MAP) syndrome**
  - Autosomal recessive; mutations in the MYH gene
  - Median number of polyps = 55
  - Mean age of polyp diagnosis = 30-50 years
  - Polyps mainly small, mildly dysplastic tubular adenomas. Some tubulovillous, hyperplastic, serrated adenomas, microadenomas
- 30% of individuals with 15-100 polyps have homozygous mutations in the MYH gene
- Genetic testing should be offered if >10-20 polyps (and APC gene testing negative)
- High single mutation carrier rate= 1/50

Additional Colon Cancer Gene

Polyposis	Non-Polyposis
POLE	CHEK2
POLD1	ATM
GREM1	NBN
STK11	TP53
BMPR1A	CDH1
SMAD4	PTEN
NTHL1	

FOUNDATIONONE

Reverse Engineering Genetics

Tumors are now being sequenced for many cancer related mutations hoping to detect actionable driver mutations (targets)

Perhaps 10% of driver mutations may be germline. We are beginning to test for tumor identified mutations that could be heritable.

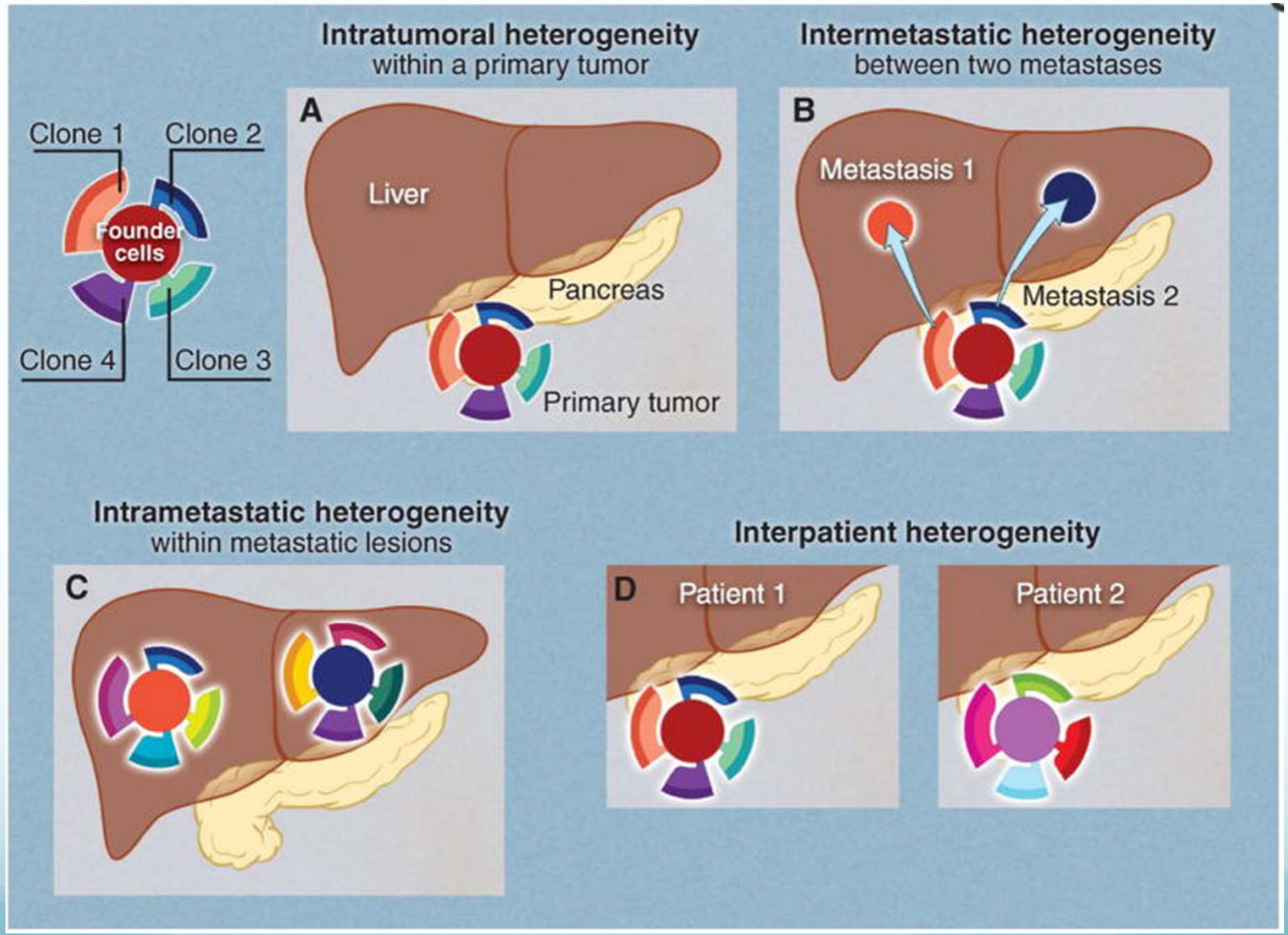
Current Gene List[4]

FoundationOne identifies all classes of alterations in each of the genes listed below.

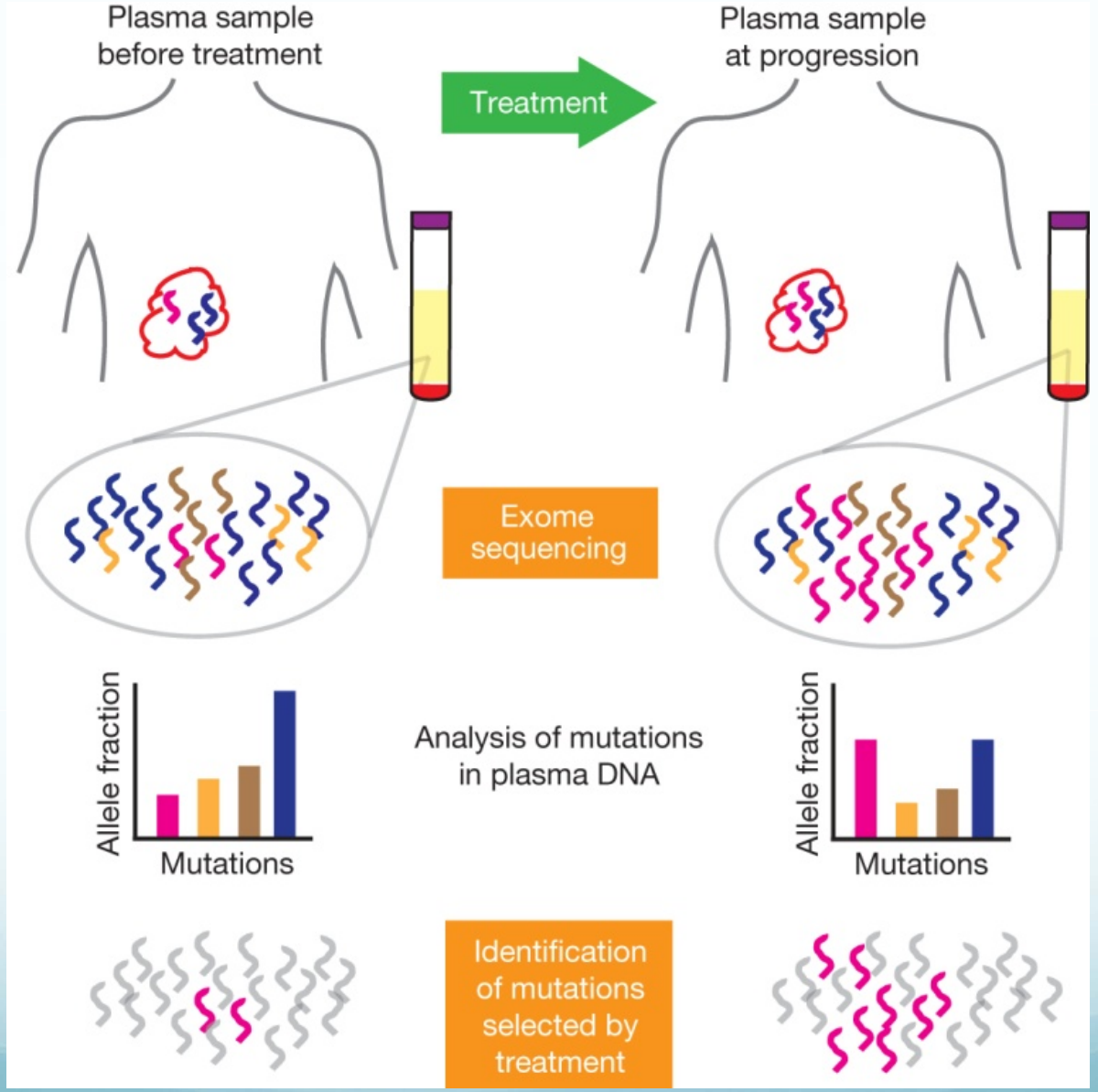
As a pan-cancer test, FoundationOne is designed to interrogate the entire coding sequence of 315 cancer-related genes plus introns from 28 genes often rearranged or altered in cancer. These genes are known to be somatically altered in solid cancers based on recent scientific and clinical literature.

CURRENT GENE LIST									
ABL1	BRAF	CHEK1	FANCC	GATA3	JAK2	MITF	PDCD1LG2	RBM10	STAT4
ABL2	BRCA1	CHEK2	FANCD2	GATA4	JAK3	MLH1	PDGFRA	RET	STK11
ACVR1B	BRCA2	CIC	FANCE	GATA6	JUN	MPL	PDGFRB	RICTOR	SUFU
AKT1	BRD4	CREBBP	FANCF	GID4 (C17orf39)	KAT6A (MYST3)	MRE11A	PDK1	RNF43	SYK
AKT2	BRIP1	CRKL	FANCG	GLI1	KDM5A	MSH2	PIK3C2B	ROS1	TAF1
AKT3	BTG1	CRLF2	FANCL	GNA11	KDM5C	MSH6	PIK3CA	RPTOR	TBX3
ALK	BTK	CSF1R	FAS	GNA13	KDM6A	MTOR	PIK3CB	RUNX1	TERC
AMER1 (FAM123B)	C11orf30 (EMSY)	CTCF	FAT1	GNAQ	KDR	MUTYH	PIK3CG	RUNX1T1	TERT (promoter only)
APC	CARD11	CTNNA1	FBXW7	GNAS	KEAP1	MYC	PIK3R1	SDHA	TET2
AR	CBFB	CTNNB1	FGF10	GPR124	KEL	MYCL (MYCL1)	PIK3R2	SDHB	TGFBR2
ARAF	CBL	CUL3	FGF14	GRIN2A	KIT	MYCN	PLCG2	SDHC	TNFAIP3
ARFRP1	CCND1	CYLD	FGF19	GRM3	KLHL6	MYD88	PMS2	SDHD	TNFRSF14
ARID1A	CCND2	DAXX	FGF23	GSK3B	KMT2A (MLL)	NF1	POLD1	SETD2	TOP1
ARID1B	CCND3	DDR2	FGF3	H3F3A	KMT2C (MLL3)	NF2	POLE	SF3B1	TOP2A
ARID2	CCNE1	DICER1	FGF4	HGF	KMT2D (MLL2)	NFE2L2	PPP2R1A	SLIT2	TP53
ASXL1	CD274	DNMT3A	FGF6	HNF1A	KRAS	NFKBIA	PRDM1	SMAD2	TSC1
ATM	CD79A	DOT1L	FGFR1	HRAS	LMO1	NKX2-1	PREX2	SMAD3	TSC2
ATR	CD79B	EGFR	FGFR2	HSD3B1	LRP1B	NOTCH1	PRKAR1A	SMAD4	TSHR
ATRX	CDC73	EP300	FGFR3	HSP90AA1	LYN	NOTCH2	PRKCI	SMARCA4	U2AF1
AURKA	CDH1	EPHA3	FGFR4	IDH1	LZTR1	NOTCH3	PRKDC	SMARCB1	VEGFA
AURKB	CDK12	EPHA5	FH	IDH2	MAGI2	NPM1	PRSS8	SMO	VHL
AXIN1	CDK4	EPHA7	FLCN	IGF1R	MAP2K1	NRAS	PTCH1	SNCAIP	WISP3
AXL	CDK6	EPHB1	FLT1	IGF2	MAP2K2	NSD1	PTEN	SOCS1	WT1
BAP1	CDK8	ERBB2	FLT3	IKBKE	MAP2K4	NTRK1	PTPN11	SOX10	XPO1
BARD1	CDKN1A	ERBB3	FLT4	IKZF1	MAP3K1	NTRK2	QKI	SOX2	ZBTB2
BCL2	CDKN1B	ERBB4	FOXL2	IL7R	MCL1	NTRK3	RAC1	SOX9	ZNF217
BCL2L1	CDKN2A	ERG	FOXP1	INHBA	MDM2	NUP93	RAD50	SPEN	ZNF703
BCL2L2	CDKN2B	ERRFI1	FRS2	INPP4B	MDM4	PAK3	RAD51	SPOP	
BCL6	CDKN2C	ESR1	FUBP1	IRF2	MED12	PALB2	RAF1	SPTA1	
BCOR	CEBPA	EZH2	GABRA6	IRF4	MEF2B	PARK2	RANBP2	SRC	
BCORL1	CHD2	FAM46C	GATA1	IRS2	MEN1	PAX5	RARA	STAG2	
BLM	CHD4	FANCA	GATA2	JAK1	MET	PBRM1	RB1	STAT3	
SELECT REARRANGEMENTS									
ALK	BRAF	BRD4	ETV4	FGFR1	KIT	MYC	NTRK2	RARA	TMPRSS2
BCL2	BRCA1	EGFR	ETV5	FGFR2	MSH2	NOTCH2	PDGFRA	RET	
BCR	BRCA2	ETV1	ETV6	FGFR3	MYB	NTRK1	RAF1	ROS1	

Tumor Heterogeneity



Liquid Biopsies



Paired Tumor/Germline: New Challenges

Research

Original Investigation

Germline Variants in Targeted Tumor Sequencing Using Matched Normal DNA

Kasmintan A. Schrader, MBBS, PhD, FRCPC, DABMG; Donavan T. Cheng, PhD; Vijai Joseph, PhD; Meera Prasad, MS; Michael Walsh, MD; Ahmet Zehir, PhD; Ai Ni, PhD; Tinu Thomas, MS; Ryma Benayed, PhD; Asad Ashraf, MS; Annie Lincoln, MS; Maria Arcila, MD; Zsofia Stadler, MD; David Solit, MD; David Hyman, MD; Liying Zhang, MD, PhD; David Klimstra, MD; Marc Ladanyi, MD; Kenneth Offit, MD; Michael Berger, PhD; Mark Robson, MD

- N=1566
- 16% had a presumed pathogenic germline variant; **12.6%** in known CA
- **59%** of these were not concordant with the patient's cancer type
- 100% had at least one VUS
- 5% have actionable therapies (expanding)
- 3.5% "incidental" mutations; need to pre-consent to disclose

JAMA. 2017 Sep 5;318(9):825-835

Mutation Detection in Patients With Advanced Cancer by Universal Sequencing of Cancer-Related Genes in Tumor and Normal DNA vs Guideline-Based Germline Testing.

Mandelker D[1] MSKCC

N=1040 patients, median age was 58 years
81.3% had stage IV prostate, renal, pancreatic, breast or colon cancer

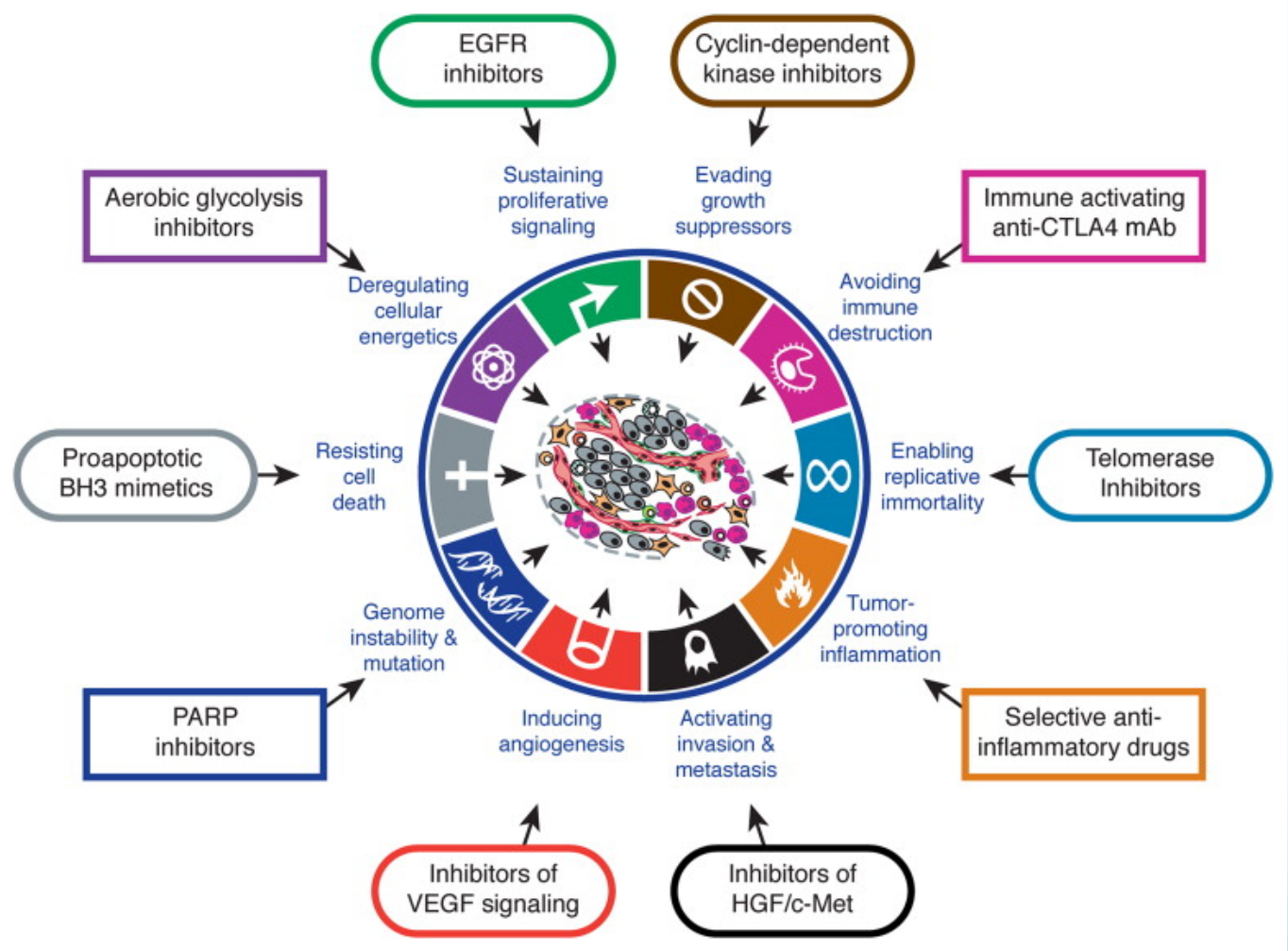
182 (**17.5%**) had germline cancer risk mutations
149 (**14.3%**) with moderate- to high-penetrance mutations;
101 patients tested (**9.7%**; CI: 8.1-11.7) did not meet clinical guidelines, including 65 (**6.25%**) with moderate- to high-penetrance mutations.

Germline findings led to discussion or initiation of change to targeted therapy in 38 patients (**4%**)

Some Mutations do not “Stay in Their Lane”

Larger panels reveal some surprising overlap between syndromes

Targeting the Hallmarks of Cancer



Hanahan D, Weinberg RA. *Cell*. 2011.

Summary (Genetics):

- Next Gen Sequencing has revolutionized hereditary testing; cost and spectrum. This creates a need for complex pre- and post test counseling
- Always try to test the most informative relative first:
  youngest, most affected, living
- Clinical overlap may require you consider more than one syndrome
- **None of these genetic tests are comprehensive**
- Empiric risk counseling is the default if no mutation is found
- Genetic counseling is time consuming but critical to predicting most likely syndrome, understanding the limits of tests, contextualizing the outcomes and options
- Balancing the individual and family needs is an art

Summary (Genomics):

- Next Gen Sequencing opened doors to massive tumor profiling to identify driver mutations
- Actionable mutations expand as pathways are defined and targeted therapies developed
- DNA maintenance genes may increase cancer risks beyond traditional associations (change lanes)
- Tumors are ever changing and can still outrun targeted treatments
- Tumor biology is complex; we can only treat a fraction of what we can test
- We can still only test a portion of cancer genes
- Liquid biopsy – currently insufficient sensitivity
- **We are moving toward an era of broad, tumor/ germline paired genetic testing; a marriage of hereditary genetics and tumor genomics**

Clinical Cancer Center

Stanford Cancer Genetics Clinic

Risk Assessment, Genetic Counseling And Interventions For Members Of Cancer Families

Program Members

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BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a,b]

The inclusion of a gene on 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	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of BC** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[c,d] • RRM: Evidence insufficient, manage based on family history.	**No increased risk of OC**	Unknown or insufficient evidence for pancreas or prostate cancer
	Comments: Insufficient evidence to recommend against radiation therapy. Counsel for risk of autosomal recessive condition in offspring.		
BRCA1	**Increased risk of BC** • See BRCA Mutation-Positive Management	**Increased risk of OC** • See BRCA Mutation-Positive Management	Prostate cancer • See BRCA Mutation-Positive Management
BRCA2	**Increased risk of BC** • See BRCA Mutation-Positive Management	**Increased risk of OC** • See BRCA Mutation-Positive Management	Pancreas, Prostate, Melanoma • See BRCA Mutation-Positive Management
BRIP1	**No increased risk of BC**	**Increased risk of OC** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of mutations in *BRIP1* appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
CDH1	**Increased risk of lobular BC** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y[c,d] • RRM: Evidence insufficient, manage based on family history.	**No increased risk of OC**	Diffuse gastric cancer • See NCCN Guidelines for Gastric Cancer: Principles of Genetic Risk Assessment for Gastric Cancer

[a]Tung N, Domchek SM, Stadler Z, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol 2017;13:581-588. See Discussion for further details regarding the rationale for different starting ages for breast screening.

[b]The following genes and others are found on some of the panels, but there is insufficient evidence to make *any* recommendations for breast MRI, RRSO, RRM: BARD1, FANCC, MRE11A, MUTYH heterozygotes, RECQL4, RAD50, RINT1, SLX4, SMARCA4, or XRCC2.

[c]May be modified based on family history (typically beginning screening 5–10 years earlier than the youngest diagnosis in the family but not later than stated in the table) or specific gene mutation.

[d]For women with mutations who are treated for breast cancer and have not had bilateral mastectomy, screening should continue as described.

BC: Breast cancer
OC: Ovarian cancer
RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a-d]

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	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
CHEK2	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y[f,g] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	Colon • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comments: Risk data are based only on frameshift pathogenic/likely pathogenic variants. The risks for most missense variants are unclear but for some pathogenic/likely pathogenic variants, such as Ile157Thr, the risk for breast cancer appears to be lower. Management should be based on best estimates of cancer risk for the specific pathogenic/likely pathogenic variant.		
MSH2, MLH1, MSH6, PMS2, EPCAM	**Unknown or insufficient evidence for breast cancer risk[g]** • Manage based on family history	**Increased risk of ovarian cancer** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	**Colon, Uterine, Others** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
NBN	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast age 40 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Unknown or insufficient evidence for ovarian cancer risk**	Unknown or insufficient evidence
	Comments: Management recommendations are based on data derived from the 657del5 Slavic truncating pathogenic/likely pathogenic variant. Although risks for other pathogenic/likely pathogenic variants have not been established it is prudent to manage patients with other truncating pathogenic/likely pathogenic variants similarly to those with 657del5. Counsel for risk of autosomal recessive condition in children.		
NF1	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis starting at age 30 y and consider breast MRI with contrast from ages 30–50 y[f,g] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	• Malignant peripheral nerve sheath tumors, GIST, others • Recommend referral to *NF1* specialist for evaluation and management
	Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Screening recommendations only apply to individuals with a clinical diagnosis of NF. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.		

Footnotes on GENE-5

RRM: Risk-reducing mastectomy

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

BREAST AND OVARIAN MANAGEMENT BASED ON GENETIC TEST RESULTS[a-d]

The inclusion of a gene on 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	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
PALB2	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Unknown or insufficient evidence for ovarian cancer risk**	Unknown or insufficient evidence
	Comments: Counsel for risk of autosomal recessive condition in offspring.		
PTEN	**Increased risk of breast cancer** • See Cowden Syndrome Management	**No increased risk of ovarian cancer**	See Cowden Syndrome Management
RAD51C	**Unknown or insufficient evidence for breast cancer risk**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51C* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
RAD51D	**Unknown or insufficient evidence for breast cancer risk**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51D* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
STK11	**Increased risk of breast cancer** • Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal • RRM: Evidence insufficient, manage based on family history	**Increased risk of non-epithelial ovarian cancer** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
TP53	**Increased risk of breast cancer** • See Li-Fraumeni Syndrome Management	**No increased risk of ovarian cancer**	See Li-Fraumeni Syndrome Management

Footnotes on GENE-5

RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MULTI-GENE TESTING

Table 4: Evaluation of CRC Genes Commonly Included on Multi-Gene Panels[c]

GENE	STRENGTH OF EVIDENCE	RISK LEVEL	ASSOCIATION	REFERENCE
APC	Well-established	High	FAP & AFAP	See *APC* and *MUTYH* Genetic Testing Criteria (APC/MUTYH-1)
APC I1307K mutation	Well-established	Moderate	Increased frequency in Ashkenazi Jewish individuals; increased risk for CRC	Boursi B, et al. Eur J Cancer 2013;49:3680-3685. Liang J, et al. Am J Epidemiol 2013;177:1169-1179.
ATM	Not well-established	Unclear – moderate at most	Increased risk for breast cancer and CRC	Thompson D, et al. J Natl Cancer Inst 2005;97:813-822. Olsen JH, et al. Br J Cancer 2005;93:260-265.
AXIN2	Not well-established	Uncertain – presumed high risk from limited case reports	Polyposis and oligodontia	Lammi L, et al. Am J Hum Genet 2004;74:1043-50. Marvin ML, et al. Am J Med Genet A 2011;155A:898-902. Rivera B, et al. Eur J Hum Genet 2014;22:423-426. Lejuene S, et al. Hum Mutat 2006;27:1064. Wong S, et al. Arch Oral Biol 2014;59:349-353.
BLM heterozygotes	Not well-established	Uncertain – none to low	Possible increased risk for CRC	Cleary SP, et al. Cancer Res 2003;3:1769-1771. Baris HN, et al. Isr Med Assoc J 2007;9:847-850. Laitman Y, et al. Cancer Genet 2016;209:70-74.
BMPR1A	Well-established	High	JPS	See Juvenile Polyposis Syndrome Guidelines (JPS-1)
CHEK2	Not well-established	Moderate	Increased risk for breast, colon, and other cancers	Xiang HP, et al. Eur J Cancer 2011;47:2546-2551. Liu C, et al. Asian Pac J Cancer Prev 2012;13:2051-2055. Gronwald J, et al. Br J Cancer 2009;100:1508-1512.
EPCAM	Well-established	High	LS	See Lynch Syndrome Guidelines (LS-1)

[c] *RPS20* is an emerging gene that is potentially linked to CRC, and there are not enough data at present to include *RPS20* on this list.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Continued

MULTI-GENE TESTING

Table 4: Evaluation of CRC Genes Commonly Included on Multi-Gene Panels[6] (continued)

GENE	STRENGTH OF EVIDENCE	RISK STATUS	ASSOCIATION	REFERENCE
GALNT12	Not well-established	Uncertain – moderate at most	Increased risk for colorectal cancer	Guda K, et al. Proc Natl Acad Sci U.S.A. 2009;106:12921-12925. Clarke E, et al. Hum Mutat 2012;33:1056-1058. Segui N, et al. Hum Mutat 2014;35:50-52.
GREM1	Not well-established	Uncertain – presumed high risk from limited case reports	Hereditary mixed polyposis syndrome due to a 40kb duplication upstream of *GREM1* in Ashkenazi Jewish ancestry only	Jaeger E, et al. Nat Genet 2012; 44:699-703.
MLH1	Well-established	High	LS	See Lynch Syndrome Guidelines (LS-1)
MSH2	Well-established	High	LS	
MSH6	Well-established	High	LS	
MSH3	Not well-established	Uncertain – presumed high risk from limited case reports	Polyposis	Adam R, et al. Am J Hum Genet 2016;99:337-51.
MUTYH biallelic mutations	Well-established	High	MAP	See *APC* and *MUTYH* Genetic Testing Criteria (APC/MUTYH-1)
MUTYH heterozygotes	Not well-established	Uncertain – moderate at most	Possible increased risk for CRC	Win AK, et al. Gastroenterology 2014;146:1208-1211.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

MULTI-GENE TESTING

Table 4: Evaluation of CRC Genes Commonly Included on Multi-Gene Panels[c] (continued)

GENE	STRENGTH OF EVIDENCE	RISK STATUS	ASSOCIATION	REFERENCE
NTHL1	Not well-established	Uncertain – presumed high from limited case reports	Polyposis	Weren RD, et al. Nat Genet 2015;47:668-671. Rivera B, et al. N Engl J Med 2015;373:1985–1986. Broderick P, et al. BMC Cancer 2006:6:243.
POLD1	Not well-established	Uncertain – presumed high risk from limited case reports	Polymerase proofreading-associated polyposis	Palles C, et al. Nat Genet 2013; 45:136-144. Spier I, et al. Int J Cancer 2015;137:320-331. Bellido F, et al. Genet Med 2016;18:325-332.
POLE	Not well-established	Uncertain – presumed high risk from limited case reports	Polymerase proofreading-associated polyposis	Bellido F, et al. Genet Med 2016;18:325-332.
PMS2	Well-established	High	LS	See Lynch Syndrome Guidelines (LS-1)
PTEN	Well-established	Moderate-High	Cowden syndrome/PTEN hamartoma syndrome	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian
SMAD4	Well-established	High	Juvenile polyposis syndrome	See Juvenile Polyposis Syndrome Guidelines (JPS-1)
STK11	Well-established	High	PJS	See Peutz-Jeghers Syndrome Guidelines (PJS-1)
TP53	Well-established	High	Li-Fraumeni syndrome	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian

[c]*RPS20* is an emerging gene that is potentially linked to CRC, and there are not enough data at present to include *RPS20* on this list.

Continued

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.