НАСЛЕДСТВЕННЫЙ РАК МОЛОЧНОЙ ЖЕЛЕЗЫ

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Цель медико-генетического консультирования в онкологии

- выявление индивидуумов с повышенным риском развития наследственных онкологических заболеваний.

НАСЛЕДСТВЕННЫЙ ОНКОЛОГИЧЕСКИЙ СИНДРОМ – генетическое заболевание, вызванное нарушением структуры и/или регуляции гена/ряда генов, характеризующееся передачей из поколения в поколение предрасположенности к развитию онкологического заболевания. Как правило имеет несколько органов-мишеней.

- ✓ Большинство имеет аутосомно-доминантный тип наследования
- ✓ Для большинства характерна не полная пенетрантность (проявляемость) поврежденного гена
- ✓ Риск развития заболевания существенно увеличивается с возрастом
- ✓ Как правило имеют специфические сочетания опухолей (кластеры), характерных для синдрома, в нескольких поколениях

Расчет риска носительства наследственной мутации

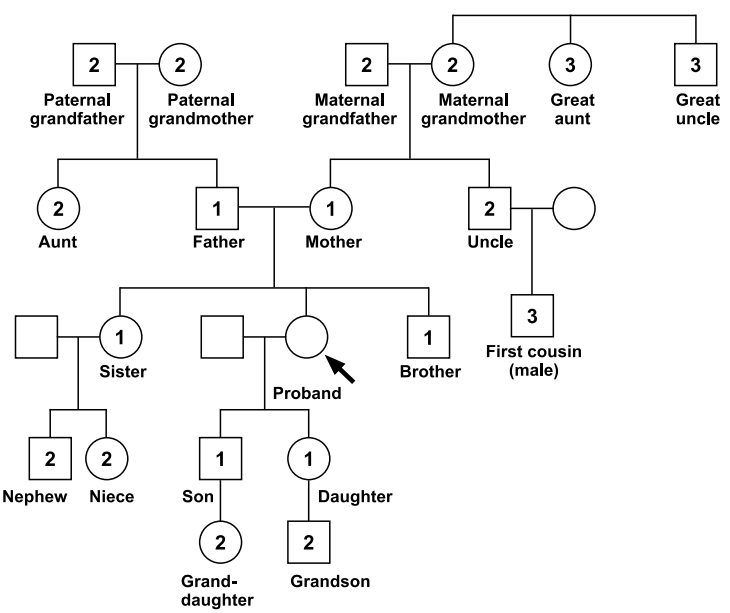
Model	Conventional threshold	Sensitivity at conventional threshold			Specificity at conventional threshold		
		All	Low risk subset	High risk subset	All	Low risk subset	High risk subset
BRCA status							
BRCAPRO	10	0.75	0.63	0.82	0.62	0.70	0.58
Manchester	15	0.58	0.39	0.64	0.71	0.73	0.72
Penn II	10	0.93	0.94	0.92	0.31	0.14	0.40
Myriad II	10	0.71	0.66	0.74	0.63	0.65	0.62
FHAT	10	0.70	0.34	0.89	0.63	0.85	0.51
IBIS	10	0.20	-	-	0.74	-	-
BOADICEA	10	0.70	0.63	0.74	0.65	0.70	0.62

1. Breast Cancer Risk Assessment Tool https://bcrisktool.cancer.gov/calculator.html
2. The **Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm** http://ccge.medschl.cam.ac.uk/boadicea/

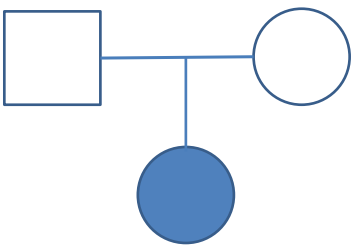
Какая информация необходима врачу-генетику перед консультацией?

- ✓ Детальные сведения семейной истории (онкологические заболевания у родственников, гистологический тип, возраст манифестации заболевания и т.д.). Желательно в 3 поколениях.
- ✓ Медицинские документы самого пациента (выписной эпикриз, гистологическое заключение, результаты проведенных клинических исследований).

Пример информативной родословной



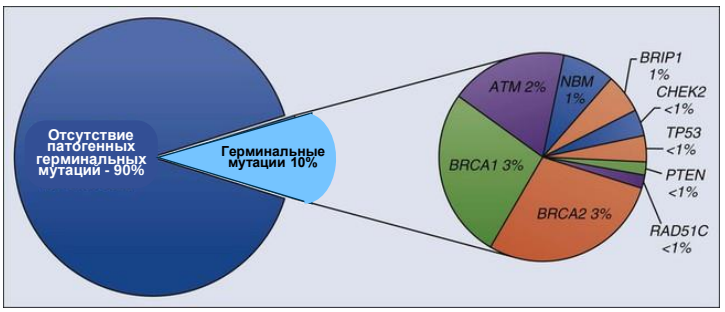
Пример типичной родословной



Факторы, снижающие информативность анализа родословной.

- Маленькие семьи
- Низкая пенетрантность мутации
- Ранняя смерть родственников
- Удаление органа при других патологиях
- Усыновление

Частота мутаций в генах, ассоциированных с наследственным РМЖ



The Cancer Genome Atlas Network., Genome sequencing centres: Washington University in St Louis., Koboldt, D. et al. Comprehensive molecular portraits of human breast tumours. Nature 490, 61–70 (2012). https://doi.org/10.1038/nature11412

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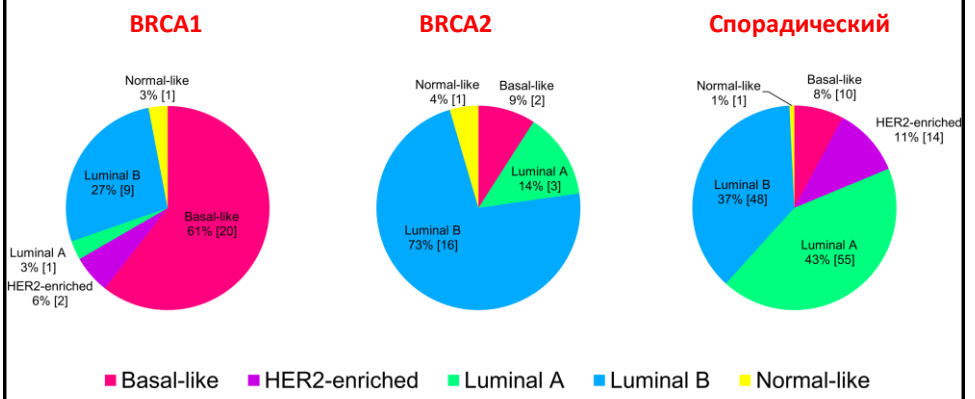
Синдромы, ассоциированные с наследственным РМЖ

Синдром	Вовлеченный ген и его локализация	Основные клинические проявления
Наследственный РМЖ и/или рак яичников (РЯ)	*BRCA1* (17q21) *BRCA2* (13q12.3)	РМЖ, РЯ, рак предстательной железы, рак поджелудочной железы, мелонома, рак толстой кишки
Синдром Ли–Фраумени	*TP53* (17p13.1) *CHEK2* (22q12.1)	РМЖ, мягкотканные саркомы, остеосаркомы, опухоли головного мозга, лейкозы, рак коры надпочечников
Синдром Линча (наследственный неполипозный рак толстой кишки)	*MSH2* (2p22-p21) *MSH3* (5q11-q12) *MSH6* (2p16) *MLH1* (3p21.3) *PMS1* (2q31-q33) *PMS2* (7p22)	Рак толстой кишки, первично-множественные злокачественные опухоли: РМЖ, РЯ, рак тела матки, желудка, тонкой кишки, мочеточника или почечной лоханки, желчных путей; возможно сочетание с опухолями головного мозга (синдром Тюрко) или множественными аденомами сальных желез (синдром Торре)
Синдром Луи–Бар	*ATM* (11q22.3)	Лимфома, мозжечковая атаксия, глиома, поражения кожи, дефицит иммунной системы, глиома, медуллобластома, РМЖ
Наследственный диффузный рак желудка	*CDH1* (16q22.1)	Рак желудка, дольковый РМЖ
Синдром Коудена	*PTEN* (10q23.31)	Поражение слизистых оболочек и кожи, множественные гамартомы (чаще в желудочно-кишечном тракте), РМЖ, рак щитовидной железы, опухоли матки и др.
Синдром Пейтца–Егерса	*STK11* (19p13.3)	Пигментация кожи, слизистой оболочки ротовой полости, множественные гамартомы желудочно-кишечного тракта, РМЖ, герминогенные опухоли
Синдром хромосомной нестабильности	*NBS1* (8q21)	Микроцефалия, комбинированный первичный иммунодефицит, повышенная чувствительность к радиоактивному излучению, РМЖ
Анемия Фанкони	*BRIP/FANCJ* (17q23.2) *PALB2/FANCN* (16p12) *FANCA* (16q24.3)	Апластическая анемия, аномалии скелета, неврологические расстройства, врожденные пороки сердца, РМЖ

(Любченко Л. И соавт., 2014)

Распределение подтипов РМЖ в зависимости от мутационного статуса



Martin Larsen et al., 2013

Тип рака	Общепопуляционная частота	Носители мутаций BRCA1	Носители мутаций BRCA2
Молочная железа	12.5%	55 – 85%	33 – 86%
Поражение второй железы	3.5%	27%	40%
Яичники	1.43%	28 – 44%	10 – 30%
Предстательная железа	4 – 6%	12 – 18%	12 – 18%
Грудная железа у мужчин	Меньше 1%	6%	4 – 14%
Поджелудочная железа	0.6%	-	6 – 7%

Частые мутации гена BRCA1 при раке молочной железы в славянской популяции.

- 5382insC (60-80% от всех мутаций)
- 185delAG
- C61G
- 4154delA

Tereschenko I.V., Basham V.M., Ponder B.A., Pharoah P.D. 2002. BRCA1 and BRCA2 mutations in Russian familial breast cancer. Hum. Mutat.

Loginova A.N., Pospekhova N.I., Lyubchenko L.N., Budilov A.V., Zakhar'ev V.M., Gar'kavtseva R.F., Ginter E.K., Karpukhin A.V. 2003. Spectrum of mutations in BRCA1 gene in hereditary forms of breast and ovarian cancer in Russian families. Bull. Exp. Biol. Med

Sokolenko A.P., Mitiushkina N.V., Buslov K.G., et al. 2006. High frequency of BRCA1 5382insC mutation in Russian breast cancer patients. Eur. J. Cancer. 42, 1380–1384.

Sokolenko A.P., Rozanov M.E., Mitiushkina N.V., et al. 2007. Founder mutations in earlyonset, familial and bilateral breast cancer patients from Russia. Fam. Cancer.

Методы анализа BRCA1 и BRCA2

- Аллель-специфическая ПЦР - только известные мутации. Только частые мутации
  1. Фаундер (характерные для какой-либо популяции). Могут встречаться от 10 до 80% в зависимости от популяции
  2. Наследственные частые (более 1%)
- Секвенирование по Сэнгеру - все мутации (50 разных исследований). Высокая трудоемкость, высокая стоимость.
- Секвенирование нового поколения (массивное параллельное секвенирование) – все мутации за одно исследование. Высокотехнологичное оборудование, высокая стоимость.
- MLPA - анализ крупных перестроек. Высокая трудоемкость, неоднозначность интерпретации.

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Кому из пациентов показано генетическое тестирование *BRCA1/2*? (рекомендации NCCN)

- Individual from a family with a known *BRCA1/2* pathogenic/likely pathogenic variant, including such variants found on research testing[b]
- Personal history of breast cancer[c] + one or more of the following:
  - Diagnosed ≤45 y
  - Diagnosed 46-50 y with:
    - An additional breast cancer primary at any age[d]
    - ≥1 close blood relative[e] with breast cancer at any age
    - ≥1 close blood relative[e] with high-grade (Gleason score ≥7) prostate cancer
    - An unknown or limited family history[a]
  - Diagnosed ≤60 y with:
    - Triple-negative breast cancer
  - Diagnosed at any age with:
    - ≥1 close blood relative[e] with:
      - breast cancer diagnosed ≤50 y; or
      - ovarian carcinoma;[f] or
      - male breast cancer; or
      - metastatic prostate cancer;[g] or
      - pancreatic cancer
    - ≥2 additional diagnoses[d] of breast cancer at any age in patient and/or in close blood relatives
  - Ashkenazi Jewish ancestry[h]
- Personal history of ovarian carcinoma[f]
- Personal history of male breast cancer
- Personal history of pancreatic cancer[i]
- Personal history of metastatic prostate cancer[g]
- Personal history of high-grade prostate cancer (Gleason score ≥7) at any age with
  - ≥1 close blood relatives[e] with ovarian carcinoma, pancreatic cancer, or metastatic prostate cancer[g] at any age or breast cancer <50 y; or
  - ≥2 close blood relatives[e] with breast, or prostate cancer (any grade) at any age; or
  - Ashkenazi Jewish ancestry[h]
- *BRCA1/2* pathogenic/likely pathogenic variant detected by tumor profiling on any tumor type in the absence of germline pathogenic/likely pathogenic variant analysis
- Regardless of family history, some individuals with an *BRCA*-related cancer may benefit from genetic testing to determine eligibility for targeted treatment[j]
- An individual who does not meet the other criteria but with ≥1 first- or second-degree blood[e] relative[k] meeting any of the above criteria. The significant limitations of interpreting test results for an unaffected individual should be discussed.

[a]For further details regarding the purposes of genetic counseling and testing, see BR(

По степени клинической значимости мутации бывают:

Класс	Описание (англ)	Описание (рус)	Вероятность патогенности
5	*Definitely Pathogenic*	Несомненно патогенная	>0.99
4	*Likely Pathogenic*	Вероятно патогенная	0.95–0.99
3	*Uncertain*	Неясной значимости	0.05–0.949
2	*Likely Not Pathogenic or of Little Clinical Significance*	Вероятно непатогенная или низкого клинического значения	0.001–0.049
1	*Not Pathogenic or of No Clinical Significance*	Непатогенная или не имеющая клинического значения	<0.001

Plon ES et al. Hum Mutat. 2008 Nov; 29(11): 1282–1291

Критерии патогенности ACMG

	Benign		Pathogenic			
	Strong	Supporting	Supporting	Moderate	Strong	Very Strong
Population Data	MAF is too high for disorder *BA1/BS1* **OR** observation in controls inconsistent with disease penetrance *BS2*			Absent in population databases *PM2*	Prevalence in affecteds statistically increased over controls *PS4*	
Computational And Predictive Data		Multiple lines of computational evidence suggest no impact on gene /gene product *BP4* Missense in gene where only truncating cause disease *BP1* Silent variant with non predicted splice impact *BP7*	Multiple lines of computational evidence support a deleterious effect on the gene /gene product *PP3*	Novel missense change at an amino acid residue where a different pathogenic missense change has been seen before *PM5* Protein length changing variant *PM4*	Same amino acid change as an established pathogenic variant *PS1*	Predicted null variant in a gene where LOF is a known mechanism of disease *PVS1*
Functional Data	Well-established functional studies show no deleterious effect *BS3*		Missense in gene with low rate of benign missense variants and path. missenses common *PP2*	Mutational hot spot or well-studied functional domain without benign variation *PM1*	Well-established functional studies show a deleterious effect *PS3*	
Segregation Data	Non-segregation with disease *BS4*		Co-segregation with disease in multiple affected family members *PP1*	Increased segregation data →		
De novo Data				*De novo* (without paternity & maternity confirmed) *PM6*	*De novo* (paternity & maternity confirmed) *PS2*	
Allelic Data		Observed in *trans* with a dominant variant *BP2* Observed in *cis* with a pathogenic variant *BP2*		For recessive disorders, detected in *trans* with a pathogenic variant *PM3*		
Other Database		Reputable source w/out shared data = benign *BP6*	Reputable source = pathogenic *PP5*			
Other Data		Found in case with an alternate cause *BP5*	Patient's phenotype or FH highly specific for gene *PP4*			

Базы мутаций BRCA1/2

https://www.ncbi.nlm.nih.gov/clinvar/

- http://www.hgmd.cf.ac.uk/ac/index.php
- https://varsome.com

http://www.umd.be/

https://databases.lovd.nl/shared/genes/

http://arup.utah.edu/database/BRCA/Variants/BRCA1

https://research.nhgri.nih.gov/bic/

https://digitalinsights.qiagen.com/products-overview/clinical-insights-portfolio/human-gene-mutation-database/?cmpid=QDI_GA_QCI&gclid=EAIaIQobChMIj-mA87nx7gIV6QWiAx3YOgsmEAAYASAAEgJOovD_BwE

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Что дает медико-генетическое консультирование?

- ✓ Выбор вариантов лечения
- ✓ Определение риска развития онкологического заболевания у других членов семьи
- ✓ Информация о ранней диагностике заболевания
- ✓ Информация о профилактике заболевания

Ведение носителей патогенных мутаций

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Potential increase in ovarian cancer risk, with insufficient evidence for recommendation of RRSO**	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.		
BARD1	**Potential increase in breast cancer risk, with insufficient evidence for management recommendations**	**Unknown or insufficient evidence for ovarian cancer risk**	N/A
BRCA1	**Increased risk of breast cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	Prostate cancer • See *BRCA* Pathogenic Variant-Positive Management
BRCA2	**Increased risk of breast cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	Pancreas, Prostate, Melanoma • See *BRCA* Pathogenic Variant-Positive Management
BRIP1	**Unknown or insufficient evidence**	**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 *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 breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y[f,g] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	Diffuse gastric cancer • See NCCN Guidelines for Gastric Cancer: Principles of Genetic Risk Assessment for Gastric Cancer

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.		

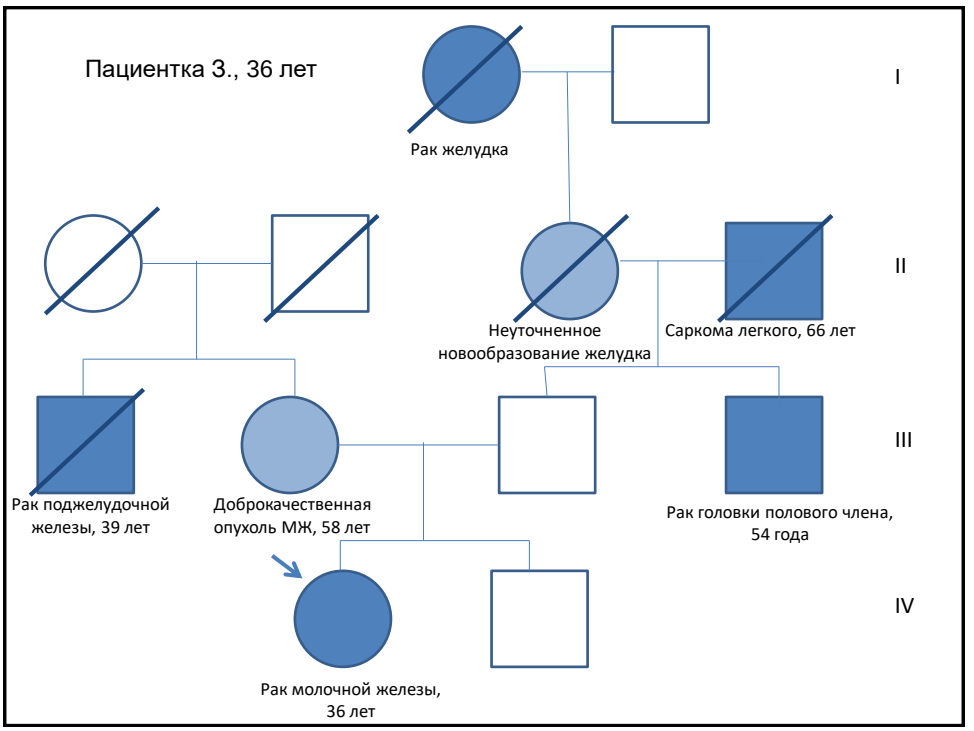
Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
PALB2	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[f,g] • RRM: Evidence insufficient, manage based 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

Ранняя диагностика у носителей мутации *BRCA 1/2*

- Самообследование МЖ с 18 лет ежемесячно
- МРТ/маммография с 25 лет каждые полгода
- Трансвагинальное УЗИ, СА-125 с 30-35 лет каждые полгода
- Обследование предстательной железы с 40 лет
- Дерматологическое обследование ежегодно

Возможные процедуры по результатам генетического теста (рекомендации NCCN)

	МРТ	Мастэктомия/органосохраняющая операция	Сальпинго-оформэктомия
Аргументированные процедуры	**ATM**	**BRCA1**	**BRCA1**
	BRCA1	**BRCA2**	**BRCA2**
	BRCA2	**CDH1**	**Синдром Линча**
	CDH1	**PTEN**	**BRIP1**
	CHEK2	**TP53**	**RAD51C**
	PALP2	**PALP2**	**RAD51D**
	PTEN		
	STK11		
	TP53		
Недостаточно данных для процедур	**BRIP1**	**ATM**	**PALB2**
		CHEK2	
		STK11	

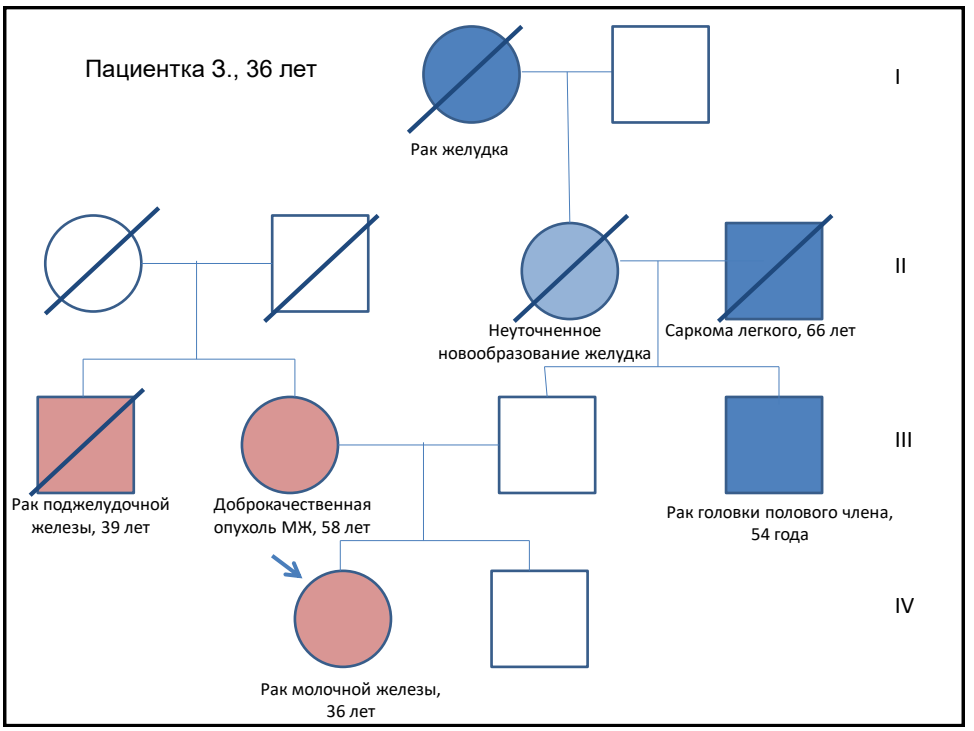


Синдромы, соответствующие составленной родословной:

1. Наследственный рак молочной железы и/или яичников (BRCA1, BRCA2)
2. Синдром Ли-Фраумени (P53)
3. Синдром наследственного рака желудка (CDH1)

Генетическое тестирование.

- Отрицательный статус 8 часто встречающихся мутаций BRCA
- Предложено мультигенное тестирование (NGS)
- Обнаружена патогенная мутация *BRCA2*:c.5193_5194del: p.H1731fs, передающаяся по материнской линии



СПАСИБО ЗА ВНИМАНИЕ!