6 ulusal CERRAHİ ONKOLOJİ KONGRESİ

24 - 27 Şubat 2022 | Gloria Golf Resort – ANTALYA

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ANKARA ÜNV. TIP FAKÜLTESİ CERRAHİ ONKOLOJİ BD

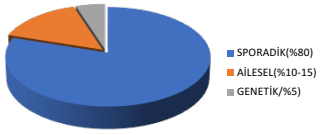
MEME KANSERİNDE MUTİPANEL GEN TESTLERİ

- Meme kanseri kadınlarda en sık izlenen kanser türüdür
- Meme kanserlerinin %5-10 kadarı genetik kökenlidir
- Ailede birden çok meme/over kanseri birlikteliği, genç yaş meme kanseri, bilateral meme kanseri, TNBC meme kanseri, erkek meme kanseri varlığı genetik yatkınlığı düşündürmelidir

Hangi Hastalarda Genetik Mutasyondan Şüphelenilmeli

- Ailede bilinen genetik mutasyon
- Aile hikayesi(Meme, Over, Pankreas, Prostat, Kolon, Mide)
- Erkek meme ca
- TNBC (%7-28 BRCA 1)
- <50 yaş meme ca
- Geçirilmiş meme/over ca(papiller seröz) hikayesi (%11 BRCA)
- Askenazi Yahudileri

MEME KANSERİ AİLESEL VE GENETİK FAKTÖRLER



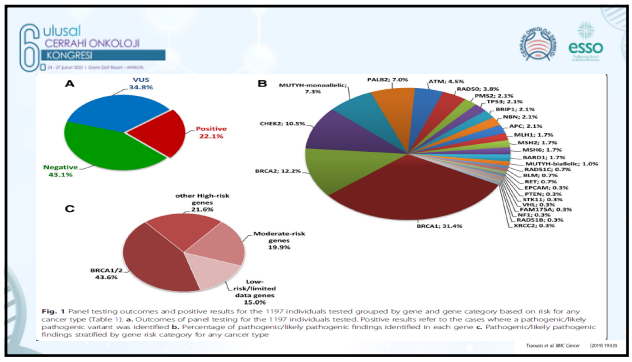
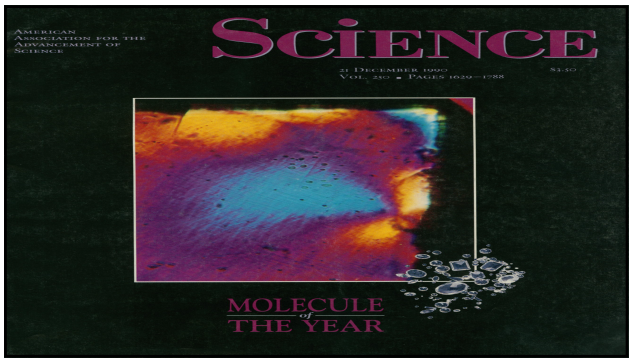
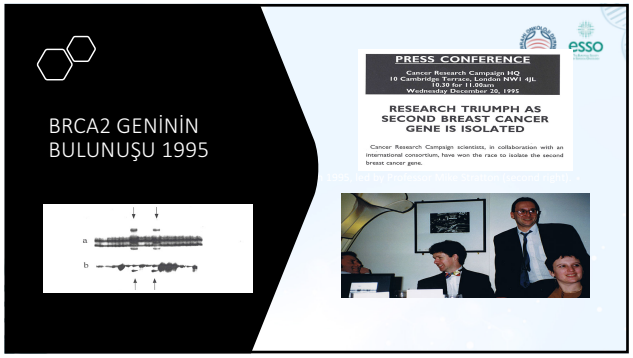


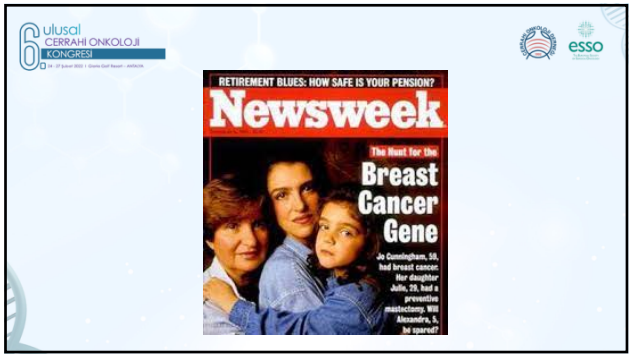
Fig. 1 Panel testing outcomes and positive results for the 1197 individuals tested grouped by gene and gene category based on risk for any cancer type (Table 1). **a.** Outcomes of panel testing for the 1197 individuals tested. Positive results refer to the cases where a pathogenic/likely pathogenic variant was identified **b.** Percentage of pathogenic/likely pathogenic findings identified in each gene **c.** Pathogenic/likely pathogenic findings stratified by gene risk category for any cancer type

MEME KANSERİNDE NONBRCA GENETİK MUTASYON

- PALB2
- CHEK2
- ATM

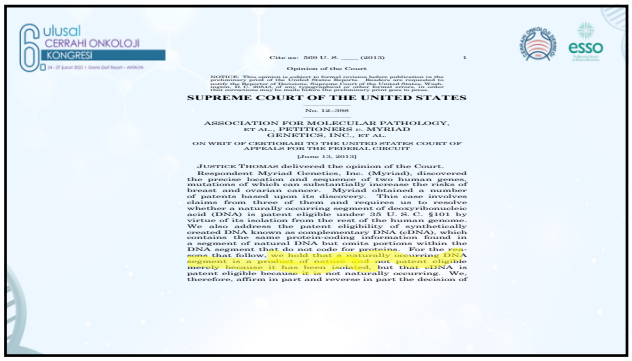






GENETİK MEME KANSERİ

- Güçlü aile hikayesine ve fenotipik özelliklere rağmen BRCA testi negatif gelen hastalarda diğer genetik mutasyonlar araştırılmalıdır
- Öncelikle bu hastaların genetik uzmanına yönlendirilmesi gerekir
- Hangi testlerin isteneceğine genetik uzmanı karar verir ve sonuçları da genetik uzmanı yorumlar
- Multigen panelleri hızlı ve çok sayıda genin analiz edilmesine olanak verir
- Her laboratuarın deneyim düzeyi farklıdır



MEME KANSERİNDE GENETİK MUTASYONLAR

Yüksek riskliler	Orta riskliler	Hafif riskliler
• BRCA • CDH1 • PTEN • STK11 • TP53	• ATM • CHEK2 • PALB2	• BARD1 • BRIP1 • NBN • RAD50 • RAD51C • RAD51D

Table 2.3 (continued)

Gene(s)	Breast cancer lifetime risk	Ovarian cancer lifetime risk	Other associated cancers/features
CDH1	39–53% (particularly lobular)	No known increase	Diffuse gastric (55–85%)
			Possibly colon
PTEN	~25–50% by most estimates (some higher estimates)	No known increase	Thyroid, endometrial, renal, and possibly colorectal cancer
			Benign breast and thyroid disease
			Uterine fibroid tumors
			Skin findings (oral papillomas, facial trichilemmomas)
			Macrocephaly
			Developmental delay
			Autism spectrum disorders
			Multiple GI polyps (including hamartomas and ganglioneuromas)
			Vascular malformations
STK11	32–54%	18–21% (mainly sex cord stromal)	Colorectal, gastric, pancreatic, uterine, small intestine, testicular, and lung cancers
			Multiple hamartomatous GI polyps mucocutaneous hyperpigmentation
TP53	Significantly increased, may be as high as 79%	Unknown/not well defined	Sarcoma, brain, adrenal cortical carcinoma, leukemia, lung, and other cancers
			Childhood onset cancers
			Multiple primary cancers

Kimler Multipanel Test(NGS) Yaptırmalıdır

- Kişisel yada ailesel çok sayıda kanser hikayesi olup, tek bir genetik mutasyonla izah edilemeyen durumlar
- Kişisel veya ailesel genç yaş geniş kanser spektrumu olan hastalar

GENETİK TEST

- NEGATİF
  - Yaklaşım kişisel ve aile hikayesine göre belirlenir
- VUS(Variant of Uncertain Significance) (%30-40)
  - Yaklaşım kişisel ve aile hikayesine göre belirlenir
- PATOJENİK
  - Spesifik gen mutasyonuna göre tıbbi yaklaşım

Variant of Uncertain Significance(VUS)

- Bu mutasyonların hastalığa sebep olup olmadığı net değildir
- VUS sonucuna göre tedavi yaklaşımı belirlemek doğru olmaz
- Zaman saptanan VUS'ların hastalık bağlantısının önemli/önemsiz olduğunu gösterecektir
- Multipanel testlerde VUS görülme olasılığı yüksektir

YÜKSEK RİSKLİ GENLER

- BRCA1-2
- CDH1
- PTEN
- TP53
- Yakın takip yada profilaktik mastektomi önerilebilir

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NCCN Guidelines Version 1.2022
Li-Fraumeni Syndrome Management

NCCN Guidelines Index
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LI-FRAUMENI SYNDROME MANAGEMENT IN ADULTS

BREAST CANCER (female)
- Breast awareness[a] starting at age 18 y.
- Clinical breast exam, every 6–12 mo, starting at age 20 y.[b]
- Breast screening
  - Age 20–29[b] y, annual breast MRI[c] screening with contrast.[d]
  - Age 30–75 y, annual breast MRI[c] screening with contrast and mammogram with consideration of tomosynthesis.
  - Age >75 y, management should be considered on an individual basis.
  - For individuals with a *TP53* pathogenic/likely pathogenic variant who are treated for breast cancer, and who have not had a bilateral mastectomy, screening with annual breast MRI and mammogram with consideration of tomosynthesis should continue as described above.
- Discuss option of risk-reducing mastectomy.
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
- Address psychosocial and quality-of-life aspects of undergoing risk-reducing mastectomy.

OTHER CANCER RISKS
- Comprehensive physical exam including neurologic examination with high index of suspicion for rare cancers and second malignancies in cancer survivors every 6–12 mo.
- Colonoscopy and upper endoscopy every 2–5 y starting at 25 y or 5 y before the earliest known colon or gastric cancer in the family, respectively.
- Annual dermatologic examination starting at 18 y.
- Annual whole body MRI[e,f,g] (category 2B).
- Annual brain MRI (category 2B) may be performed as part of the whole body MRI or as a separate exam.

NCCN recommendations have been developed to be inclusive of individuals of all sexual and gender identities to the greatest extent possible. On this page, the terms males and females refer to sex assigned at birth.

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Cowden Syndrome/PTEN Hamartoma Tumor Syndrome Management

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COWDEN SYNDROME/PHTS MANAGEMENT

GENERAL
- Annual comprehensive physical exam starting at age 18 y or 5 y before the youngest age of diagnosis of a component cancer in the family (whichever comes first), with particular attention to thyroid exam.
- Education regarding the signs and symptoms of cancer.

BREAST CANCER (female)
- Breast awareness[b] starting at age 18 years.
- Clinical breast exam, every 6–12 months, starting at age 25 years or 5–10 years before the earliest known breast cancer in the family (whichever comes first).
- Breast screening
  - Annual mammography with consideration of tomosynthesis and breast MRI screening with contrast starting at age 35 years or 10 years before the earliest known breast cancer in the family (whichever comes first).[c,d]
  - Age >75 years, management should be considered on an individual basis.
  - For individuals with a *PTEN* pathogenic/likely pathogenic variant who are treated for breast cancer, and have not had a bilateral mastectomy, screening with annual mammogram with consideration of tomosynthesis and breast MRI should continue as described abov
- Discuss option of risk-reducing mastectomy in individuals with pathogenic/likely pathogenic variants identified. For those with clinical CS/ PTHS syndrome, consideration of risk-reducing surgery should be based on family history.
  - Counseling should include a discussion regarding degree of protection, reconstruction options, and risks. In addition, the family history and residual breast cancer risk with age and life expectancy should be considered during counseling.
- Address psychosocial and quality-of-life aspects of undergoing risk-reducing mastectomy.

COLON
- Colonoscopy, starting at age 35 y unless symptomatic or if close relative with colon cancer before age 40 y, then start 5–10 y before the earliest known colon cancer in the family. Colonoscopy should be done every 5 y or more frequently if patient is symptomatic or polyps are found.

CDH1 GEN MUTASYONU

Herediter diffüz gastrik kanser	Lobüler meme kanseri
•Yakın takip? •Profilaktik gastrektomi?	•Yakın takip? •Profilaktik mastektomi?

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ORTA RİSKLİ GENLER

- CHEK
- PALB2
- ATM
- Tarama ve profilaktik mastektomi konuları tartışmalı

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Yeni Tanımlanmış Genler

- BARD1
- BRIP1
- FANCC
- NBN
- RAD51C
- RAD51D
- XRCC2

Bu mutasyonlarda risk ve genel yaklaşım belli değil

Table I. The Prevalence of non-*BRCA4* genes and the Rate of VUS in Individuals with Inherited Breast Cancer- Literature Results

No	Study	Patients	No. of genes tested	Prevalence	VUS
1	Walsh et al (2006) [21]	300	5	6% mutations in *CHEK2, TP53, PTEN*	Not specified
2	Kuusisto et al (2011) [22]	466	7	12.1% *CHEK2, PALB2, BRIP1,RAD50, CDH1*	Not specified
3	Walsh et al (2011) [23]	360	12	6.1%-*BARD1,BRIP1, CHEK2,MRE11A,MSH6,NBN,PALB2,RAD50, RAD51C, TP53*	Not specified
4	Mauer et al (2014) [24]	1233	22	10% mutations in non-*BRCA* genes	30%
5	Kurian et al (2014) [25]	198	42	11.4% mutations in non-*BRCA* genes	88%
6	Castera et al (2014) [26]	708	27	3% *CHEK2, RAD51C, RAD50,PALB2,MRE11A, ATM, NBS1, CDH1, MSH2,PMS2,BARD1, PMS1, MLH1*	Not specified
7	LaDuca et al (2014) [27]	2079	14-22	7.2-9.6% mutations in non-*BRCA* genes	15.1-25.6%
8	Churpek et al (2014) [28]	289	8	4.4% mutations in non-BRCA genes: *PALB2, CHEK2, BARD1, ATM, PTEN, TP53*	0.6%
9	Chong et al (2014) [29]	3000	6	11% *TP53*, 2.3% *PTEN*,1.2% *CDH1*, 0.6% *STK11*	Not specified
10	Cybulski et al (2015) [30]	144	8	2.8% *PALB2*, 1.3% *ATM*	Not specified
11	Doherty et al (2015) [31]	134	6	0%	6.7%
12	Maxwell et al (2015) [32]	278	22	11% mutations in non-*BRCA* genes	19%
13	Tung et al (2015) [33]	2158	25	4.32% mutations in non-*BRCA* genes: *CHEK2,PALB2, ATM, MSH6, PMS2*	41.7%
14	Couch et al (2015) [34]	1824	17	3.7% mutations in non-*BRCA* genes: *PALB2, BARD1, RAD51D, RAD51C, BRIP1*	Not specified
15	Schroeder et al (2015) [35]	620	10	0.97% *CHEK2*, 0.65% *ATM*, 0.48% *CDH1*, 0.32% *PALB2*, 0.32% *NBN*, 0.16% *TP53*	Not specified
16	Yang et al (2015) [36]	99	152	3% *TP53*, 1%-*PALB2*, 1% *RAD51C*, 1% *RAD50*, 1% *CDH1*	Not specified
17	Lincoln et al (2015) [37]	1062	29	3.9% mutations in non-BRCA genes: *ATM, PALB2, CHEK2, MLH1,MSH2, MSH6, PMS2.*	41%
18	Alorasifi et al (2015) [38]	104	312	5%-*ATM*, 3%-*RAD50*, 2% *CHEK2*, 1% *TP53*, 1% *PALB2*, 1% *MRE11A*	Not specified
19	Kapoor et al (2015) [39]	966	15	3.9% *PALB2, CHEK2, ATM*	16.9%
20	Desmond et al (2015) [40]	1046	29	3.8% mutations in non-*BRCA* genes: *CHEK2, ATM, PALB2*	Not specified
21	Thompson et al (2016) [41]	3097	18	0.6% *PALB2*, 0.1% *TP53*, <0.1% *CDH1, PTEN, ATM;*	Not specified
22	Tung et al (2016) [42]	488	25	4.1% *CHEK2, ATM, PALB2, PTEN, NBN, RAD51C, RAD51D, MSH6, PMS2*	33.2%
23	Couch et al (2017) [43]	65 057	21	1.73% *CHEK2*, 1.06% *ATM*, 0.87% *PALB2*	Not specified
	TOTAL	87318	5-312	1-12%	0.6-88%

Table 1 Sample Gene Panel Test Options for Assessing Breast Cancer Risk as of July 2014

Company/Laboratory	University of Washington	Myriad Genetics	Ambry Genetics				GeneDX		Baylor		Invitae		
Panel Name	BROCA	myRisk	BRCAplus	GYNplus	BreastNext	OvaNext	High-Risk Breast	Breast/Ovarian	High-Risk Hereditary Breast	Breast/Ovarian	High-Risk Hereditary Breast	Women's Hereditary Cancers	Custom Panel
Total No. of Genes	49	25	6	9	18	23	6	21	7	23	6	17	≤29
Gene													
AKT1	×												
APC[a]	×	×											×
ATM[b]	×	×			×	×		×		×		×	×
ATR[b]	×												
BAP1	×												
BARD1	×	×			×	×		×		×			
BMPR1A	×	×											×
BRCA1[a]	×	×	×	×	×	×	×	×	×	×	×	×	×
BRCA2[a,b]	×	×	×	×	×	×	×	×	×	×	×	×	×
BRIP1[b]	×	×			×	×		×		×		×	×
CDH1[a]	×	×	×		×	×	×	×	×	×	×	×	×
CDK4	×	×											×
CDKN2A	×	×											×
CHEK1	×												
CHEK2	×	×			×	×		×		×		×	×
CTNNA1	×												
EPCAM[a]	×	×		×		×		×		×		×	×
FAM175A	×												
FANCC[b]								×					
GALNT12	×												
GEN1	×												
GREM1	×												
HOXB13	×												
MLH1[a]	×	×		×		×		×		×		×	×
MRE11A[b]	×				×	×				×			
MSH2[a]	×	×		×		×		×		×		×	×
MSH6[a]	×	×		×		×		×		×		×	×
MUTYH[a]	×	×			×	×				×			×
NBN[b]	×	×			×	×		×		×		×	×
NF1[b]					×	×							
PALB2[b]	×	×			×	×		×	×	×		×	×
PIK3CA	×												
PMS1										×			
PMS2[a]	×	×		×		×		×		×		×	×
POLD1	×												
POLE	×												
PRSS1	×												
PTEN[a]	×	×	×	×	×	×	×	×	×	×	×	×	×
RAD50[b]	×				×	×				×			
RAD51	×												
RAD51C[b]	×	×			×	×		×		×		×	×
RAD51D[b]	×	×			×	×		×		×			
RET[a]	×												×
SDHB	×												
SDHC	×												
SDHD	×												
SMAD4	×	×											×
STK11[a]	×	×	×		×	×	×	×	×	×	×	×	×
TP53[a]	×	×	×	×	×	×	×	×	×	×	×	×	×
TP53BP1	×												
VHL[a]	×												×
XRCC2	×							×					

[a]Genes with professional or consensus guidelines for medical management. Additional genes, such as the *SDH* genes *SMAD4*, *CDKN2A*, *NF1*, and *BMPR1A*, are used in clinical management but may not have consensus guidelines.
[b]Biallelic mutations manifest as a recessive disorder with additional disease risks.

Inherited Cancer Gene Panel Testing

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Breast/Ovarian Panels	Ambry Genetics	BRCAplus[24]	6	*BRCA1, BRCA2, CDH1, PALB2, PTEN, TP53*
		BreastNext[25]	17	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, TP53*
		OvaNext[26]	23	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMARCA4, STK11, TP53*
	Invitae	Breast and Gynecologic Cancers Guidelines Based Panel[27]	14	*ATM, BRCA1, BRCA2, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2,PTEN, STK11, TP53*
		Breast Cancer Guidelines Based Panel[28]	9	*ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53*
	Color Genomics[29]	Color	19	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MHL1, MSH2, MSH6, NBM, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53*
	GeneDx	Breast Cancer High/Moderate Risk Panel[21]	9	*ATM, BRCA1, BRCA2, CDH1, CHEK2, PALB2, PTEN, STK11, TP53*
		Breast/Ovarian Cancer Panel[21]	21	*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCC, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11, TP53, XRCC2*

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TABLE 4. Pros and Cons of Single/Limited Gene Testing and Multigene Panels

	Single/Limited Gene Testing	Multigene Panels
Advantages	Phenotype-directed testing Cancer risks and management options often more established Lower likelihood of detecting VUS More rapid turnaround time	More cost effective (less expensive per gene cost) More time efficient Decrease in testing fatigue for patients and providers Efficient use of single specimen Higher mutation detection rate, genes individually rare but collectively significant
Disadvantages	Higher risk of loss to follow-up during sequential testing multiple single genes (test fatigue) Less comprehensive	Increased prevalence of VUS Cancer risks and management options often not well-defined, particularly for some moderate- and low-penetrance genes Unexpected findings such as "off-phenotypic-target" gene mutation Longer turnaround time Panels may include genes that patients don't wish to test for

Abbreviation: VUS, variants of uncertain significance.

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SONUÇ

- Meme kanserinde genetik mutasyonların %50 kadarı BRCA mutasyonlarına bağlıdır
- Güçlü aile hikayesi ve fenotipe rağmen BRCA testi negatif gelen hastalarda diğer genetik mutasyonlar araştırılmalıdır
- NGS hızlı ve pratik çok sayıda gen analizine olanak sağlar
- Genetik meme kanseri olduğu düşünülen vakalarda test öncesi ve sonrası klinik yaklaşımı belirlemede genetik uzmanının değerlendirmesi hayati öneme sahiptir