SYNLAB

BRCA+16 GENES

Hereditary predisposition to breast, ovarian and endometrial cancer

SYNLAB

BRCA+16 GENES

Κληρονομική προδιάθεση για καρκίνο του μαστού, των ωοθηκών και του ενδομητρίου

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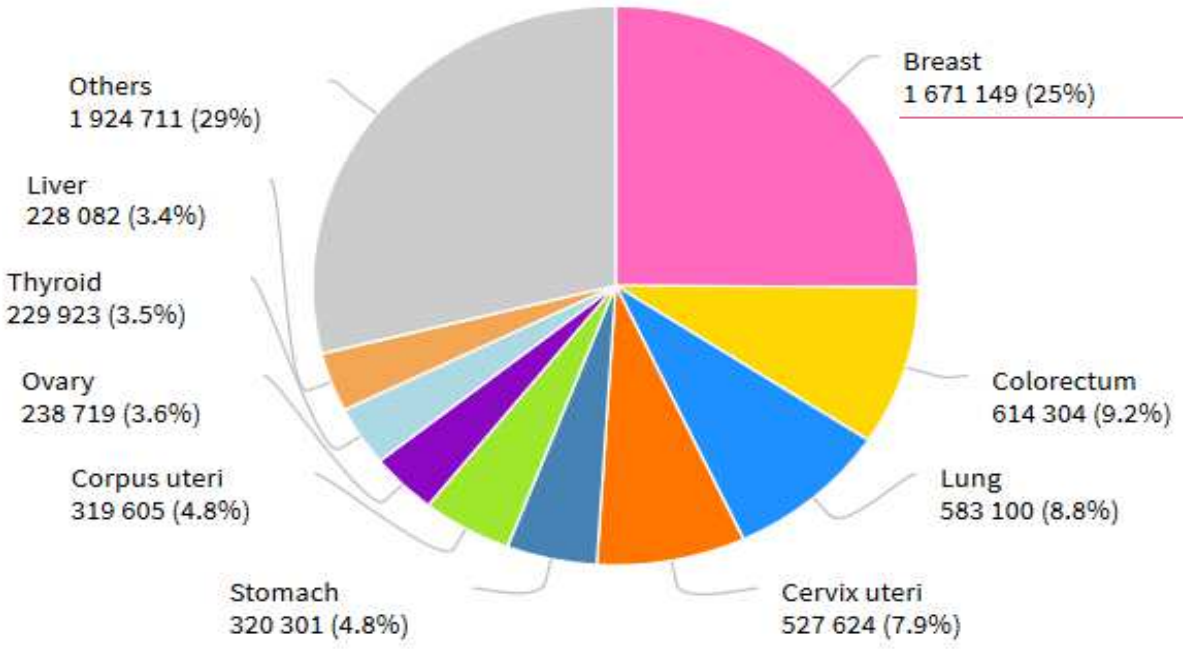
Breast and ovarian cancer

According to the International Agency for Research on Cancer:[1]

- **Breast cancer** is the most common type of cancer in women worldwide.
- It mainly affects women, although it can also affect men.



Estimated number of incident cases, females, worldwide (top 10 cancer sites) in 2012

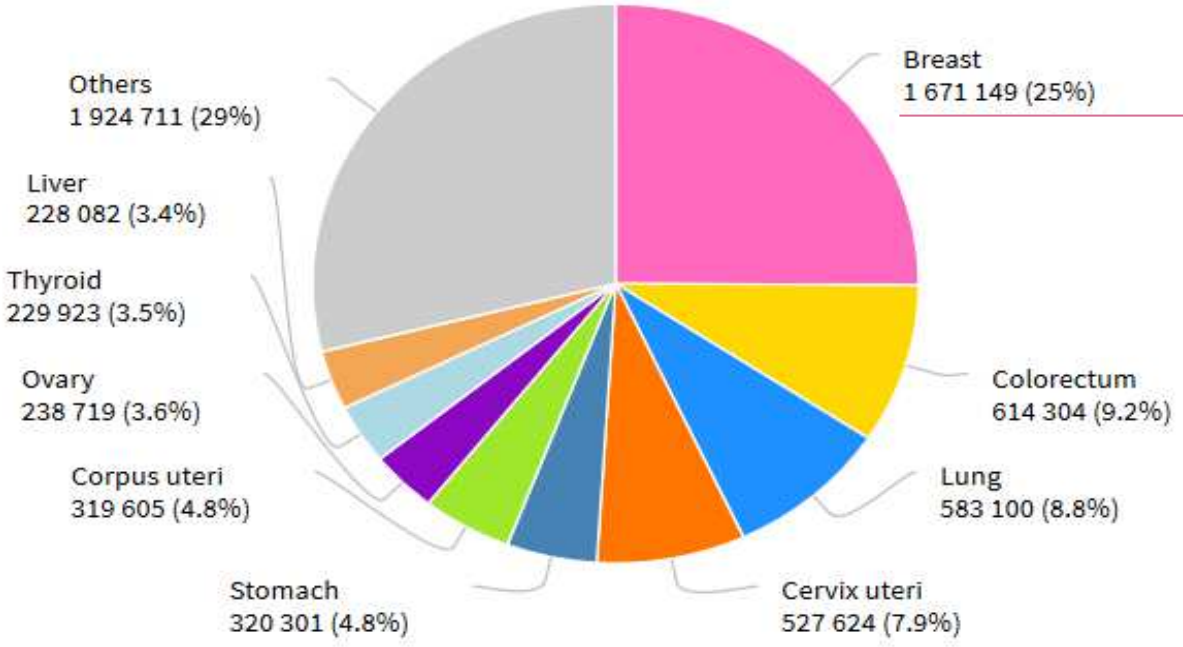
A quarter of the tumours detected in women are breast tumours.[2]

1.GLOBOCAN 2008.Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010.
2. Spanish Association Against Cancer (AECC).

Καρκίνος του μαστού και των ωοθηκών

Σύμφωνα με τη Διεθνή Υπηρεσία Έρευνας για τον Καρκίνο:[1]

- Ο **καρκίνος του μαστού** είναι ο πιο κοινός τύπος καρκίνου στις γυναίκες παγκοσμίως.
- Κυρίως επηρεάζει τις γυναίκες, όμως μπορεί επίσης να επηρεάσει και τους άντρες.



Εκτιμώμενος αριθμός περιστατικών σε γυναίκες παγκοσμίως (top 10 cancer sites) το 2012

Το ένα τέταρτο των όγκων που ανιχνεύονται στις γυναίκες είναι στο στήθος.[2]

1.GLOBOCAN 2008.Cancer Incidence and Mortality Worldwide: IARC Cancer Base No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010.
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Breast and ovarian cancer

BREAST CANCER

More than **1,600,000 new cases** are diagnosed per year worldwide.[1]

Approximately **1 in 8 women** will be diagnosed with breast cancer during their **lifetime**.[2]

5-10% of cases are **hereditary.**[3]

OVARIAN CANCER

Over **230,000 new cases** diagnosed per year worldwide.[1]

Approximately **20%** are **hereditary**.[3]

1. *Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136:E359-86.*
2. *European commission initiative on breast cancer website: http://ecibc.jrc.ec.europa.eu/recommendations/*
3. *Nielsen FC et al. Hereditary breast and ovarian cancer: new genes in confined pathways. Nature Reviews. 2016;16:599-612.*

Καρκίνος του μαστού και των ωοθηκών

ΚΑΡΚΙΝΟΣ ΤΟΥ ΜΑΣΤΟΥ

Περισσότερα από **1,600,000 νέα περιστατικά** διαγιγνώσκονται κάθε χρόνο παγκοσμίως.[1]

Περίπου **1 στις 8 γυναίκες** θα διαγνωστούν με καρκίνο του μαστού κατά τη διάρκεια της ζωής τους.[2]
5-10% των περιπτώσεων είναι **κληρονομικές.**[3]

ΚΑΡΚΙΝΟΣ ΤΩΝ ΩΟΘΗΚΩΝ

Πάνω από **230,000 νέα περιστατικά** διαγιγνώσκονται κάθε χρόνο παγκοσμίως.[1]

Περίπου **20%** των περιπτώσεων είναι **κληρονομικές**.[3]

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Breast and ovarian cancer: Risk factors

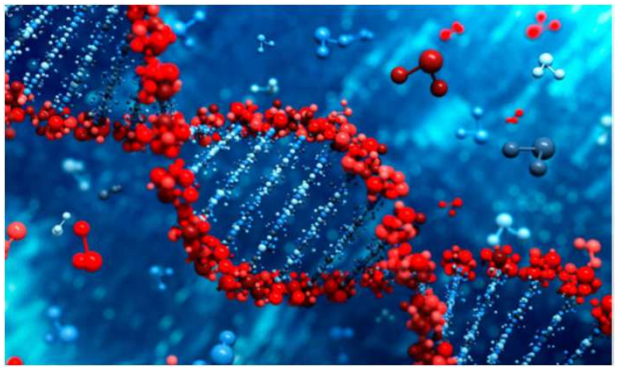
Lifestyle-related Risk Factors

- Drinking alcohol (breast)
- Being overweight or obese (both)
- Not being physically active (breast)
- Not having children (both)
- Not breastfeeding (breast)
- Birth control (breast)
- Fertility treatment (ovarian)
- Hormone therapy after menopause (both)

Risk Factors You Cannot Change

- Being a woman (both)
- Getting older (both)
- Certain inherited genes (both)
- Family cancer syndromes (both)
- Family history of breast cancer (breast)
- Personal history of breast cancer (both)
- Early menarche before age 12 (breast)
- Late menopause after age 55 (breast)

https://www.cancer.org/cancer/



Καρκίνος του μαστού και των ωοθηκών: Παράγοντες κινδύνου

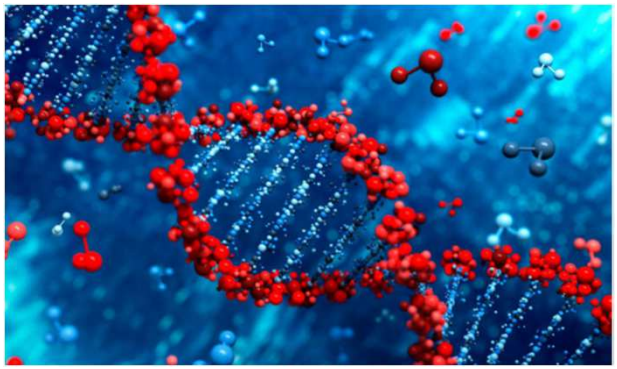
Παράγοντες κινδύνου που σχετίζονται με τον τρόπο ζωής

- Κατανάλωση αλκοόλ (μαστού)
- Παχυσαρκία (και τα δύο)
- Καμία φυσική άσκηση (μαστού)
- Χωρίς τεκνοποίηση (και τα δύο)
- Χωρίς θηλασμό (μαστού)
- Αντισύλληψη (μαστού)
- Θεραπεία γονιμότητας (ωοθηκών)
- Ορμονική θεραπεία μετά την εμμηνόπαυση (και τα δύο)

Παράγοντες κινδύνου που δεν μπορούμε να αλλάξουμε

- Όντας γυναίκα (και τα δύο)
- Μεγαλώνοντας (και τα δύο)
- Συγκεκριμένα γονίδια (και τα δύο)
- Κληρονομικά σύνδρομα καρκίνου (και τα δύο)
- Οικογενειακό ιστορικό καρκίνου του μαστού (μαστού)
- Προσωπικό ιστορικό καρκίνου του μαστού (και τα δύο)
- Πρόωρη εμμηνάρχη πριν την ηλικία των 12 (μαστού)
- Ύστερη εμμηνόπαυση μετά την ηλικία των 55 (μαστού)

https://www.cancer.org/cancer/



Breast and ovarian cancer: Hereditary cancer

- **Between 5 to 10%** of cases of **breast cancer and 20% of ovarian cancer** are associated with a **hereditary** nature.
- Characterised by its incidence at **early ages**, even before 40 years of age.
- Frequently associated to mutations in ***BRCA1*** **and** ***BRCA2*** **genes, tumour suppressor genes** involved in maintaining DNA integrity.
- There are other genes related with these cancer types that must be studied since it is estimated that only **around 25% of hereditary breast and ovarian cancer cases are due to mutations in *BRCA1* and *BRCA2* genes.**[1]

Approximately **50% of women with mutations in the *BRCA1* or *BRCA2* genes do not have a history of breast or ovarian cancer.**[2]

1. *Nielsen FC et al. Hereditary breast and ovarian cancer: new genes in confined pathways. Nature Reviews. 2016;16:599-612.*
2. *King MC, Levy-Lahad E, Lahad A. Population-Based Screening for BRCA1 and BRCA2: 2014 Lasker Award. JAMA. 2014;312(11):1091-2.*

Καρκίνος του μαστού και των ωοθηκών: Κληρονομικός καρκίνος

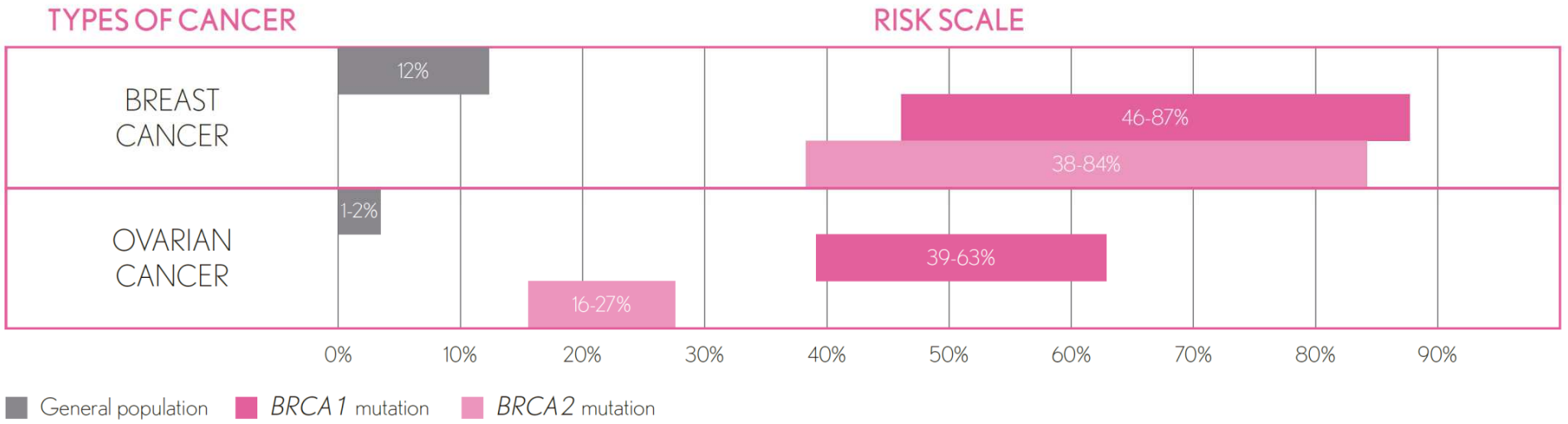
- **Μεταξύ 5 με 10%** των περιπτώσεων των **καρκίνων του μαστού και 20% των καρκίνων των ωοθηκών** είναι συσχετισμένα με **κληρονομικότητα**.
- Χαρακτηρίζονται με την εμφάνισή τους σε **νεαρές ηλικίες**, ακόμα και πριν την ηλικία των 40.
- Συχνά συσχετίζεται με μεταλλάξεις στα γονίδια ***BRCA1* και *BRCA2*, γονίδια ογκοκατασταλτικά** που εμπλέκονται στη διατήρηση της σταθερότητας του DNA.
- Υπάρχουν κι άλλα γονίδια συσχετισμένα με αυτούς τους τύπους καρκίνου που πρέπει να μελετηθούν αφού υπολογίζεται ότι μόνο ένα **25% περίπου των περιπτώσεων κληρονομικού καρκίνου του μαστού και των ωοθηκών οφείλονται σε μεταλλάξεις στα γονίδια *BRCA1* και *BRCA2*.**[1]

Γύρω στο **50% των γυναικών με μεταλλάξεις στα γονίδια *BRCA1* ή *BRCA2* δεν έχουν ιστορικό για καρκίνο του μαστού ή των ωοθηκών.**[2]

1. *Nielsen FC et al. Hereditary breast and ovarian cancer: new genes in confined pathways. Nature Reviews. 2016;16:599-612.*
2. *King MC, Levy-Lahad E, Lahad A. Population-Based Screening for BRCA1 and BRCA2: 2014 Lasker Award. JAMA. 2014;312(11):1091-2.*

Breast and ovarian cancer: Hereditary cancer

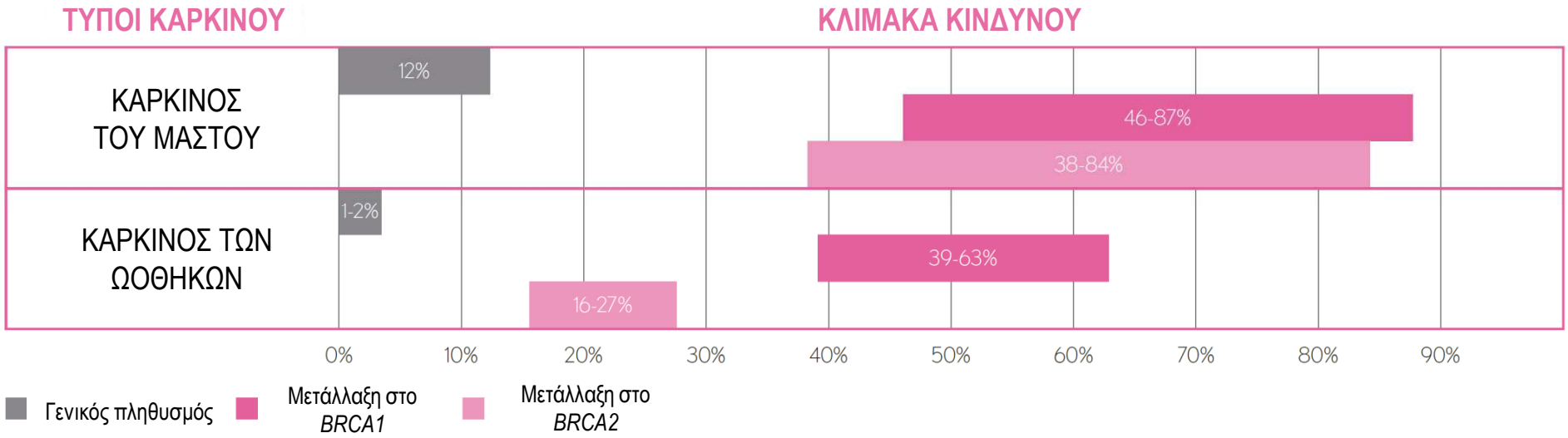
- Cumulative risk of developing breast and ovarian cancer throughout life in people with and without *BRCA1* and *BRCA2* mutations.



Modified from: Petrucelli N. et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews. Last Update: December 15, 2016. Available at: www.ncbi.nlm.nih.gov/books/NBK1247/

Καρκίνος του μαστού και των ωοθηκών: Κληρονομικός καρκίνος

- Αθροιστικός κίνδυνος ανάπτυξης καρκίνου του μαστού και των ωοθηκών κατά τη διάρκεια της ζωής ενός ανθρώπου με ή χωρίς μεταλλάξεις στα γονίδια *BRCA1* και *BRCA2*.



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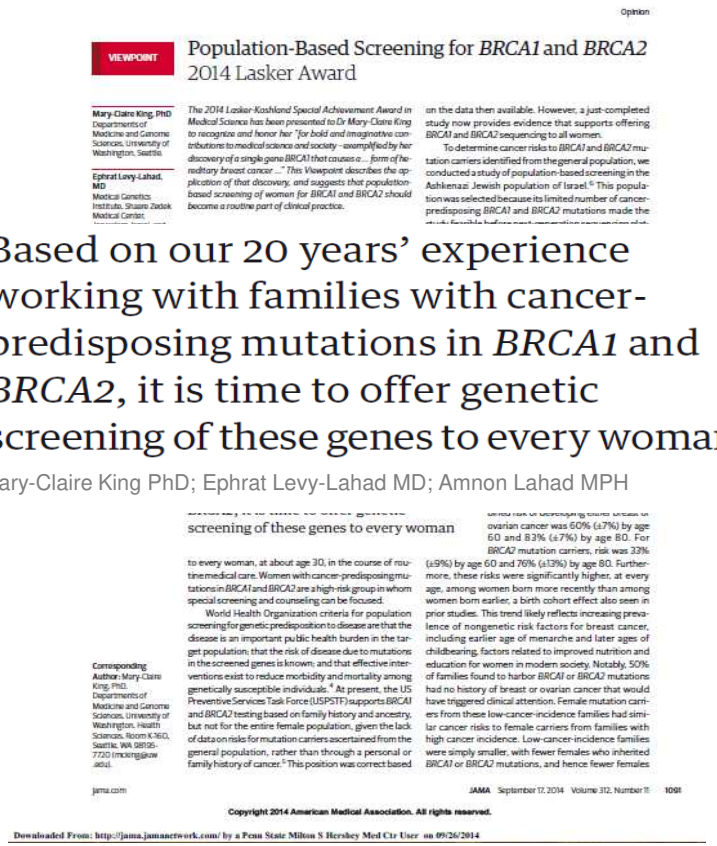
Breast and ovarian cancer: Hereditary cancer

International experts recommend the screening of *BRCA1* and *BRCA2* genes in women ≥ 30 years in the course of routine medical care.[1]



Opinion

VIEWPOINT

Population-Based Screening for *BRCA1* and *BRCA2*
2014 Lasker Award

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Departments of Medicine and Genome Sciences, University of Washington, Seattle.

Ephrat Levy-Lahad, MD
Medical Genetics Institute, Shaare Zedek Medical Center,

The 2014 Lasker-Koshland Special Achievement Award in Medical Science has been presented to Dr Mary-Claire King to recognize and honor her "for bold and imaginative contributions to medical science and society - exemplified by her discovery of a single gene BRCA1 that causes a... form of hereditary breast cancer ..." This Viewpoint describes the application of that discovery, and suggests that population-based screening of women for BRCA1 and BRCA2 should become a routine part of clinical practice.

on the data then available. However, a just-completed study now provides evidence that supports offering *BRCA1* and *BRCA2* sequencing to all women.

To determine cancer risks to *BRCA1* and *BRCA2* mutation carriers identified from the general population, we conducted a study of population-based screening in the Ashkenazi Jewish population of Israel.[5] This population was selected because its limited number of cancer-predisposing *BRCA1* and *BRCA2* mutations made the

Based on our 20 years' experience working with families with cancer-predisposing mutations in *BRCA1* and *BRCA2*, it is time to offer genetic screening of these genes to every woman

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World Health Organization criteria for population screening for genetic predisposition to disease are that the disease is an important public health burden in the target population; that the risk of disease due to mutations in the screened genes is known; and that effective interventions exist to reduce morbidity and mortality among genetically susceptible individuals.[4] At present, the US Preventive Services Task Force (USPSTF) supports *BRCA1* and *BRCA2* testing based on family history and ancestry, but not for the entire female population, given the lack of data on risks for mutation carriers ascertained from the general population, rather than through a personal or family history of cancer.[5] This position was correct based

ovarian cancer was 60% (±7%) by age 60 and 83% (±7%) by age 80. For *BRCA2* mutation carriers, risk was 33% (±9%) by age 60 and 76% (±13%) by age 80. Furthermore, these risks were significantly higher, at every age, among women born more recently than among women born earlier, a birth cohort effect also seen in prior studies. This trend likely reflects increasing prevalence of nongenetic risk factors for breast cancer, including earlier age of menarche and later ages of childbearing, factors related to improved nutrition and education for women in modern society. Notably, 50% of families found to harbor *BRCA1* or *BRCA2* mutations had no history of breast or ovarian cancer that would have triggered clinical attention. Female mutation carriers from these low-cancer-incidence families had similar cancer risks to female carriers from families with high cancer incidence. Low-cancer-incidence families were simply smaller, with fewer females who inherited *BRCA1* or *BRCA2* mutations, and hence fewer females

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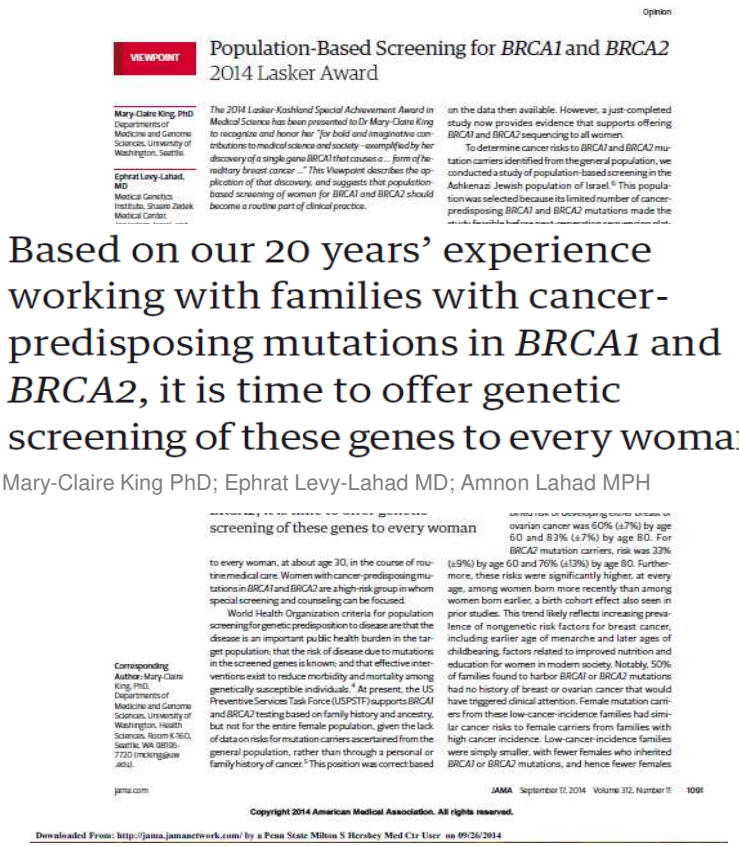

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JAMA September 17, 2014 Volume 312, Number 11 1091

Κριτήρια του **Παγκόσμιου Οργανισμού Υγείας** για γενετικό έλεγχο του πληθυσμού για προδιάθεση για ασθένειες:

- Η ασθένεια να αποτελεί **σημαντική επιβάρυνση της δημόσιας υγείας στον πληθυσμό στόχο**
- Το **ρίσκο για ασθένεια** μετά από ύπαρξη μετάλλαξης στα γονίδια που ελέγχονται να είναι **γνωστό**
- Να υπάρχουν **αποτελεσματικές παρεμβάσεις που να μειώνουν τη νοσηρότητα και τη θνησιμότητα** στα άτομα που επηρεάζονται γενετικά

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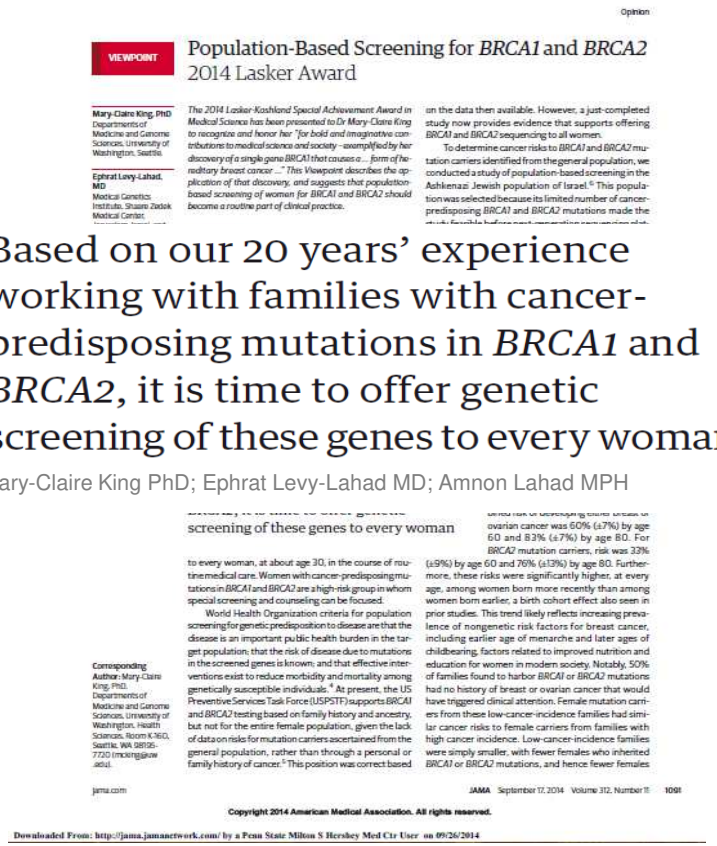

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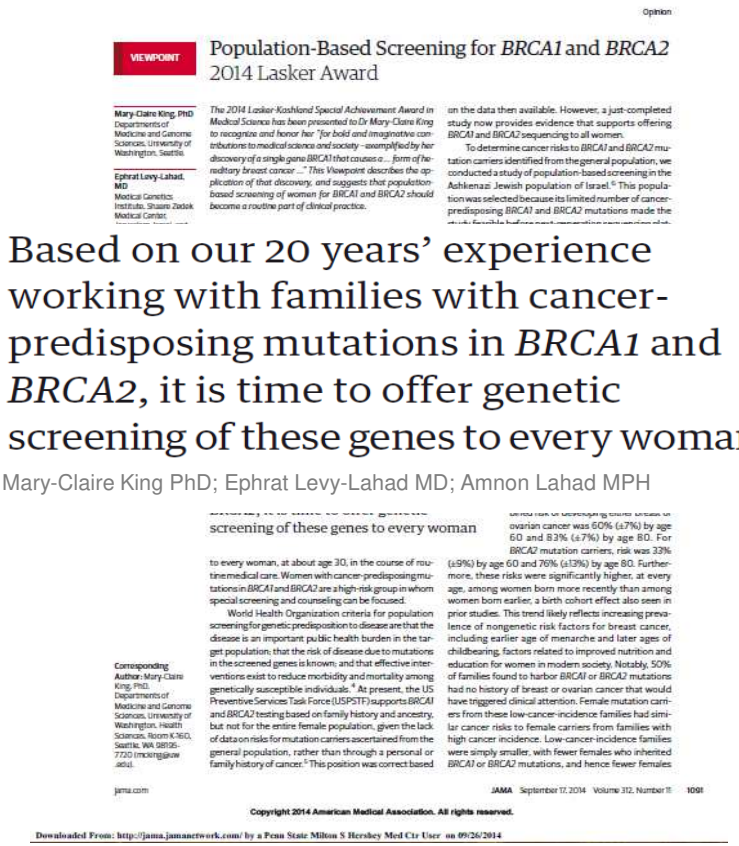
- **Low-cancer-incidence families were simply smaller**, with **fewer females who inherited *BRCA1* or *BRCA2* mutations**, and hence fewer females who developed breast or ovarian cancer. Absent population-wide screening, **women with *BRCA1* or *BRCA2* mutations from such families would not have been identified until they developed cancer.**
- As population-based screening for *BRCA1* and *BRCA2* among adult women becomes a routine part of clinical practice, **other genes are expected to be phased into the process.**

1. *King MC, Levy-Lahad E, Lahad A. Population-Based Screening for BRCA1 and BRCA2: 2014 Lasker Award. JAMA. 2014;312(11):1091-2.*

Καρκίνος του μαστού και των ωοθηκών: Κληρονομικός καρκίνος

Διεθνείς εμπειρογνώμονες συστήνουν τον έλεγχο των γονιδίων *BRCA1* και *BRCA2* σε γυναίκες ≥ 30 ετών στα πλαίσια της ρουτίνας του ιατρικού ελέγχου.[1]



Opinion

VIEWPOINT

Population-Based Screening for *BRCA1* and *BRCA2*
2014 Lasker Award

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Ephrat Levy-Lahad, MD
Medical Genetics Institute, Shaare Zedek Medical Center,

The 2014 Lasker-Koshland Special Achievement Award in Medical Science has been presented to Dr Mary-Claire King to recognize and honor her "for bold and imaginative contributions to medical science and society - exemplified by her discovery of a single gene BRCA1 that causes a... form of hereditary breast cancer ..." This Viewpoint describes the application of that discovery, and suggests that population-based screening of women for BRCA1 and BRCA2 should become a routine part of clinical practice.

Based on our 20 years' experience working with families with cancer-predisposing mutations in *BRCA1* and *BRCA2*, it is time to offer genetic screening of these genes to every woman

Mary-Claire King PhD; Ephrat Levy-Lahad MD; Amnon Lahad MPH

screening of these genes to every woman

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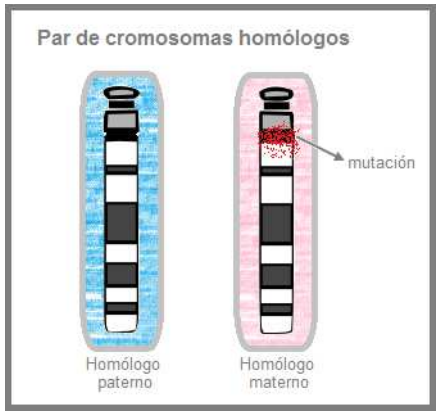
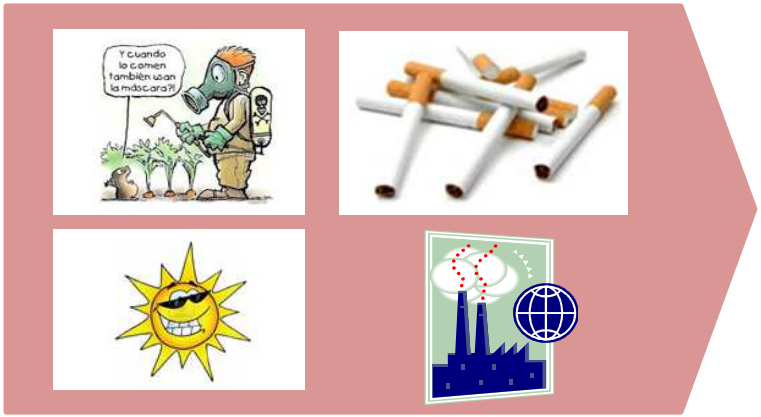
JAMA September 17, 2014 Volume 312, Number 11 1091

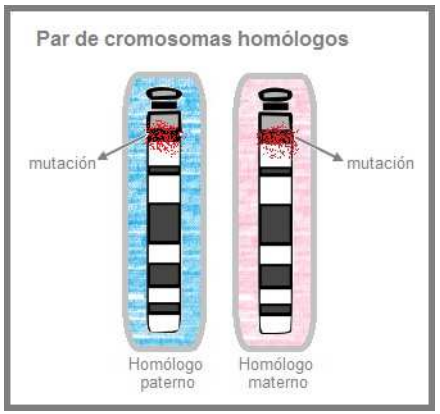
- **Οι οικογένειες με χαμηλή συχνότητα εμφάνισης καρκίνου ήταν απλώς μικρότερες,** με **λιγότερες γυναίκες να κληρονομούν μεταλλαγμένα *BRCA1* ή *BRCA2***, κι επομένως λιγότερες γυναίκες να αναπτύσσουν καρκίνο του μαστού ή των ωοθηκών. Χωρίς τον έλεγχο σε πληθυσμιακό επίπεδο, **γυναίκες με μεταλλάξεις στα γονίδια *BRCA1* ή *BRCA2* σε τέτοιες οικογένειες δεν θα ανιχνεύονται μέχρι να εμφανίσουν οι ίδιες καρκίνο.**
- Όταν ο έλεγχος σε πληθυσμιακό επίπεδο στα γονίδια *BRCA1* και *BRCA2* σε ενήλικες γυναίκες γίνει μέρος της ρουτίνας της κλινικής πρακτικής, **κι άλλα γονίδια αναμένεται να μπουν σταδιακά στη διαδικασία.**

1. *King MC, Levy-Lahad E, Lahad A. Population-Based Screening for BRCA1 and BRCA2: 2014 Lasker Award. JAMA. 2014;312(11):1091-2.*

Breast and ovarian cancer: Hereditary cancer







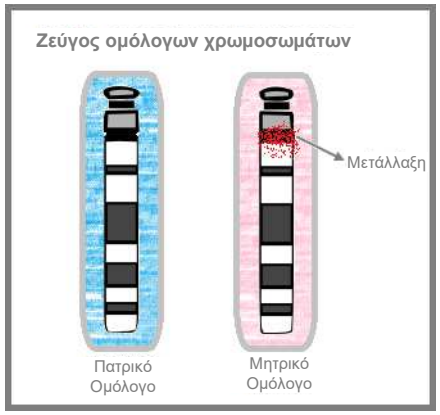
- Every individual inherits 2 copies of each gene, one from the mother and the other from the father.
- In BRCA, if we inherit altered copy, only the not affected gene will protect the cell from tumour development (heterocygous).
- People with only one altered BRCA copy have a greater predisposition to tumour development.

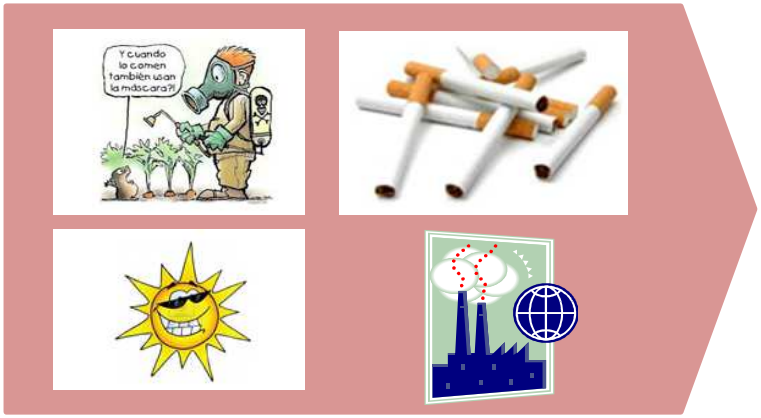
External factors are especially important in people carrying mutations since they may alter the unaffected gene

Facing the exposure to different risk factors, the no mutated gene is altered and lose its functionality

In these situations, the probability of developing a tumour is very high.

Καρκίνος του μαστού και των ωοθηκών: Κληρονομικός καρκίνος





- Ο κάθε ένας κληρονομεί 2 αντίγραφα του κάθε γονιδίου, ένα από τη μητέρα και ένα από τον πατέρα του.
- Στη περίπτωση του *BRCA*, εάν κληρονομήσουμε μεταλλαγμένο αντίγραφο, μόνο το μη επηρεασμένο αντίγραφο γονιδίου θα προστατέψει το κύτταρο από την καρκινογένεση (ετερόζυγο).
- Άτομα με μόνο ένα αντίγραφο μεταλλαγμένου *BRCA* έχουν μεγαλύτερη προδιάθεση για ανάπτυξη καρκίνου.

Οι εξωτερικοί παράγοντες είναι ιδιαίτερα σημαντικοί σε ανθρώπους που έχουν μεταλλάξεις καθώς μπορεί να τροποποιήσουν και το αντίγραφο του γονιδίου που δεν ήταν επηρεασμένο από πριν.

Με το να ερχόμαστε σε επαφή με διάφορους παράγοντες κινδύνου, το μη μεταλλαγμένο γονίδιο μπορεί να τροποποιηθεί και να χάσει τη λειτουργικότητά του.

Σε αυτές τις περιπτώσεις, η πιθανότητα να αναπτυχθεί όγκος είναι πολύ υψηλός.

- **Breast and ovarian cancer**
- **BRCA$^{+16\ GENES}$**
  - Genes panel and associated risk
  - Analysis technology
  - Recommendations from medical associations
  - Indications
  - Important considerations
  - Advantages
  - Sample collection kit
  - Test Requisition Form and Informed Consent
  - Results
  - Key points
- **Contact**

- **Καρκίνος του μαστού και των ωοθηκών**
- **BRCA$^{+16\ GENES}$**

  Πάνελ γονιδίων και το σχετικό ρίσκο

  Τεχνολογία ανάλυσης

  Συστάσεις από ιατρικούς συλλόγους

  Ενδείξεις

  Σημαντικές εκτιμήσεις

  Πλεονεκτήματα

  Πακέτο συλλογής δείγματος

  Φόρμα αίτησης και εγκεκριμένη συγκατάθεση

  Αποτελέσματα

  Βασικά σημεία

- **Επικοινωνία**

BRCA+16GENES

BRCA+16GENES TEST

BRCA1 + BRCA2 + 16 genes

ATM	BRCA1	BRCA2	BRIP1	CDH1	CHEK2
EPCAM	MLH1	MSH2	MSH6	NBN	PALB2
PMS2	PTEN	RAD51C	RAD51D	STK11	TP53

- Genes ***BRCA1***, ***BRCA2*** **+ 16 genes** associated to breast, ovarian and endometrial cancer.
- **Designed and developed by genetic SYNLAB group experts, in line with the NCCN guidelines**, including the most relevant genes for which the guidelines recommend a specific patient management.
- **NGS sequencing** (*Next Generation Sequencing*) **with paired-end reads** of the genes of the panel, which allows to detect any pathogenic mutation or variant of uncertain significance (VUS).
- **Large deletions and duplications analysis** in *BRCA1*, *BRCA2* and *EPCAM* genes through MLPA *(Multiplex Ligation Probe Amplification).*
- **Pathogenic and probably pathogenic mutations** are confirmed by **Sanger sequencing**.

NCCN: National Comprehensive Cancer Network

BRCA+16GENES

BRCA+16GENES TEST

BRCA1 + *BRCA2* + 16 γονίδια

ATM	BRCA1	BRCA2	BRIP1	CDH1	CHEK2
EPCAM	MLH1	MSH2	MSH6	NBN	PALB2
PMS2	PTEN	RAD51C	RAD51D	STK11	TP53

- Τα γονίδια ***BRCA1*, *BRCA2* + 16 γονίδια** συσχετίζονται με καρκίνους του μαστού, των ωοθηκών και του ενδομητρίου.
- **Σχεδιάστηκε και αναπτύχθηκε από ομάδα εμπειρογνωμόνων γενετιστών της SYNLAB, σύμφωνα με τις κατευθυντήριες γραμμές της NCCN**, περιλαμβάνοντας τα πιο σχετικά γονίδια για τα οποία οι κατευθυντήριες οδηγίες συνιστούν ειδική διαχείριση για τους ασθενείς.
- **Αλληλούχηση NGS** (*Next Generation Sequencing*) **με paired-end reads** για τα γονίδια του πάνελ, που επιτρέπει την ανίχνευση οποιασδήποτε παθογόνας μετάλλαξης ή αλλαγής με αβέβαιη σημαντικότητα (VUS).
- **Ανάλυση μεγάλων διαγραφών και διπλασιασμών** στα γονίδια *BRCA1*, *BRCA2* και *EPCAM* με τη μέθοδο MLPA *(Multiplex Ligation Probe Amplification).*
- **Παθογόνες και πιθανώς παθογόνες μεταλλάξεις** επιβεβαιώνονται με **αλληλούχιση κατά Sanger**.

NCCN: National Comprehensive Cancer Network

BRCA+16GENES

- The genes included in **BRCA+16 GENES** are involved in **cell cycle control and DNA repair** during cell division.
- Mutations in these genes lead to a **loss of cell control and capacity for DNA repair**, which may implies a greater risk of developing cancer than the general population.
- Abnormalities in the genes included in the **BRCA+16 GENES** panel represent an **increased risk of suffering from hereditary breast, ovarian and endometrial cancer**.

ANALYTIC PERFORMANCE

SENSITIVITY	SPECIFICITY	MINIMUM COVERAGE
99%	>96%	20x

BRCA+16GENES

- Τα γονίδια που περιλαμβάνονται στο **BRCA**+16 GENES συσχετίζονται στον **έλεγχο του κυτταρικού κύκλου και στην επιδιόρθωση του DNA** κατά την κυτταρική διαίρεση.
- Μεταλλάξεις σε αυτά τα γονίδια οδηγούν στην **απώλεια του ελέγχου του κυτταρικού κύκλου και της ιδιότητας για επιδιόρθωση του DNA**, το οποίο μπορεί να επιφέρει μεγαλύτερο ρίσκο για ανάπτυξη καρκίνου σε σχέση με τον γενικό πληθυσμό.
- Ανωμαλίες στα γονίδια που περιλαμβάνονται στο πάνελ του **BRCA**+16 GENES αντιπροσωπεύουν τον **αυξημένο κίνδυνο να υποφέρει κάποιος από κληρονομικό καρκίνο του μαστού, των ωοθηκών και του ενδομητρίου.**

ΑΝΑΛΥΤΙΚΗ ΑΠΟΔΟΣΗ

ΕΥΑΙΣΘΗΣΙΑ	ΕΙΔΙΚΟΤΗΤΑ	ΕΛΑΧΙΣΤΗ ΚΑΛΥΨΗ
99%	>96%	20x

BRCA+16GENES: Gene panel and associated risk

HIGH RISK GENES	LIFETIME RISK	OTHER CANCERS
BRCA1	38-84% breast cancer	Ovarian, prostate, pancreas
BRCA2	38-84% breast cancer	Ovarian, prostate, pancreas
TP53 (Li Fraumeni syndrome)	≤79% breast cancer	Gastric, sarcoma, brain tumor
PTEN (Cowden syndrome)	25-50% breast cancer	Melanoma, prostate, endometrium
CDH1 (Hereditary diffuse gastric cancer)	39-52% breast cancer	Gastric
STK11 (Peutz-Jeghers syndrome)	32-54% breast cancer	Pancreas, gastrointestinal, sex cord–gonadal stromal tumour

MODERATE RISK GENES	LIFETIME RISK	OTHER CANCERS
PALB2	44% breast cancer	Pancreas
CHEK2	32% breast cancer	Pancreas, lung
ATM	30% breast cancer	Pancreas
NBN	30% breast cancer	Ovarian

BRCA+16GENES: Πάνελ γονιδίων και συσχετισμένο ρίσκο

ΓΟΝΙΔΙΑ ΥΨΗΛΟΥ ΚΙΝΔΥΝΟΥ	ΚΙΝΔΥΝΟΣ	ΑΛΛΟΙ ΚΑΡΚΙΝΟΙ
BRCA1	38-84% καρκίνος του μαστού	Ωοθηκών, προστάτη, παγκρέατος
BRCA2	38-84% καρκίνος του μαστού	Ωοθηκών, προστάτη, παγκρέατος
TP53 (Li Fraumeni syndrome)	≤79% καρκίνος του μαστού	Γαστρικός, σάρκωμα, καρκίνος του εγκεφάλου
PTEN (Cowden syndrome)	25-50% καρκίνος του μαστού	Μελάνωμα, προστάτη, ενδομητρίου
CDH1 (Hereditary diffuse gastric cancer)	39-52% καρκίνος του μαστού	Γαστρικός
STK11 (Peutz-Jeghers syndrome)	32-54% καρκίνος του μαστού	Παγκρέατος, γαστρεντερικός, sex cord–gonadal stromal tumour

ΓΟΝΙΔΙΑ ΜΕΤΡΙΟΥ ΚΙΝΔΥΝΟΥ	ΚΙΝΔΥΝΟΣ	ΑΛΛΟΙ ΚΑΡΚΙΝΟΙ
PALB2	44% καρκίνος του μαστού	Παγκρέατος
CHEK2	32% καρκίνος του μαστού	Παγκρέατος, πνεύμονα
ATM	30% καρκίνος του μαστού	Παγκρέατος
NBN	30% καρκίνος του μαστού	Ωοθηκών

BRCA+16GENES: Gene panel and associated risk

REPAIR GENES	LIFETIME RISK	OTHER CANCERS
RAD51C	6,1% ovarian cancer	Breast
RAD51D	13,5% ovarian cancer	Breast
BRIP1	4-12% ovarian cancer	Breast

LYNCH SYNDROME	LIFETIME RISK	OTHER CANCERS
MLH1, MSH2, MSH6, PMS2, EPCAM	4-12% ovarian cancer	Colorectal
	16-60% endometrial cancer	

REFERENCES

1. *Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med. 2015;372(23):2243-57*
2. *Kurian AW, Hare EE, Mills MA, et al. Clinical evaluation of a multiple-gene sequencing panel for hereditary cancer risk assessment. J Clin Oncol. 2014;32(19):2001-9.*
3. *Tung N, Domchek SM, Stadler Z. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol. 2016;13(9):581-8.*
4. *Giardiello FM, Brensinger JD, Tersmette AC, et al. Very High Risk of Cancer in Familial Peutz-Jeghers Syndrome. GASTROENTEROLOGY 2000;119:1447–1453.*
5. *Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut. 2017. doi: 10.1136/gutjnl-2017-314057.*
6. *Petrucelli N. et al. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. GeneReviews. Last Update: December 15, 2016. Available at: www.ncbi.nlm.nih.gov/books/NBK1247*
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8. *OMIM databes: Online Mendelian Inheritance in Man® An Online Catalog of Human Genes and Genetic Disorders - https://www.omim.org/*

BRCA+16GENES: Πάνελ γονιδίων και συσχετισμένο ρίσκο

ΕΠΙΔΙΟΡΘΩΤΙΚΑ ΓΟΝΙΔΙΑ	ΚΙΝΔΥΝΟΣ	ΑΛΛΟΙ ΚΑΡΚΙΝΟΙ
RAD51C	6,1% καρκίνος των ωοθηκών	Μαστού
RAD51D	13,5% καρκίνος των ωοθηκών	Μαστού
BRIP1	4-12% καρκίνος των ωοθηκών	Μαστού

LYNCH SYNDROME	ΚΙΝΔΥΝΟΣ	ΑΛΛΟΙ ΚΑΡΚΙΝΟΙ
MLH1, MSH2, MSH6, PMS2, EPCAM	4-12% καρκίνος των ωοθηκών	Παχέος εντέρου
	16-60% καρκίνος του ενδομητρίου	

REFERENCES
1. *Easton DF, Pharoah PD, Antoniou AC, et al. Gene-panel sequencing and the prediction of breast-cancer risk. N Engl J Med. 2015;372(23):2243-57*
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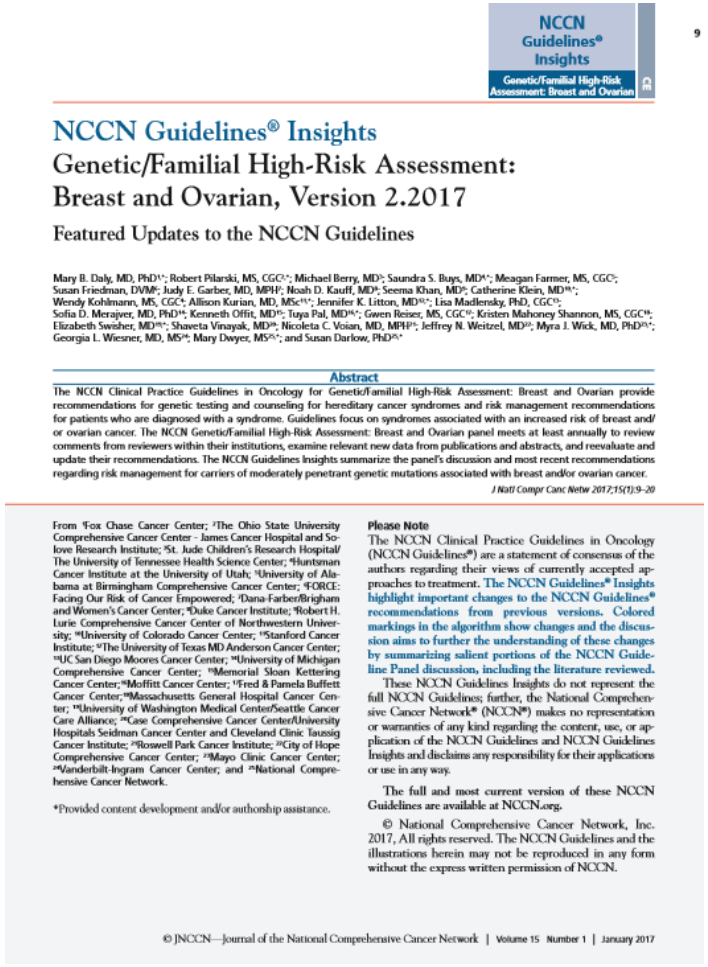
BRCA+16GENES: International Guidelines



NCCN Guidelines® Insights
Genetic/Familial High-Risk Assessment: Breast and Ovarian

9

NCCN Guidelines® Insights
Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017
Featured Updates to the NCCN Guidelines

Mary B. Daly, MD, PhD[1,*]; Robert Pilarski, MS, CGC[2,*]; Michael Berry, MD[3]; Saundra S. Buys, MD[4,*]; Meagan Farmer, MS, CGC[5]; Susan Friedman, DVM[6]; Judy E. Garber, MD, MPH[7]; Noah D. Kauff, MD[8]; Seema Khan, MD[9]; Catherine Klein, MD[10,*]; Wendy Kohlmann, MS, CGC[4]; Allison Kurian, MD, MSc[11,*]; Jennifer K. Litton, MD[12,*]; Lisa Madlensky, PhD, CGC[13]; Sofia D. Merajver, MD, PhD[14]; Kenneth Offit, MD[15]; Tuya Pal, MD[16,*]; Gwen Reiser, MS, CGC[17]; Kristen Mahoney Shannon, MS, CGC[18]; Elizabeth Swisher, MD[19,*]; Shaveta Vinayak, MD[20]; Nicoleta C. Voian, MD, MPH[21]; Jeffrey N. Weitzel, MD[22]; Myra J. Wick, MD, PhD[23,*]; Georgia L. Wiesner, MD, MS[24]; Mary Dwyer, MS[25,*]; and Susan Darlow, PhD[25,*]

Abstract

The NCCN Clinical Practice Guidelines in Oncology for Genetic/Familial High-Risk Assessment: Breast and Ovarian provide recommendations for genetic testing and counseling for hereditary cancer syndromes and risk management recommendations for patients who are diagnosed with a syndrome. Guidelines focus on syndromes associated with an increased risk of breast and/or ovarian cancer. The NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian panel meets at least annually to review comments from reviewers within their institutions, examine relevant new data from publications and abstracts, and reevaluate and update their recommendations. The NCCN Guidelines Insights summarize the panel's discussion and most recent recommendations regarding risk management for carriers of moderately penetrant genetic mutations associated with breast and/or ovarian cancer.

J Natl Compr Canc Netw 2017;15(1):9–20

From [1]Fox Chase Cancer Center; [2]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [3]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [4]Huntsman Cancer Institute at the University of Utah; [5]University of Alabama at Birmingham Comprehensive Cancer Center; [6]FORCE: Facing Our Risk of Cancer Empowered; [7]Dana-Farber/Brigham and Women's Cancer Center; [8]Duke Cancer Institute; [9]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [10]University of Colorado Cancer Center; [11]Stanford Cancer Institute; [12]The University of Texas MD Anderson Cancer Center; [13]UC San Diego Moores Cancer Center; [14]University of Michigan Comprehensive Cancer Center; [15]Memorial Sloan Kettering Cancer Center; [16]Moffitt Cancer Center; [17]Fred & Pamela Buffett Cancer Center; [18]Massachusetts General Hospital Cancer Center; [19]University of Washington Medical Center/Seattle Cancer Care Alliance; [20]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [21]Roswell Park Cancer Institute; [22]City of Hope Comprehensive Cancer Center; [23]Mayo Clinic Cancer Center; [24]Vanderbilt-Ingram Cancer Center; and [25]National Comprehensive Cancer Network.

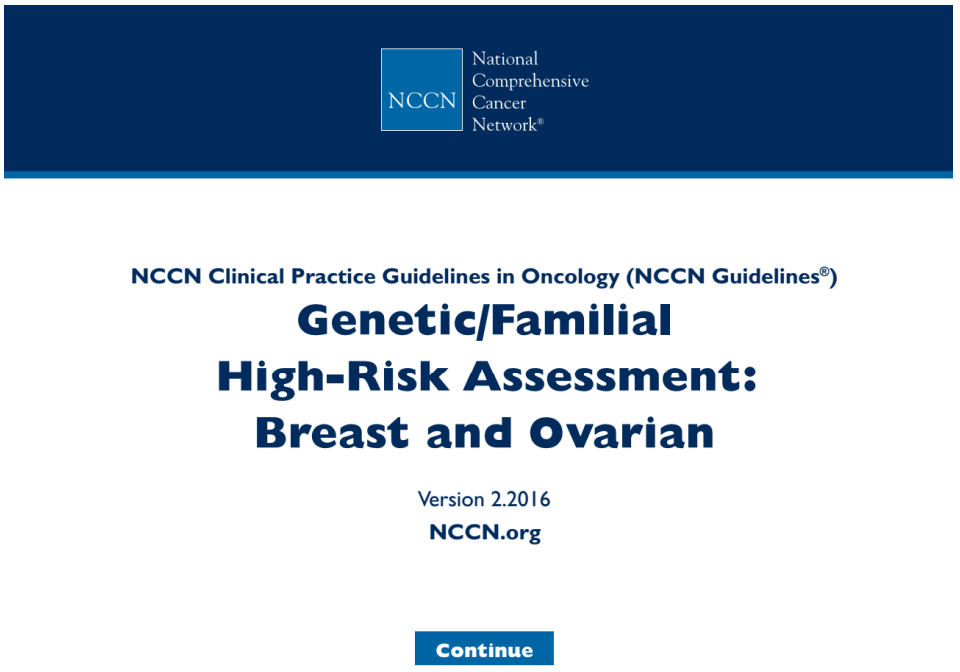
*Provided content development and/or authorship assistance.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes to the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the NCCN Guideline Panel discussion, including the literature reviewed.**

These NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding the content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their applications or use in any way.

The full and most current version of these NCCN Guidelines are available at NCCN.org.



NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast and Ovarian

Version 2.2016
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BRCA+16GENES: Διεθνείς κατευθυντήριες γραμμές

NCCN Guidelines® Insights
Genetic/Familial High-Risk Assessment: Breast and Ovarian

9

NCCN Guidelines® Insights
Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017

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Mary B. Daly, MD, PhD[1,*]; Robert Pilarski, MS, CGC[2,*]; Michael Berry, MD[3]; Saundra S. Buys, MD[4,*]; Meagan Farmer, MS, CGC[5]; Susan Friedman, DVM[6]; Judy E. Garber, MD, MPH[7]; Noah D. Kauff, MD[8]; Seema Khan, MD[9]; Catherine Klein, MD[10,*]; Wendy Kohlmann, MS, CGC[4]; Allison Kurian, MD, MSc[11,*]; Jennifer K. Litton, MD[12,*]; Lisa Madlensky, PhD, CGC[13]; Sofia D. Merajver, MD, PhD[14]; Kenneth Offit, MD[15]; Tuya Pal, MD[16,*]; Gwen Reiser, MS, CGC[17]; Kristen Mahoney Shannon, MS, CGC[18]; Elizabeth Swisher, MD[19,*]; Shaveta Vinayak, MD[20]; Nicoleta C. Voian, MD, MPH[21]; Jeffrey N. Weitzel, MD[22]; Myra J. Wick, MD, PhD[23,*]; Georgia L. Wiesner, MD, MS[24]; Mary Dwyer, MS[25,*]; and Susan Darlow, PhD[25,*]

Abstract

The NCCN Clinical Practice Guidelines in Oncology for Genetic/Familial High-Risk Assessment: Breast and Ovarian provide recommendations for genetic testing and counseling for hereditary cancer syndromes and risk management recommendations for patients who are diagnosed with a syndrome. Guidelines focus on syndromes associated with an increased risk of breast and/or ovarian cancer. The NCCN Genetic/Familial High-Risk Assessment: Breast and Ovarian panel meets at least annually to review comments from reviewers within their institutions, examine relevant new data from publications and abstracts, and reevaluate and update their recommendations. The NCCN Guidelines Insights summarize the panel's discussion and most recent recommendations regarding risk management for carriers of moderately penetrant genetic mutations associated with breast and/or ovarian cancer.

J Natl Compr Canc Netw 2017;15(1):9–20

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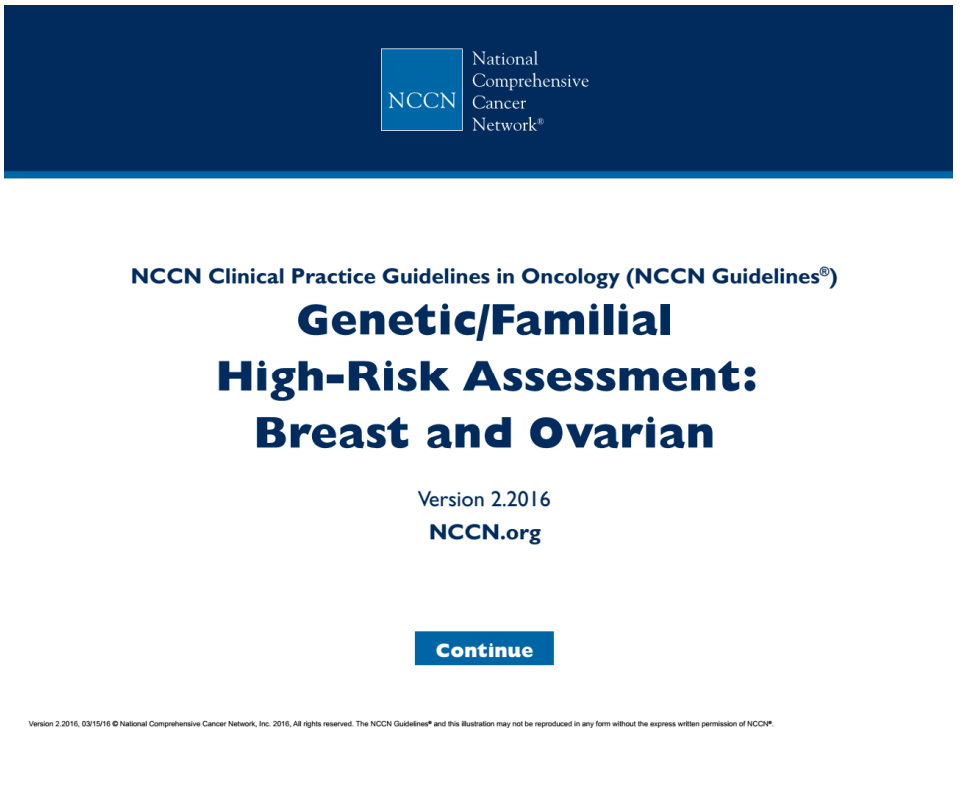
*Provided content development and/or authorship assistance.

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines® Insights highlight important changes to the NCCN Guidelines® recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the NCCN Guideline Panel discussion, including the literature reviewed.**

These NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding the content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their applications or use in any way.

The full and most current version of these NCCN Guidelines are available at NCCN.org.



NCCN National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Genetic/Familial High-Risk Assessment: Breast and Ovarian

Version 2.2016
NCCN.org

Continue

BRCA+16GENES: International Guidelines

Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017

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 and consider breast MRI with contrast starting at age 40 y[c] • RRM: Consider 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. The 7271T>G missense mutation may act in a dominant–negative fashion, resulting in a lifetime breast cancer risk as high as 60% by age 80 (which is higher than truncating mutations, where risks are in the range of 30-40%). 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 and consider breast MRI with contrast starting at age 30 y[c] • RRM: Consider based on family history	**No increased risk of OC**	Diffuse gastric cancer • See NCCN Guidelines for Gastric Cancer

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

[a]Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, Offit K, Robson ME. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol 2016;13:581-588.
[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, or RRM: BARD1, FANCC, MRE11A, MUTYH heterozygotes, REQL, RAD50, RET1, SLX4, SMARCA4, or XRCC2.
[c]May be modified based on family history or specific gene mutation.

Continued

BRCA+16GENES: Διεθνείς κατευθυντήριες γραμμές

Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017

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

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Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of BC** • Screening: Annual mammogram and consider breast MRI with contrast starting at age 40 y[c] • RRM: Consider based on family history	**No increased risk of OC**	Unknown or insufficient evidence for pancreas or prostate cancer
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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.		
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[c]May be modified based on family history or specific gene mutation.

Continued

BRCA+16GENES: International Guidelines

Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017

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

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
CHEK2	**Increased risk of BC** • Screening: Annual mammogram and consider breast MRI with contrast age 40 y[c] • RRM: Evidence insufficient, manage based on family history.	**No increased risk of OC**	Colon • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comments: Risk data are based only on frameshift mutations. The risks for most missense mutations are unclear.		
MSH2, MLH1, MSH6, PMS2, EPCAM	**Unknown or insufficient evidence for BC risk[d]** • Manage based on family history	**Increased risk of OC** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
NBN	**Increased risk of BC** • Screening: Annual mammogram and consider breast MRI with contrast age 40 y[c] • RRM: Evidence insufficient, manage based on family history	**Unknown or insufficient evidence for OC risk**	Unknown or insufficient evidence
	Comments: Management recommendations are based on data derived from the 657del5 Slavic truncating mutation. Although risks for other mutations have not been established it is prudent to manage patients with other truncating mutations similarly to those with 675del5. Counsel for risk of autosomal recessive condition in children.		
NF1	**Increased risk of BC** • Screening: Annual mammogram starting at age 30 y and consider breast MRI with contrast from ages 30–50 y • RRM: Evidence insufficient, manage based on family history.	**No increased risk of OC**	• Malignant peripheral nerve sheath tumors, GIST, others • Recommend referral to NF specialist for evaluation and management.
	Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y.		

[a]Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, Offit K, Robson ME. Counselling framework for moderate-penetrance cancer-susceptibility mutations. Nat Rev Clin Oncol 2016;13:581-588.
[c]May be modified based on family history or specific gene mutation.
[d]There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations.

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

Continued

BRCA+16GENES: Διεθνείς κατευθυντήριες γραμμές

Genetic/Familial High-Risk Assessment: Breast and Ovarian, Version 2.2017

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

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Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
CHEK2	**Increased risk of BC** • Screening: Annual mammogram and consider breast MRI with contrast age 40 y[c] • RRM: Evidence insufficient, manage based on family history.	**No increased risk of OC**	Colon • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comments: Risk data are based only on frameshift mutations. The risks for most missense mutations are unclear.		
MSH2, MLH1, MSH6, PMS2, EPCAM	**Unknown or insufficient evidence for BC risk[d]** • Manage based on family history	**Increased risk of OC** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
NBN	**Increased risk of BC** • Screening: Annual mammogram and consider breast MRI with contrast age 40 y[c] • RRM: Evidence insufficient, manage based on family history	**Unknown or insufficient evidence for OC risk**	Unknown or insufficient evidence
	Comments: Management recommendations are based on data derived from the 657del5 Slavic truncating mutation. Although risks for other mutations have not been established it is prudent to manage patients with other truncating mutations similarly to those with 675del5. Counsel for risk of autosomal recessive condition in children.		
NF1	**Increased risk of BC** • Screening: Annual mammogram starting at age 30 y and consider breast MRI with contrast from ages 30–50 y • RRM: Evidence insufficient, manage based on family history.	**No increased risk of OC**	• Malignant peripheral nerve sheath tumors, GIST, others • Recommend referral to NF specialist for evaluation and management.
	Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y.		

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

Continued

BRCA+16GENES: BRCA mutation patient management

BRCA mutations

1. Breast awareness starting at age **18 y**.
2. Clinical breast exam, every 6–12 mo, starting at age **25** y.
3. Breast screening
   - Age **25–29** y, annual breast MRI screening (preferred) or mammogram if MRI is unavailable or individualized based on family history if a breast cancer diagnosis before age 30 is present.
   - Age **30–75** y, annual mammogram and breast MRI screening.
   - Age **>75** y, management should be considered on an individual basis.
4. For women with a BRCA mutation who are treated for breast cancer, screening of remaining breast tissue with annual mammography and breast MRI should continue.
5. Discuss option of risk-reducing mastectomy. Counselling may include a discussion regarding degree of protection, reconstruction options, and risks.
6. Recommend risk-reducing salpingo-oophorectomy (RRSO), typically between 35 and 40 y, and upon completion of child bearing. Because ovarian cancer onset in patients with *BRCA2* mutations is an average of 8–10 years later than in patients with *BRCA1* mutations, it is reasonable to delay RRSO until age 40–45 y in patients with *BRCA2* mutations who have already maximized their breast cancer prevention (i.e., undergone bilateral mastectomy).

CDH1 mutations

Germline mutations in *CDH1* have reported a **cumulative lifetime risk for breast cancer of 39% to 52%** NCCN recommends **screening with annual mammogram** (or consideration of breast MRI) **beginning at age 30 years**. Screening may be considered earlier in patients with a family history of early-onset breast cancer. The option of **risk-reducing mastectomy should be discussed for these carriers.**

BRCA+16GENES: Μεταλλάξεις στα *BRCA* και διαχείριση των ασθενών

Μεταλλάξεις στα *BRCA*

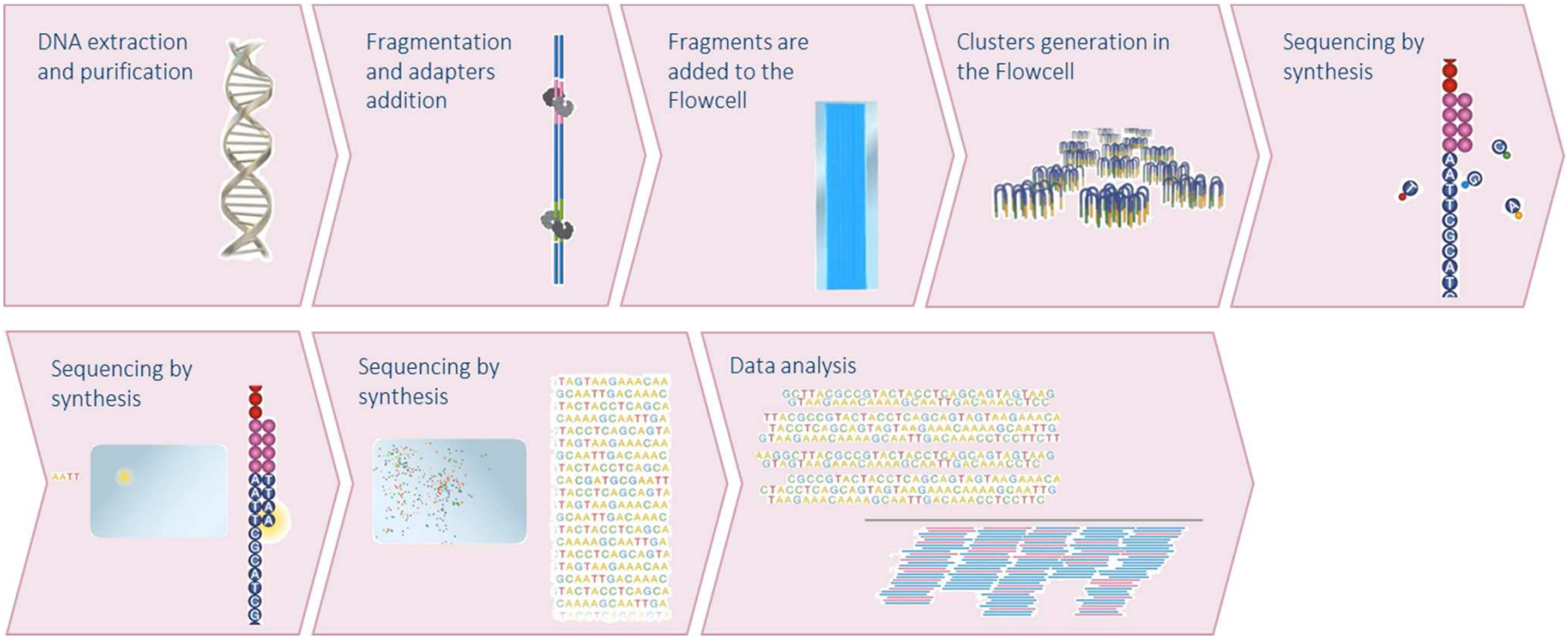
1. Ενημέρωση για τον καρκίνο του μαστού ξεκινά από την **ηλικία των 18**.
2. Κλινική εξέταση μαστού, κάθε 6-12 μήνες, ξεκινώντας από την **ηλικία των 25**.
3. Εξέταση μαστού
   - Στην ηλικία των **25–29**, το ετήσιο MRI screening του μαστού ή η μαστογραφία εάν το MRI δεν είναι διαθέσιμο ή εξατομικευμένο βασισμένο στο οικογενειακό ιστορικό, να γίνεται εάν υπάρχει διάγνωση καρκίνου του μαστού πριν τα 30.
   - Στην ηλικία των **30–75**, να γίνεται ετήσια μαστογραφία και MRI screening μαστού.
   - Σε ηλικίες **>75**, η διαχείριση θα πρέπει να εξετάζεται σε ατομική βάση.
4. Για γυναίκες με μετάλλαξη στα *BRCA* που θεραπεύονται από καρκίνο του μαστού, έλεγχος του εναπομείναντα ιστού του μαστού με ετήσια μαστογραφία και MRI μαστού πρέπει να συνεχίσουν.
5. Συζήτηση της επιλογής για μαστεκτομή ώστε να μειωθεί το ρίσκο. Η συμβουλευτική μπορεί να περιλαμβάνει συζήτηση σχετικά με το βαθμό προστασίας, τις επιλογές ανασυγκρότησης και τους κινδύνους.
6. Πρόταση για σαλπιδο-ωοθηκεκτομή (RRSO) ώστε να μειωθεί ο κίνδυνος, συνήθως μεταξύ των ηλικιών 35 και 40, και μετά την ολοκλήρωση της τεκνοποίησης. Λόγω του ότι ο καρκίνος των ωοθηκών σε ασθενείς με μεταλλάξεις στο *BRCA2* ξεκινά κατά μέσο όρο 8–10 χρόνια αργότερα σε σχέση με ασθενείς με μεταλλάξεις στο *BRCA1.* Είναι εύλογο να καθυστερήσει το RRSO μέχρι την ηλικία των 40–45 σε ασθενείς με μεταλλάξεις στο *BRCA2* που έχουν ήδη μεγιστοποιήσει την προφύλαξή τους για καρκίνο του μαστού (π.χ. έχουν υποβληθεί σε διμερή μαστεκτομή).

Μεταλλάξεις στο *CDH1*

Γαμετικές μεταλλάξεις στο *CDH1* έχουν αναφερθεί να προκαλούν **συσσωρευτικό κίνδυνο καθ' όλη τη διάρκεια της ζωής για καρκίνο του μαστού σε ποσοστό 39% με 52%**. Το NCCN συστήνει **έλεγχο με ετήσια μαστογραφία** (ή εξέταση MRI μαστού) **ξεκινώντας από την ηλικία των 30 ετών**. Ο έλεγχος μπορεί να ξεκινήσει πιο γρήγορα σε ασθενείς με οικογενειακό ιστορικό καρκίνου του μαστού πρώιμης έναρξης. Η επιλογή για **μαστεκτομή για μείωση του κινδύνου θα πρέπει να συζητηθεί για αυτούς τους φορείς**.

BRCA+16GENES: Analysis technology

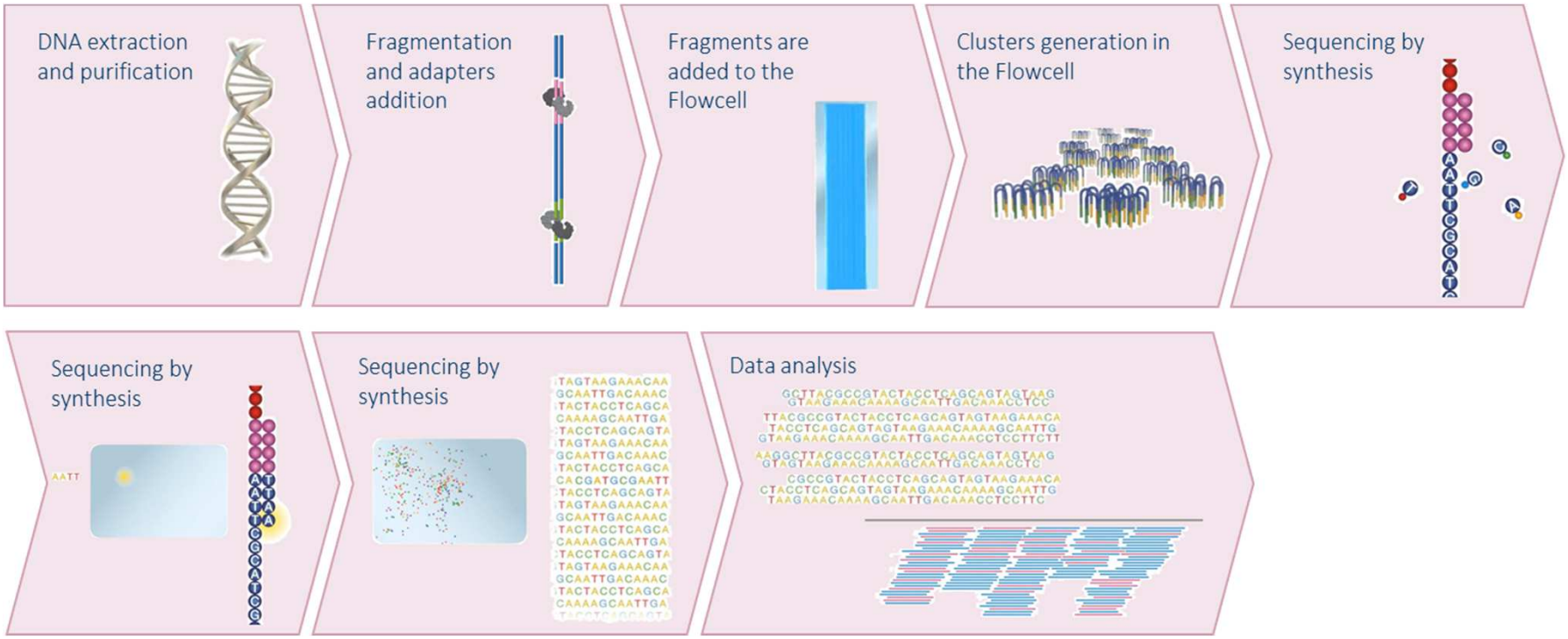
Next-generation sequencing (NGS) with paired-end reads



- The sequencing process consists of several steps. First, samples must be prepared for sequencing. To do this, DNA is extracted, purified and fragmented, and adaptors are added.
- The sample is placed on a glass slide called a flow cell, which acts as a working surface. The surface of the flow cell features additional probes with adapters added to the DNA so that the sample may be fixed to the surface. Next, sequencing by synthesis begins. This process generates large amounts of information, which will be analysed using a sophisticated software system.

BRCA+16GENES: Τεχνολογία ανάλυσης

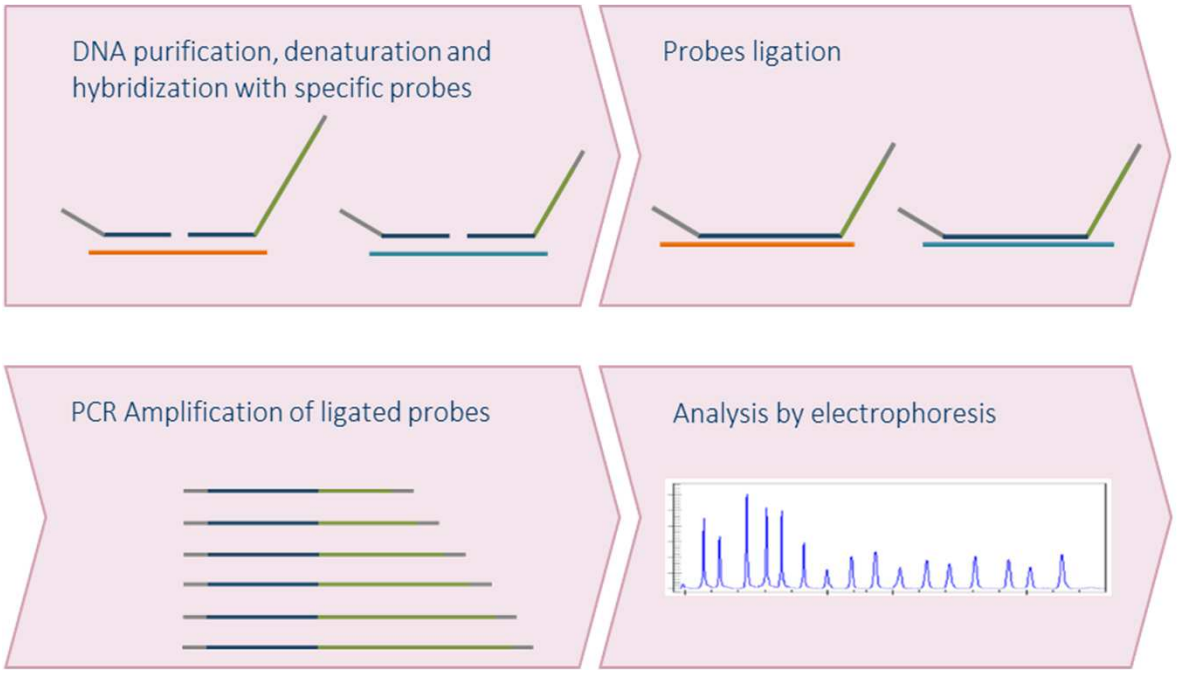
Next-generation sequencing (NGS) με paired-end reads



- Η διαδικασία αλληλούχισης αποτελείται από διάφορα βήματα. Αρχικά, τα δείγματα πρέπει να προετοιμαστούν για την αλληλούχιση. Για να γίνει αυτό, το DNA εξάγεται, καθαρίζεται, κομματιάζεται και προστίθενται ποσαρμοστές.
- Το δείγμα τοποθετείται σε γυάλινο πλακίδιο που ονομάζεται flow cell και λειτουργεί σαν επιφάνεια εργασίας. Η επιφάνεια του flow cell διαθέτει επιπρόσθετους ανιχνευτές με προσαρμοστές που ενώνονται με το DNA ώστε το δείγμα να σταθεροποιηθεί στη επιφάνεια. Ακολούθως, η αλληλούχιση με τη σύνθεση ξεκινά. Αυτή η διαδικασία δημιουργεί μεγάλο φορτίο πληροφοριας, που θα αναλυθεί με τη χρήση εξελιγμένου συστήματος λογισμικού.

BRCA+16GENES: Analysis technology

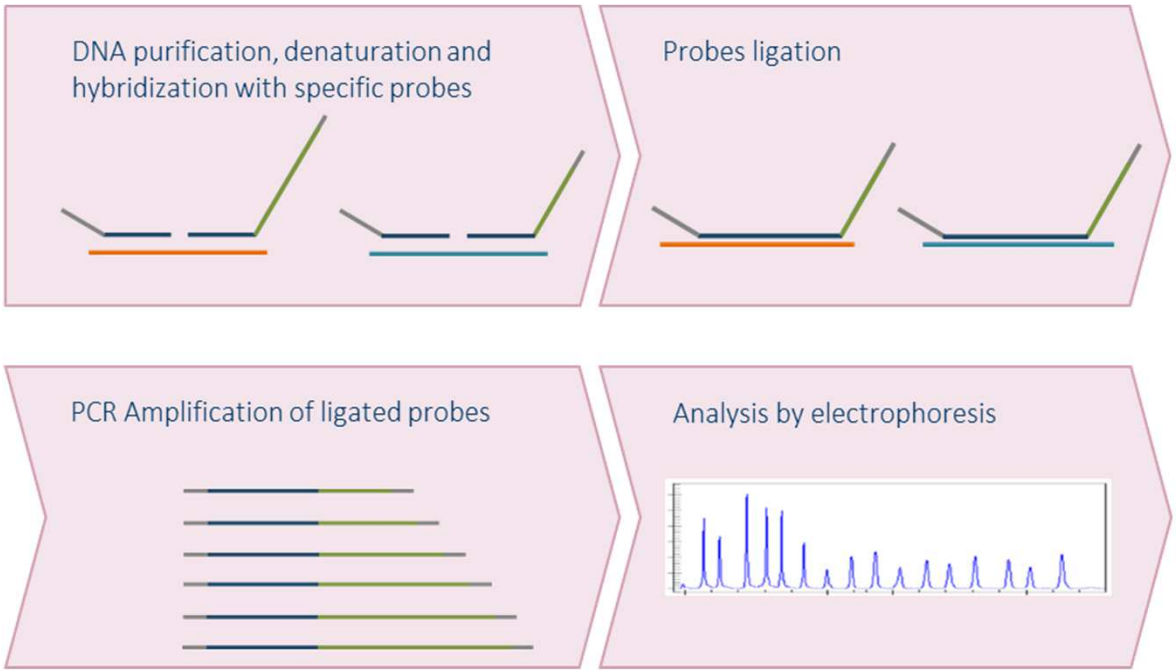
MLPA *(Multiplex Ligation-dependent Probe Amplification)*



- Performing the MLPA technique requires carrying out an initial DNA denaturing process and then a hybridisation process with specific probes. Once the probes have bound to the study region, the products are simultaneously amplified by PCR.
- The products are analysed using electrophoresis, which separates the fragments by size in order to detect potential deletions and duplications.

BRCA+16GENES: Τεχνολογία ανάλυσης

MLPA *(Multiplex Ligation-dependent Probe Amplification)*



- Εκτελώντας την τεχνική MLPA , απαιτεί την πραγματοποίηση μιας αρχικής διαδικασίας μετουσίωσης του DNA και ακολούθως μιας διαδικασίας υβριδοποίησης με συγκεκριμένους ανιχνευτές. Μόλις οι ανιχνευτές προσδεθούν στην περιοχή ενδιαφέροντος, τα παράγωγα ταυτόχρονα πολλαπλασιάζονται με PCR.
- Τα παράγωγα αναλύονται με ηλεκτροφόρηση, που διαχωρίζει τα κομμάτια με βάση το μέγεθός τους ώστε να ανιχνευτούν πιθανές διαγραφές και διπλασιασμοί.

BRCA+16GENES: Indications from various medical associations

Patients suffering from cancer					
INDICATION	SEOM	SGO	ASCO	ACMG	ESMO
Women with high-grade epithelial carcinoma regardless of age		●	●	●	
Breast cancer at or before 50 years of age				●	
Breast cancer at or before 45 years of age		●	●		
Breast cancer at or before 40 years of age	●				
Bilateral breast cancer or diagnosis of two primary breast cancers, the first being before 50 years of age	●	●	●	●	●
Triple-negative breast cancer before 60 years of age		●		●	●
Breast cancer with first-, second- or third-degree relative with breast cancer at or before 50 years of age or ovarian cancer at any age	●	●	●	●	
Breast cancer with two or more relatives with pancreatic cancer or prostate cancer (Gleason > 7)		●		●	
Breast cancer in males	●	●	●		●

SEOM: Sociedad Española de Oncología Médica
SGO: Society of Gynecologic Oncology
ASCO: American Society of Clinical Oncology
ACMG: American College of Medical Genetics and Genomics
ESMO: European Society for Medical Oncology

BRCA+16GENES: Ενδείξεις από διάφορες ιατρικές ενώσεις

Δεν καταλαβαίνω τι θέλει να πει η διαφάνεια

Ασθενείς που πάσχουν από καρκίνο					
ΕΝΔΕΙΞΕΙΣ	SEOM	SGO	ASCO	ACMG	ESMO
Γυναίκες με υψηλού βαθμού κακοήθεια με επιθηλιακό καρκίνωμα ανεξαρτήτως ηλικίας		●	●	●	
Καρκίνος του μαστού σε ηλικία πριν τα 50				●	
Καρκίνος του μαστού σε ηλικία πριν τα 45		●	●		
Καρκίνος του μαστού σε ηλικία πριν τα 40	●				
Καρκίνος και στους δύο μαστούς ή διάγνωση δύο πρωτογενή καρκίνους του μαστού, με τον πρώτο να εμφανίζεται πριν τα 50 έτη	●	●	●	●	●
Τριπλά – αρνητικός καρκίνος του μαστού πριν την ηλικία των 60		●		●	●
Καρκίνος του μαστού σε συνδυασμό με πρώτου, δεύτερου ή τρίτου βαθμού συγγενή με καρκίνο του μαστού πριν την ηλικία των 50 ή καρκίνο των ωοθηκών σε όποια ηλικία	●	●	●	●	
Καρκίνος του μαστού με δύο ή περισσότερους συγγενείς με καρκίνο του παγκρέατος ή του προστάτη (Gleason > 7)		●		●	
Καρκίνος του μαστού σε άντρες	●	●	●		●

SEOM: Sociedad Española de Oncología Médica
SGO: Society of Gynecologic Oncology
ASCO: American Society of Clinical Oncology
ACMG: American College of Medical Genetics and Genomics
ESMO: European Society for Medical Oncology

BRCA+16GENES: Indications from various medical associations

Relatives of patients suffering from cancer				
INDICATION	SEOM	SGO	ASCO	ACMG
Person with a male relative with breast cancer	●	●	●	
Person with a relative with breast cancer and another relative with diffuse gastric cancer, at least one with a diagnosis before 50 years of age				●
Person with a relative who is a carrier of a known mutation in *BRCA1/BRCA2*	●	●	●	●
Person with a first-degree relative with breast cancer before 45 years of age or with ovarian cancer at any age	●	●	●	●
Person with a first-degree relative or more than one first-, second- or third-degree relative with breast cancer and descendent from Ashkenazi Jews		●		
Person with a first-degree relative or more than one first-, second- or third-degree relative with triple-negative breast cancer before 60 years of age		●		

SEOM: Sociedad Española de Oncología Médica
SGO: Society of Gynecologic Oncology
ASCO: American Society of Clinical Oncology
ACMG: American College of Medical Genetics and Genomics

BRCA+16GENES: Ενδείξεις από διάφορες ιατρικές ενώσεις

Συγγενείς των ασθενών που πάσχουν από καρκίνο				
ΕΝΔΕΙΞΕΙΣ	SEOM	SGO	ASCO	ACMG
Άτομο συγγενή με άντρα ασθενή με καρκίνο του μαστού	●	●	●	
Άτομο συγγενή με άτομο με καρκίνο του μαστού και με άτομο με diffuse gastric cancer, τουλάχιστον τον ένα από τους δύο να είναι διαγνωσμένος πριν τα 50				●
Άτομο με συγγενή φορέα γνωστής μετάλλαξης στα *BRCA1/BRCA2*	●	●	●	●
Άτομο με πρώτου βαθμού συγγένεια με ασθενή καρκίνου του μαστού πριν την ηλικία των 45 ή καρκίνου των ωοθηκών σε κάθε ηλικία	●	●	●	●
Άτομο με έναν πρώτου βαθμού συγγενή ή περισσότερους από έναν πρώτου, δεύτερου ή τρίτου βαθμού συγγενείς με καρκίνο του μαστού και απόγονο των Εβραίων Ashkenazi		●		
Άτομο με έναν πρώτου βαθμού συγγενή ή περισσότερους από έναν πρώτου, δεύτερου ή τρίτου βαθμού συγγενείς με τριπλά αρνητικό καρκίνο του μαστού πριν την ηλικία των 60		●		

SEOM: Sociedad Española de Oncología Médica
SGO: Society of Gynecologic Oncology
ASCO: American Society of Clinical Oncology
ACMG: American College of Medical Genetics and Genomics

BRCA+16GENES: Indications

- Women with a **family history of breast cancer** (female or male) and/or **ovarian cancer.**
- Women with a **relative affected with family cancer syndrome.**
- **Patients with these type of tumours** in order to determine their potential hereditary nature.
- **Women ≥ 30 years of age with no prior family history**, to determine the genetic risk of breast and ovarian hereditary cancer and evaluate the different preventive options.[1]

First-degree relatives of a carrier of the mutation have a higher risk of being a carrier and developing the disease.

1. *King MC, Levy-Lahad E, Lahad A. Population-Based Screening for BRCA1 and BRCA2: 2014 Lasker Award. JAMA. 2014;312(11):1091-2.*

BRCA+16GENES: Ενδείξεις

- Γυναίκες με **οικογενειακό ιστορικό καρκίνου του μαστού** (γυναίκα ή άντρα) και / ή **καρκίνο των ωοθηκών.**
- Γυναίκες με **συγγενή επηρεασμένο από οικογενή καρκινικά σύνδρομα.**
- **Ασθενείς με αυτού του τύπου καρκίνους** ώστε να διαπιστωθεί η πιθανή κληρονομική φύση.
- **Γυναίκες ≥30 ετών χωρίς προηγούμενο οικογενειακό ιστορικό**, ώστε να διαπιστωθεί ο γενετικός κίνδυνος για κληρονομικό καρκίνο του μαστού και των ωοθηκών και να αξιολογηθούν οι διάφορες επιλογές πρόληψης.[1]

Πρώτου βαθμού συγγενείς φορέα με μετάλλαξη έχουν αυξημένο ρίσκο να είναι και οι ίδιοι φορείς και να αναπτύξουν την ασθένεια.

1. *King MC, Levy-Lahad E, Lahad A. Population-Based Screening for BRCA1 and BRCA2: 2014 Lasker Award. JAMA. 2014;312(11):1091-2.*

BRCA+16GENES: Important considerations

The presence of mutations in the genes of the panel associated to breast, ovarian and endometrial cancer may also imply a **higher risk for other type of cancers or hereditary cancer syndromes (e.g. Lynch, Cowden and Li-Fraumeni syndromes).** This information, if applies, may be included in the results report.

SYNLAB BRCA+16 GENES

Patient report
Hereditary predisposition to breast, ovarian and endometrial cancer

PATIENT INFORMATION

Firts name:
Last names:
Gender:
Date of birth (Day/Month/Year):

ORDERING PHYSICIAN/CLINIC INFORMATION

Doctor:
Medical speciality:
Center/Hospital:

SAMPLE INFORMATION

Draw date:
Receipt date:
Sample ID:
Sample origin ID:
Report date:

REASON FOR THE STUDY

RESULT

NO MUTATION DETECTED

INTERPRETATION

Type here
No mutations classified as pathogenic, probably pathogenic or of uncertain significance have been identified in this study.
A result without pathogenic or probably pathogenic mutation detected does not eliminate the risk of breast, ovary and endometrial cancer.
This report is to be interpreted in the clinical context and family history of the patient.

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BRCA+16GENES: Σημαντικές εκτιμήσεις

Η παρουσία μεταλλάξεων στα γονίδια του πάνελ που σχετίζονται με καρκίνο του μαστού, των ωοθηκών και του ενδομητρίου μπορεί επίσης να συνεπάγει και **αυξημένο ρίσκο για άλλους τύπους καρκίνου ή κληρονομικά καρκινικά σύνδρομα (π.χ. Lynch, Cowden και Li-Fraumeni syndromes).** Αυτή η πληροφορία, στην περίπτωση που ισχύει θα περιλαμβάνεται στο δελτίο αποτελέσματος.

SYNLAB BRCA+16 GENES

Patient report
Hereditary predisposition to breast, ovarian and endometrial cancer

PATIENT INFORMATION

Firts name:
Last names:
Gender:
Date of birth (Day/Month/Year):

ORDERING PHYSICIAN/CLINIC INFORMATION

Doctor:
Medical speciality:
Center/Hospital:

SAMPLE INFORMATION

Draw date:
Receipt date:
Sample ID:
Sample origin ID:
Report date:

REASON FOR THE STUDY

RESULT

NO MUTATION DETECTED

INTERPRETATION

Type here
No mutations classified as pathogenic, probably pathogenic or of uncertain significance have been identified in this study.
A result without pathogenic or probably pathogenic mutation detected does not eliminate the risk of breast, ovary and endometrial cancer.
This report is to be interpreted in the clinical context and family history of the patient.

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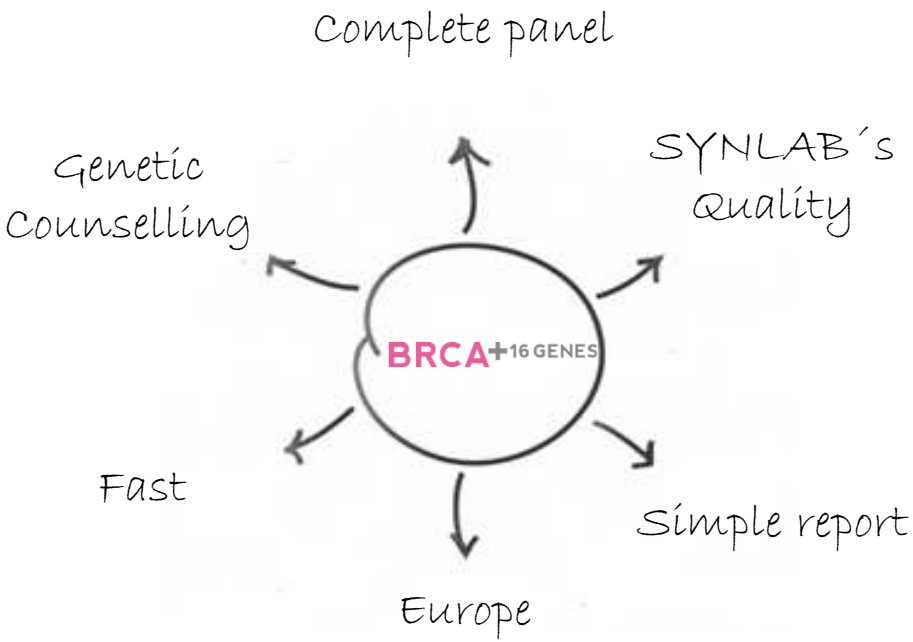
BRCA+16GENES: Advantages



✓ **COMPREHENSIVE**

Includes the genes with robust scientific evidence related with these types of cancer, for which **a specific patient management is described on the NCCN guidelines**, not solely *BRCA1* and *BRCA2*.

NCCN: National Comprehensive Cancer Network.

✓ **RELIABLE**

- NGS sequencing with paired-end reads of the genes included on the panel.
- Duplications and deletions in *BRCA1*, *BRCA2* and *EPCAM* genes.
- Positive results confirmation with Sanger sequencing.

✓ **EASY AND SIMPLE**

Saliva or blood sample available.

✓ **DATA BASES**

Classification and study of variants with the most complete databases.

✓ **COMPREHENSIVE AND SIMPLE TEST REPORT**

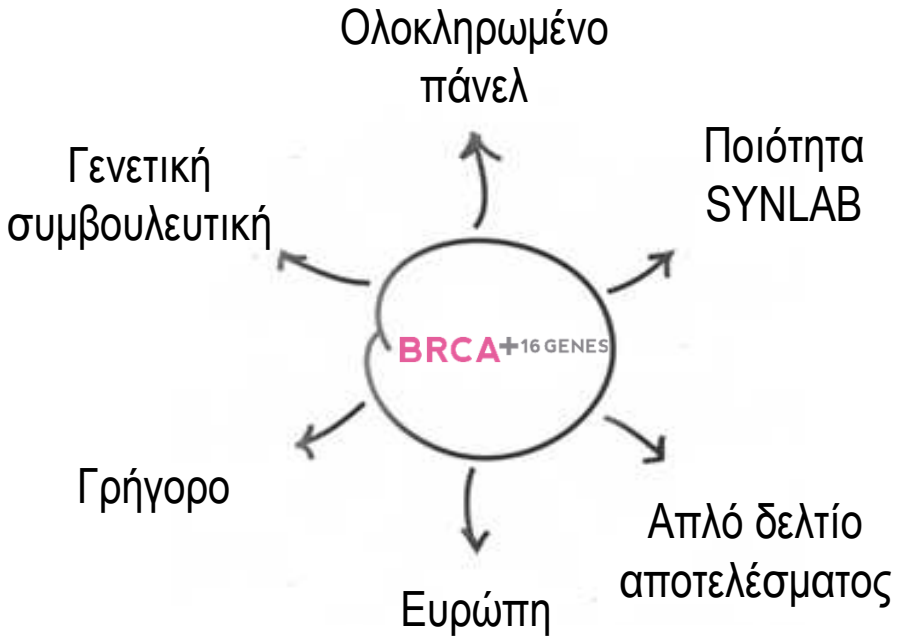
Report designed to facilitate the result interpretation.

BRCA+16GENES: Πλεονεκτήματα

✓ ΠΕΡΙΕΚΤΙΚΟ

Περιλαμβάνει τα γονίδια με ισχυρά επιστημονικά στοιχεία ότι σχετίζονται με αυτούς τους τύπους καρκίνου, για τα οποία **συγκεκριμένη διαχείριση των ασθενών περιγράφεται στις κατευθυντήριες γραμμές του NCCN**, όχι μόνο τα γονίδια *BRCA1* και *BRCA2*.

NCCN: National Comprehensive Cancer Network.



✓ ΑΞΙΟΠΙΣΤΑ

- Αλληλούχιση NGS των γονιδίων που περιλαμβάνονται στο πάνελ με paired-end reads.
- Διπλασιασμοί και διαγραφές στα γονίδια *BRCA1*, *BRCA2* και *EPCAM*.
- Θετικά αποτελέσματα επιβεβαιώνονται με αλληλούχιση κατά Sanger.

✓ ΕΥΚΟΛΗ ΚΑΙ ΑΠΛΗ

Επιλογή δείγματος από σάλιο ή αίμα.

✓ ΒΑΣΕΙΣ ΔΕΔΟΜΕΝΩΝ

Κατηγοριοποίηση και μελέτη των διαφόρων μεταλλάξεων με τις πιο ολοκληρωμένες βάσεις δεδομένων.

✓ ΠΕΡΙΕΚΤΙΚΟ ΚΑΙ ΑΠΛΟ ΔΕΛΤΙΟ ΑΠΟΤΕΛΕΣΜΑΤΟΣ

Δελτίο αποτελέσματος σχεδιασμένο για να διευκολύνει την ερμηνεία των αποτελεσμάτων.

BRCA+16GENES: Advantages

- ✓ **FAST AND AFORDABLE**
  The high degree of automation allows to obtain results in 10 working days.
- ✓ **PERFORMED ENTIRELY AT SYNLAB'S LABORATORIES**
- ✓ **SYNLAB QUALITY AND EXPERTISE**
  Developed by the genetic experts of SYNLAB group, Europe's number one medical diagnostics provider.
- ✓ **GENETIC COUNSELLING**
  SYNLAB put at your disposal without additional cost:

ON MEDICALL

With access to our genetic counselling platform where you will receive genetic advice from our experts via videoconference. You can also contact us sending an e-mail to:
genetic.counselling@synlab.com

BRCA+16GENES: Advantages

- ✓ **ΓΡΗΓΟΡΟ ΚΑΙ ΟΙΚΟΝΟΜΙΚΑ ΠΡΟΣΙΤΟ**
  Ο υψηλός βαθμός αυτοματισμού επιτρέπει την έκδοση των αποτελεσμάτων σε 10 εργάσιμες μέρες.
- ✓ **ΠΡΑΓΜΑΤΟΠΟΙΗΤΑΙ ΑΠΟΚΛΙΣΤΙΚΑ ΣΤΑ ΕΡΓΑΣΤΗΡΙΑ ΤΗΣ SYNLAB**
- ✓ **ΠΟΙΟΤΗΤΑ ΚΑΙ ΕΞΕΙΔΙΚΕΥΣΗ ΤΗΣ SYNLAB**
  Αναπτύχθηκε από τους γενετιστές εμπειρογνώμονες της SYNLAB, τον νούμερο ένα ευρωπαϊκό παροχό στην ιατρική διαγνωστική.
- ✓ **ΓΕΝΕΤΙΚΗ ΣΥΜΒΟΥΛΕΥΤΙΚΗ**
  Η SYNLAB βρίσκεται στη διάθεση σας χωρίς επιπλέον χρέωση:

ON MEDICALL

Με πρόσβαση στη δική μας πλατφόρμα γενετικής συμβουλευτικής από όπου θα λαμβάνετε γενετικές συμβουλές από τους ειδικούς μας μέσω τηλεδιάσκεψης. Μπορείτε επίσης να επικοινωνήσετε μαζί μας μέσω e-mail στο:
genetic.counselling@synlab.com

BRCA+16GENES: Sampling kit

BRCA+16 GENES kit

The sample collection kit includes:

- Device to collect saliva
- Test requisition form and informed consent
- Instructions
- Material for sending the sample

BRCA+16GENES: Πακέτο δειγματοληψίας

Πακέτο BRCA+16 GENES

Το πακέτο δειγματοληψίας περιλαμβάνει:

- Συσκευή για συλλογή σάλιου
- Έντυπο αίτησης της εξέτασης και φόρμα συγκατάθεσης
- Οδηγίες
- Υλικό για αποστολή του δείγματος

BRCA+16GENES: Test Requisition Form and Informed Consent

SYNLAB BRCA+16 GENES

SYNLAB BARCODE LABEL

Test Requisition Form

PATIENT INFORMATION

Name:	Surname(s):	
Gender: ☐ Male ☐ Female	National ID #:	Date of birth: / / (day/month/year)
Telephone:	Email:	Address:

SAMPLE INFORMATION

Type of sample: ☐ Blood ☐ Saliva	Sample ID:	Draw date: / / (day/month/year)

ORDERING PHYSICIAN / CENTRE INFORMATION

Name and surname(s):	Medical license #:	Client code:
Email:	Telephone:	Specialty:
Centre/hospital name:	Address:	

PATIENT'S CLINICAL HISTORY

Ancestry (tick all that apply):

☐ Western/Northern European ☐ Central/Eastern European ☐ Southern European ☐ African
☐ Latin American/Caribbean ☐ Native American ☐ Near Eastern/Middle Eastern ☐ Asian
☐ Ashkenazi ☐ Other: _____

Patient's personal history of cancer (tick all that apply):

☐ No personal history of cancer
☐ Breast cancer - age at diagnosis: ____ years ☐ Bilateral ☐ Premenopausal ☐ Triple-negative
☐ Ovarian cancer - age at diagnosis: ____ years
☐ Other type: _____ - age at diagnosis: ____ years

Family history of cancer:

☐ No known family history ☐ Known family history - fill in the table below:

					If breast cancer		
Type of cancer	Family relationship	Maternal	Paternal	Age at diagnosis	Bilateral	Premenopausal	Triple-negative
		☐	☐		☐	☐	☐
		☐	☐		☐	☐	☐
		☐	☐		☐	☐	☐

Other significant information:

- Smoker: ☐ Yes ☐ No
- Has received a bone marrow transplant: ☐ Yes ☐ No
- In women who have given birth, breast-feeding for at least 1 year: ☐ Yes ☐ No

ORDERING PHYSICIAN'S SIGNATURE

By signing this form I certify that, prior to performing the BRCA+16GENES test, I have informed the patient of the risks and implications that performing this test represents. I certify that all the patient's questions have been resolved and that I have received the patient's explicit consent to perform the test.

Physician's signature: Draw: / / (day/month/year)

PATIENT'S INFORMED CONSENT

By signing this form I confirm that I have read and agreed to the information contained on both sides of the form, or that it has been read to me, and that I have understood its content. I have received genetic counselling from my physician (or another person indicated by my physician) regarding the purpose of the test and its potential risks and limitations. I have been given the opportunity to ask any questions I had; I have received answers to all my questions and I have been given enough time to reflect on the information and my decision to undergo this test. I consent to undergo this test and discuss the results and appropriate medical management with my specialist. I agree to my biological sample being used solely and exclusively for the test specified in this requisition form, and for no other type of test under any circumstances. I understand that my physician has determined that this test is appropriate for me and I authorise **SYNLAB DIAGNOSTICOS GLOBALES SA**, with corporate tax ID no. A-59845875, and registered address at C/ Verge de Guadalupe 18, 08950 Esplugues de Llobregat, Spain, **[INSERT LOCAL SYNLAB COUNTRY ENTITY]** with registered office at **[INSERT LOCAL SYNLAB COUNTRY ENTITY ADDRESS]** and its affiliates (collectively referred to as "**SYNLAB**") to perform the BRCA+16GENES test, as well as the results being sent to my specialist. By signing below I agree to the foregoing and the terms of the Patient Informed Consent.

Patient's or legal representative's signature: Draw: / / (day/month/year)

BILLING DETAILS

☐ Patient ☐ Insurance company: _____ ☐ Ordering physician ☐ Other: _____

SYNLAB BRCA+16 GENES

Patient Informed Consent

(Copy for the laboratory)

The BRCA+16GENES test consists of extracting and quantifying the DNA in the sample received and DNA sequencing by Next-Generation Sequencing (NGS). This technique is capable of detecting point mutations and small insertions/deletions throughout the coding sequence and the flanking intronic region of the *ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11* and *TP53* genes. The technique is supplemented with Multiplex Ligation-dependent Probe Amplification (MLPA) of the *BRCA1, BRCA2* and *EPCAM* genes to detect large deletions and duplications. The pathogenic and probably pathogenic variants detected using next-generation sequencing are confirmed through Sanger sequencing.

The genes included in the BRCA+16GENES test are involved in cell cycle control and DNA repair during cell division. Mutations in these genes lead to a loss of cell control and capacity for DNA repair, which may imply a greater risk of developing cancer than that of the general population. Abnormalities in the genes included in the BRCA+16GENES test represent an increased risk of suffering from hereditary breast, ovarian and endometrial cancer. Mutations can be inherited from both the mother and the father. The probability of transmitting a mutation to the offspring is 50%. The presence of a *de novo* (non-inherited) mutation cannot be excluded.

The BRCA+16GENES test has certain limitations in determining the risk of the patient and/or the patient's family members of having hereditary breast, ovarian and endometrial cancer. Identifying a pathological genetic abnormality represents an increased risk of having the associated disease, but does not necessarily imply its development. If a relevant genetic abnormality is identified, it will be useful to perform a genetic study of the immediate family members (parents, children, siblings, etc.). If the family members tested did not have the previously detected abnormality, this would mean that the risk of eventually developing the disease is not increased, that is to say, is equal to that of the general population. Should pathological variants not be detected, this DOES NOT ELIMINATE the possibility of the patient having cancer or other genetic diseases. The presence of mutations in the genes of the panel related to breast, ovarian and endometrial cancer may also imply a higher risk for other cancer types or hereditary cancer syndromes (e. g. Lynch, Cowden and Li-Fraumeni syndromes). This information, if applicable, will be included on the report.

In compliance with the provisions of the current legislation, the patient accepts and recognizes at all the effects that the service will be deemed to have been fully executed once the sample has been taken. Once such circumstance has occurred, the patient will lose its right to cancel the contracted service and **SYNLAB** will not be obliged to reimburse the amounts received for that service.

The sample will be stored as set out by the regulations that apply to clinical diagnostic laboratories. Once the result has been issued, if there is any surplus sample, it will be stored for 1 month after being analysed, and once this period has elapsed it will be destroyed. The result of the BRCA+16GENES test is confidential. The patient's results will only be given to the patient's physician or another professional involved in the patient's medical care, unless the communication of this information is required by mandatory law or by order of authorities to disclose the patient's data to authorities or third parties, such as regulatory authorities. The healthcare professional is responsible for explaining the specific use and limitations of this test to the patient. It is recommended that the results are reported to the patient by a specialist in a medical consultation. The result may occasionally be delayed or a second sample required. Performing the test does not include free direct genetic counselling for the patient; however, **SYNLAB** offers this service through its **Genetic Counselling Unit** (genetic.consulting@synlab.com).

The patient agrees that their biological samples and a copy of this executed Test Requisition Form and all personal data about them contained in this form are transferred to and processed by to the laboratory **SYNLAB DIAGNOSTICOS GLOBALES SA** with registered office at C/ Verge de Guadalupe 18, 08950 Esplugues de Llobregat Spain, and that the test results and the personal data may be processed and stored both by **[INSERT LOCAL SYNLAB COUNTRY ENTITY]** with registered office at **[INSERT LOCAL SYNLAB COUNTRY ENTITY ADDRESS]** and its affiliates (collectively referred to as "**SYNLAB**"), where the level of protection may not be the same as in the patient's country. The patient has a right to withdraw their consent, but in this case it is understood that the BRCA+16GENES test cannot be provided. The patient's personal data will only be used to perform the test, to communicate with them and for invoicing purposes. The patient further understands that their personal data will be stored for a duration of **[...]** after the test has been performed; that they may exercise the rights of access, rectification and, as applicable, restriction, opposition or erasure by sending an email to **[INSERT LOCAL SYNLAB COUNTRY ENTITY AND ADDRESS]** at: **[INSERT LOCAL SYNLAB COUNTRY ENTITY EMAIL]**; and that they have a right to lodge a complaint with the competent Supervisory Authority in their country. They also agree that the results of the test will be communicated by the testing laboratory to **[INSERT LOCAL SYNLAB COUNTRY ENTITY]** and to the physician mentioned on this form or its/their representatives.

Pursuant to the best practices and quality standards of clinical laboratories, the patient acknowledges that **SYNLAB** may use the leftover specimen and the patient's medical and genetic information, in an anonymized form (unless forbidden by applicable legislation) for research or quality assurance purposes. Such uses may result in the development of commercial products and services. The patient will not receive notice of any specific uses and will not receive any compensation for these uses. In any event, all such uses will be in compliance with applicable legislation.

☐ **Tick the box if you would not like your sample to be used for research purposes.**

In compliance with Law 14/2007, of 3 July, on Biomedical Research, specifically its Articles 47 and 48, the prescribing physician must obtain informed consent to perform genetic tests. The patient's signature on this consent form is aimed at complying with this requirement.

Patient's name and surname(s):

Patient's or legal representative's signature: **Date:** / / (day/month/year)

BRCA+16GENES: Έντυπο αίτησης της εξέτασης και φόρμα συγκατάθεσης

SYNLAB

BRCA+16 GENES

SYNLAB BARCODE LABEL

Test Requisition Form

PATIENT INFORMATION

Name:	Surname(s):	
Gender: ☐ Male ☐ Female	National ID #:	Date of birth: / / (day/month/year)
Telephone:	Email:	Address:

SAMPLE INFORMATION

Type of sample: ☐ Blood ☐ Saliva	Sample ID:	Draw date: / / (day/month/year)

ORDERING PHYSICIAN / CENTRE INFORMATION

Name and surname(s):	Medical license #:	Client code:
Email:	Telephone:	Specialty:
Centre/hospital name:	Address:	

PATIENT'S CLINICAL HISTORY

Ancestry (tick all that apply):

☐ Western/Northern European ☐ Central/Eastern European ☐ Southern European ☐ African
☐ Latin American/Caribbean ☐ Native American ☐ Near Eastern/Middle Eastern ☐ Asian
☐ Ashkenazi ☐ Other: _____

Patient's personal history of cancer (tick all that apply):

☐ No personal history of cancer
☐ Breast cancer - age at diagnosis: ____ years ☐ Bilateral ☐ Premenopausal ☐ Triple-negative
☐ Ovarian cancer - age at diagnosis: ____ years
☐ Other type: _____ - age at diagnosis: ____ years

Family history of cancer:

☐ No known family history ☐ Known family history - fill in the table below:

					If breast cancer		
Type of cancer	Family relationship	Maternal	Paternal	Age at diagnosis	Bilateral	Premenopausal	Triple-negative
		☐	☐		☐	☐	☐
		☐	☐		☐	☐	☐
		☐	☐		☐	☐	☐

Other significant information:

- Smoker: ☐ Yes ☐ No
- Has received a bone marrow transplant: ☐ Yes ☐ No
- In women who have given birth, breast-feeding for at least 1 year: ☐ Yes ☐ No

ORDERING PHYSICIAN'S SIGNATURE

By signing this form I certify that, prior to performing the BRCA+16GENES test, I have informed the patient of the risks and implications that performing this test represents. I certify that all the patient's questions have been resolved and that I have received the patient's explicit consent to perform the test.

Physician's signature: Draw: / / (day/month/year)

PATIENT'S INFORMED CONSENT

By signing this form I confirm that I have read and agreed to the information contained on both sides of the form, or that it has been read to me, and that I have understood its content. I have received genetic counselling from my physician (or another person indicated by my physician) regarding the purpose of the test and its potential risks and limitations. I have been given the opportunity to ask any questions I had; I have received answers to all my questions and I have been given enough time to reflect on the information and my decision to undergo this test. I consent to undergo this test and discuss the results and appropriate medical management with my specialist. I agree to my biological sample being used solely and exclusively for the test specified in this requisition form, and for no other type of test under any circumstances. I understand that my physician has determined that this test is appropriate for me and I authorise **SYNLAB DIAGNOSTICOS GLOBALES SA**, with corporate tax ID no. A-59845875, and registered address at C/ Verge de Guadalupe 18, 08950 Esplugues de Llobregat, Spain, **[INSERT LOCAL SYNLAB COUNTRY ENTITY]** with registered office at **[INSERT LOCAL SYNLAB COUNTRY ENTITY ADDRESS]** and its affiliates (collectively referred to as "**SYNLAB**") to perform the BRCA+16GENES test, as well as the results being sent to my specialist. By signing below I agree to the foregoing and the terms of the Patient Informed Consent.

Patient's or legal representative's signature: Draw: / / (day/month/year)

BILLING DETAILS

☐ Patient ☐ Insurance company: _____ ☐ Ordering physician ☐ Other: _____

SYNLAB

BRCA+16 GENES

Patient Informed Consent

(Copy for the laboratory)

The BRCA+16GENES test consists of extracting and quantifying the DNA in the sample received and DNA sequencing by Next-Generation Sequencing (NGS). This technique is capable of detecting point mutations and small insertions/deletions throughout the coding sequence and the flanking intronic region of the *ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MSH2, MSH6, NBN, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11* and *TP53* genes. The technique is supplemented with Multiplex Ligation-dependent Probe Amplification (MLPA) of the *BRCA1, BRCA2* and *EPCAM* genes to detect large deletions and duplications. The pathogenic and probably pathogenic variants detected using next-generation sequencing are confirmed through Sanger sequencing.

The genes included in the BRCA+16GENES test are involved in cell cycle control and DNA repair during cell division. Mutations in these genes lead to a loss of cell control and capacity for DNA repair, which may imply a greater risk of developing cancer than that of the general population. Abnormalities in the genes included in the BRCA+16GENES test represent an increased risk of suffering from hereditary breast, ovarian and endometrial cancer. Mutations can be inherited from both the mother and the father. The probability of transmitting a mutation to the offspring is 50%. The presence of a *de novo* (non-inherited) mutation cannot be excluded.

The BRCA+16GENES test has certain limitations in determining the risk of the patient and/or the patient's family members of having hereditary breast, ovarian and endometrial cancer. Identifying a pathological genetic abnormality represents an increased risk of having the associated disease, but does not necessarily imply its development. If a relevant genetic abnormality is identified, it will be useful to perform a genetic study of the immediate family members (parents, children, siblings, etc.). If the family members tested did not have the previously detected abnormality, this would mean that the risk of eventually developing the disease is not increased, that is to say, is equal to that of the general population. Should pathological variants not be detected, this DOES NOT ELIMINATE the possibility of the patient having cancer or other genetic diseases. The presence of mutations in the genes of the panel related to breast, ovarian and endometrial cancer may also imply a higher risk for other cancer types or hereditary cancer syndromes (e. g. Lynch, Cowden and Li-Fraumeni syndromes). This information, if applicable, will be included on the report.

In compliance with the provisions of the current legislation, the patient accepts and recognizes at all the effects that the service will be deemed to have been fully executed once the sample has been taken. Once such circumstance has occurred, the patient will lose its right to cancel the contracted service and **SYNLAB** will not be obliged to reimburse the amounts received for that service.

The sample will be stored as set out by the regulations that apply to clinical diagnostic laboratories. Once the result has been issued, if there is any surplus sample, it will be stored for 1 month after being analysed, and once this period has elapsed it will be destroyed. The result of the BRCA+16GENES test is confidential. The patient's results will only be given to the patient's physician or another professional involved in the patient's medical care, unless the communication of this information is required by mandatory law or by order of authorities to disclose the patient's data to authorities or third parties, such as regulatory authorities. The healthcare professional is responsible for explaining the specific use and limitations of this test to the patient. It is recommended that the results are reported to the patient by a specialist in a medical consultation. The result may occasionally be delayed or a second sample required. Performing the test does not include free direct genetic counselling for the patient; however, **SYNLAB** offers this service through its **Genetic Counselling Unit** (genetic.conselling@synlab.com).

The patient agrees that their biological samples and a copy of this executed Test Requisition Form and all personal data about them contained in this form are transferred to and processed by to the laboratory **SYNLAB DIAGNOSTICOS GLOBALES SA** with registered office at C/ Verge de Guadalupe 18, 08950 Esplugues de Llobregat Spain, and that the test results and the personal data may be processed and stored both by **[INSERT LOCAL SYNLAB COUNTRY ENTITY]** with registered office at **[INSERT LOCAL SYNLAB COUNTRY ENTITY ADDRESS]** and its affiliates (collectively referred to as "**SYNLAB**"), where the level of protection may not be the same as in the patient's country. The patient has a right to withdraw their consent, but in this case it is understood that the BRCA+16GENES test cannot be provided. The patient's personal data will only be used to perform the test, to communicate with them and for invoicing purposes. The patient further understands that their personal data will be stored for a duration of **[...]** after the test has been performed; that they may exercise the rights of access, rectification and, as applicable, restriction, opposition or erasure by sending an email to **[INSERT LOCAL SYNLAB COUNTRY ENTITY AND ADDRESS]** at: **[INSERT LOCAL SYNLAB COUNTRY ENTITY EMAIL]**; and that they have a right to lodge a complaint with the competent Supervisory Authority in their country. They also agree that the results of the test will be communicated by the testing laboratory to **[INSERT LOCAL SYNLAB COUNTRY ENTITY]** and to the physician mentioned on this form or its/their representatives.

Pursuant to the best practices and quality standards of clinical laboratories, the patient acknowledges that **SYNLAB** may use the leftover specimen and the patient's medical and genetic information, in an anonymized form (unless forbidden by applicable legislation) for research or quality assurance purposes. Such uses may result in the development of commercial products and services. The patient will not receive notice of any specific uses and will not receive any compensation for these uses. In any event, all such uses will be in compliance with applicable legislation.

☐ **Tick the box if you would not like your sample to be used for research purposes.**

In compliance with Law 14/2007, of 3 July, on Biomedical Research, specifically its Articles 47 and 48, the prescribing physician must obtain informed consent to perform genetic tests. The patient's signature on this consent form is aimed at complying with this requirement.

Patient's name and surname(s):

Patient's or legal representative's signature: **Date:** / / (day/month/year)

BRCA+16GENES: Results

BRCA+16 GENES results are reported as follows:

- ✓ **Pathogenic mutations**: Variants linked to disease (class V).
- ✓ **Probably pathogenic mutations:** Variants probably linked to disease (class IV).
- ✓ **Variants of uncertain significance:** Variants suspected of pathogenicity without decisive evidence (class III).
- ✓ **No mutations detected:** No mutations have been identified.

BRCA+16GENES: Αποτελέσματα

Τα αποτελέσματα του BRCA+16 GENES αναφέρονται ως ακολούθως:

- ✓ **Παθογόνες μεταλλάξεις**: Αλλαγές που σχετίζονται με ασθένεια (class V).
- ✓ **Πιθανώς παθογόνες μεταλλάξεις:** Αλλαγές που πιθανώς να σχετίζονται με ασθένεια (class IV).
- ✓ **Μεταλλαγές αβέβαιης σημαντικότητας:** Αλλαγές ύποπτες για παθογένεια χωρίς βέβαιη απόδειξη (class III).
- ✓ **Καμία μεταλλαγή δεν ανιχνεύτηκε:** Δεν ταυτοποιήθηκε καμία μετάλλαξη.

BRCA+16GENES: Results

SYNLAB

BRCA+16 GENES

Patient report
Hereditary predisposition to breast, ovarian and endometrial cancer

PATIENT INFORMATION	ORDERING PHYSICIAN/CLINIC INFORMATION
Firts name:	Doctor:
Last names:	Medical speciality:
Gender:	Center/Hospital:
Date of birth (Day/Month/Year):	

SAMPLE INFORMATION

Draw date:	Sample ID:
Receipt date:	Sample origin ID:
	Report date:

REASON FOR THE STUDY

RESULT

NO MUTATION DETECTED

INTERPRETATION

Type here

No mutations classified as pathogenic, probably pathogenic or of uncertain significance have been identified in this study.

A result without pathogenic or probably pathogenic mutation detected does not eliminate the risk of breast, ovary and endometrial cancer.

This report is to be interpreted in the clinical context and family history of the patient.

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BRCA+16GENES: Αποτελέσματα

SYNLAB

BRCA+16 GENES

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BRCA+16GENES: Key points

- ✓ **BRCA+16 GENES** is a complete panel that **includes the genes contemplated by the NCCN guidelines in which specific patient management is established.**

- ✓ International experts recommend, based on experience, a **genetic screening for breast and ovarian cancer** that allows to stablish **specific prevention strategies for mutation carriers**. This type of screening is not contemplated in clinical guidelines for this purpose, but it is in certain patients with a history of risk.

- ✓ Aimed to the **healthcare providers** but **patients** can also be a target (high diffusion of the relationship between breast and ovarian cancer and genetic tests in the media).

- ✓ When a mutation is detected with **BRCA+16 GENES**, it is advisable to perform the analysis of the specific **mutation or deletion/duplication in the relatives**.

- ✓ **Genetic counselling** is key.

BRCA+16GENES: Σημεία κλειδιά

- ✓ Το BRCA+16 GENES αποτελεί ένα ολοκληρωμένο πάνελ που **περιλαμβάνει τα γονίδια που προβλέπονται από τις κατευθυντήριες γραμμές του NCCN στις οποίες έχει καθοριστεί ειδική διαχείριση των ασθενών.**

- ✓ Διεθνείς ειδικοί προτείνουν, βάση πείρας, **γενετική εξέταση για τους καρκίνους του μαστού και των ωοθηκών** που να επιτρέπει τον καθορισμό **συγκεκριμένες στρατηγικές πρόληψης για τους φορείς μεταλλάξεων**. Αυτού του τύπου η εξέταση δεν συμπεριλαμβάνεται στις κλινικές κατευθυντήριες γραμμές για αυτό το λόγο, όμως συμπεριλαμβάνεται στους ασθενείς με ιστορικό κινδύνου.

- ✓ Απευθύνεται στους **παρόχους υγειονομικής περίθαλψης** όμως και οι **ασθενείς** μπορούν να αποτελέσουν στόχο (υψηλή διάχυση της σχέσης μεταξύ των καρκίνων του μαστού και των ωοθηκών, με τις γενετικές εξετάσεις στα μέσα επικοινωνίας).

- ✓ Όταν μια μετάλλαξη ανιχνευτεί με το BRCA+16 GENES, συστήνεται να γίνεται ανάλυση της συγκεκριμένης **μετάλλαξης ή διαγραφής/ διπλασιασμού στους συγγενείς**.

- ✓ Η **γενετική συμβουλευτική** είναι το κλειδί.

Πιστεύω περιττό slide

- **Breast and ovarian cancer**
- **BRCA$^{+16\ GENES}$**

  Genes panel and associated risk

  Analysis technology

  Recommendations from medical associations

  Indications

  Important considerations

  Advantages

  Sample collection kit

  Test Requisition Form and Informed Consent

  Results

  Key points
- **Contact**

- **Καρκίνος του μαστού και των ωοθηκών**
- **BRCA$^{+16\ GENES}$**

  Πάνελ γονιδίων και το σχετικό ρίσκο

  Τεχνολογία ανάλυσης

  Συστάσεις από ιατρικούς συλλόγους

  Ενδείξεις

  Σημαντικές εκτιμήσεις

  Πλεονεκτήματα

  Πακέτο συλλογής δείγματος

  Φόρμα αίτησης και εγκεκριμένη συγκατάθεση

  Αποτελέσματα

  Βασικά σημεία

- **Επικοινωνία**


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