무증상 유전적 돌연변이의 이상적 관리

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정재학
(원광대학교)

DECLARATION OF INTERESTS

Nothing to declare

Case

Patient : 32y, asymptomatic, G1P1, desires preg.

FHx : older sister – Triple negative breast cancer(TNBC) at 38y(BRCA1 positive)
maternal aunt – Ovarian cancer at 52y

Genetic testing : Cascade testing – BRCA1 germline PV

Workup : TVUS, CA125: WNL, MRI: non-specific finding

Case

Q : Most appropriate management recommendation with RRM?

A : Routine TVUS and serum CA125 every 6-12 months

B : Risk-reducing salpingo-oophorectomy (RRSO)

C : Risk-reducing salpingectomy alone

D: Advise expedited childbearing followed by RRSO before age 40

Introduction

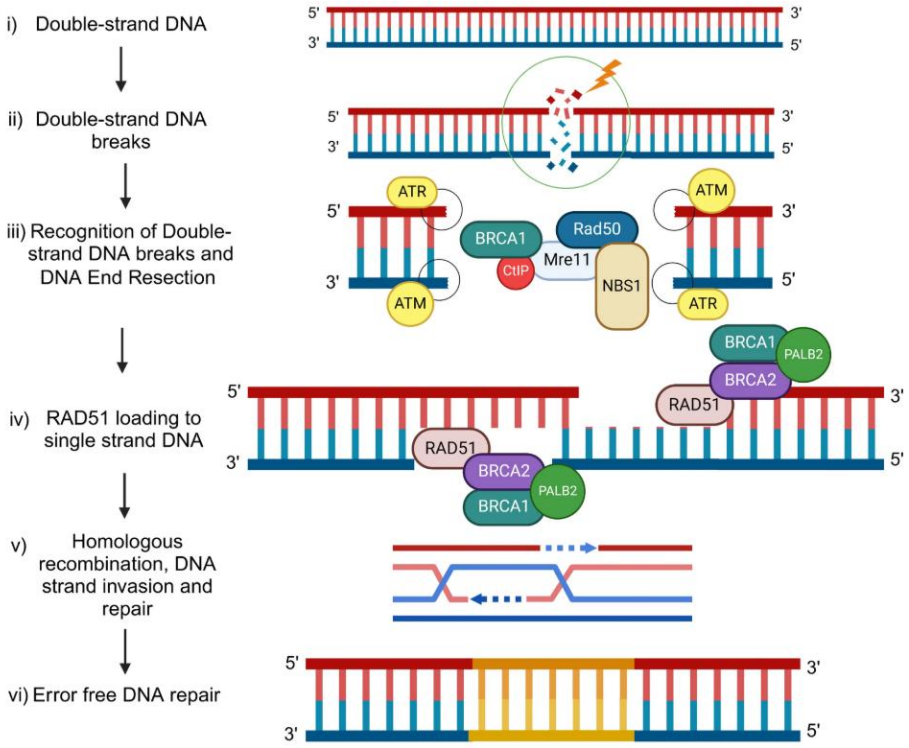
Hereditary Breast and Ovarian Cancer syndrome(ACOG)

An inherited cancer-susceptibility syndrome characterized by multiple family members with breast cancer, ovarian cancer, or both.

BRCA1/2, BRIP1, RAD51C/D, PALB2…

BRCA 1/2 Mutation

BRCA1 and BRCA2 maintain genomic integrity via the Homologous Recombination Repair (HRR) pathway



BRCA1 and BRCA2 molecular mechanisms of DNA damage response during homologous recombination. (i) A double-strand DNA molecule

Parameter	BRCA1	BRCA2
Gene location	17q21	13q12
Lifetime breast cancer risk	60-72%	55-69%
Lifetime ovarian cancer risk	39-58%	13-29%
Receptor status	Often triple-negative	Often ER+/PR+
Age of onset	Earlier(<40y)	Slightly later

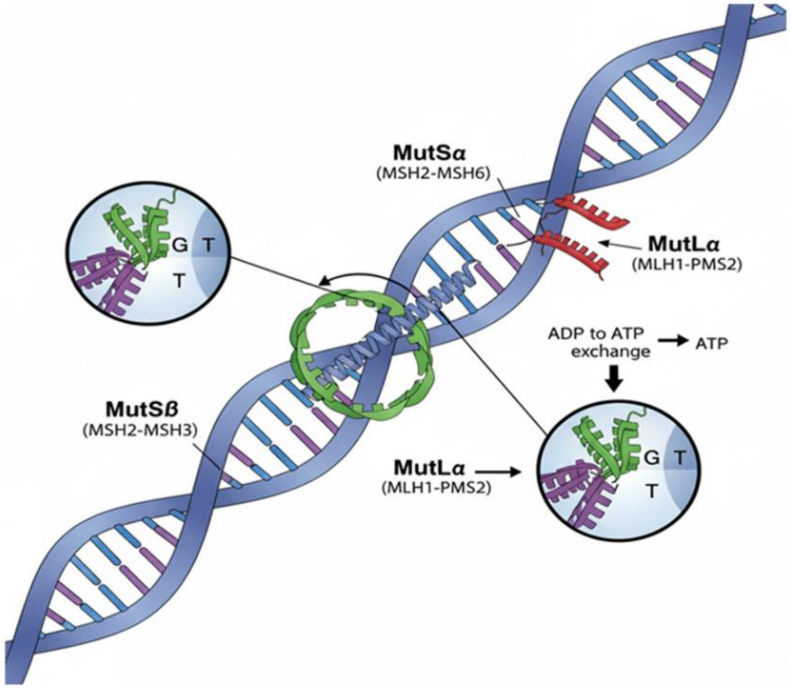
Panagopoulou, M., Panou, T., Gkountakos, A. *et al. BRCA1* & *BRCA2* methylation as a prognostic and predictive biomarker in cancer: Implementation in liquid biopsy in the era of precision medicine. *Clin Epigenet* **16**, 178 (2024). https://doi.org/10.1186/s13148-024-01787-8

Lynch Syndrome

Known as hereditary nonpolyposis colorectal cancer(HNPCC)

An autosomally dominant inherited genetic disease

MSI(microsatellite instability)/MMR(mismatch repair)



gene	MLH1	MSH2	MSH6	PMS2	EPCAM
complex	MutLα	MutSα	MutSα	MutLα	MSH2 involvement
EC	34-54%	21-57%	16-49%	13-26%	21-57% (*12-25%)
OC	4-20%	8-38%	≤1-13%	1.1-3%	8-38%

Kluk A, Gryczka H, Braszka M, Ałtyn R, Markiewicz H, Ślężak JK, Dwojak E, Czerniak J, Zieliński P, Płachno BJ, et al. Hereditary Endometrial Cancer: Lynch Syndrome, Mismatch Repair Deficiency, and Emerging Genetic Predispositions—A Comprehensive Review with Clinical and Laboratory Guidelines. *International Journal of Molecular Sciences*. 2026; 27(3):1304. https://doi.org/10.3390/ijms27031304

BRCA-mutated Ovarian Cancer

SOLO-1(olaparib)

Median PFS prolonged significantly

PAOLA-1(Olaparib+bevacizumab)

PFS benefit

PRIMA(Niraparib)

PFS benefit








The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 27, 2018 VOL. 379 NO. 26

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

K. Moore, N
G.S. Sonke, (


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer

I. Ray-Coquard, P. Pautier, S. Pignata, D. Pérol, A. González-Martín, R. Berger, K. Fujiwara, I. Vergote, N. Colombo, J. Mäenpää, F. Selle, J. Sehouli, D. Lorusso, E.M. Guerra Alía, A. Reinthaller, S. Nagao, C. Lefeuvre-Plesse, U. Canzler, G. Scar
P. Bu


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 19, 2019 VOL. 381 NO. 25

Niraparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

A. González-Martín, B. Pothuri, I. Vergote, R. DePont Christensen, W. Graybill, M.R. Mirza, C. McCormick, D. Lorusso, P. Hoskins, G. Freyer, K. Baumann, K. Jardon, A. Redondo, R.G. Moore, C. Vulsteke, R.E. O'Cearbhaill, B. Lund, F. Backes, P. Barretina-Ginesta, A.F. Haggerty, M.J. Rubio-Pérez, M.S. Shahin, G. Mangili, W.H. Bradley, I. Bruchim, K. Sun, I.A. Malinowska, Y. Li, D. Gupta, and B.J. Monk, for the PRIMA/ENGOT-OV26/GOG-3012 Investigators*

Immune checkpoint inhibitor

GARNET trial(2nd line on EC)

RUBY trial(1st line with chemotherapy)

NRG-GY018(1st line with chemotherapy)



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dostarlimab for Primary Advanced or Recurrent Endometrial Cancer

M.R. Mirza, D.M. Chase, B.M. Slomovitz, R. dePont Christensen, Z. Novák, D. Black, L. Gilbert, S. Sharma, G. Valabrega, L.M. Landrum, L.C. Hanker, A. Stuckey, I. Boere, M.A. Gold, A. Auranen, B. Pothuri, D. Cibula, C. McCourt, F. Raspagliesi, M.S. Shahin, S.E. Gill, B.J. Monk, J. Buscema, T.J. Herzog, L.J. Copeland, M
and

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

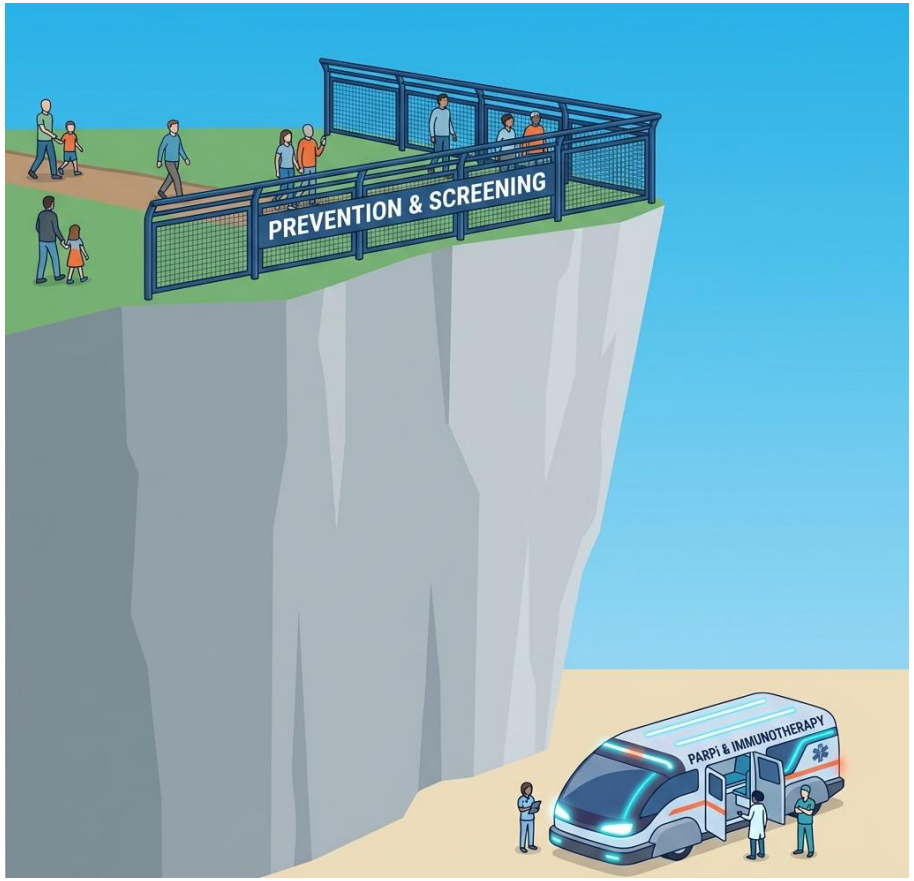
Pembrolizumab plus Chemotherapy in Advanced Endometrial Cancer

Ramez N. Eskander, M.D., Michael W. Sill, Ph.D., Lindsey Beffa, M.D., Richard G. Moore, M.D., Joanie M. Hope, M.D., Fernanda B. Musa, M.D., Robert Mannel, M.D., Mark S. Shahin, M.D., Guilherme H. Cantuaria, M.D., Eugenia Girda, M.D., Cara Mathews, M.D., Juraj Kavecansky, M.D., Charles A. Leath III, M.D., M.S.P.H., Lilian T. Gien, M.D., Emily M. Hinchcliff, M.D., M.P.H., Shashikant B. Lele, M.D., Lisa M. Landrum, M.D., Floor Backes, M.D., Roisin E. O'Cearbhaill, M.D., Tareq Al Baghdadi, M.D., Emily K. Hill, M.D., Premal H. Thaker, M.D., Veena S. John, M.D., Stephen Welch, M.D., Amanda N. Fader, M.D., Matthew A. Powell, M.D., and Carol Aghajanian, M.D.

Beyond Treatment

In the era of PARPi and immunotherapy, must we wait until cancer develops?

What is the current status of genetic screening and risk-reducing strategies prior to active treatment?





Genetic Testing Criteria

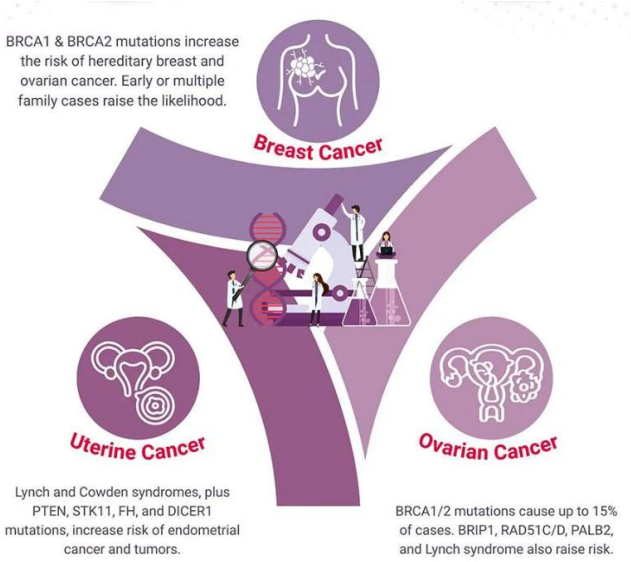
MGPT(Multigene Panel Testing)

Multigene Panel Testing(MGPT)

Comprehensive germline MGPT is preferred over narrow single-gene testing to avoid missed diagnoses across overlapping hereditary cancer phenotypes.

ACMG/AMP variant guideline

Pathogenic, Likely pathogenic, Variant of Uncertain Significance(VUS), Likely benign, Benign



https://nycgyne.com/genetic-testing/cancer-risk/women-cancer-genetics/

Genetic Testing Criteria

1. Cascade testing

Any asymptomatic individual with a blood relative harboring a known pathogenic/likely pathogenic(P/LP) variant in some genes(BRCA1/2, MMR genes, etc.)

Genetic Testing Criteria

2. High risk family history

HBOC susceptibility criteria:

- ≥1 1st- or 2nd-degree relative with epithelial ovarian, fallopian tube, or primary peritoneal cancer at any age
- ≥1 1st- or 2nd-degree relative with breast cancer meeting high-risk features:
  - Diagnosed at age ≤50 years
  - Triple-negative breast cancer (TNBC) at any age
  - Male breast cancer at any age
  - Multiple primary breast cancers
- ≥1 close blood relative with exocrine pancreatic cancer
- ≥1 1st- or 2nd-degree relative with metastatic, node-positive, or high-/very-high-risk prostate cancer
- ≥3 diagnoses of breast and/or prostate cancer on the same side of the family

Genetic Testing Criteria

2. High risk family history

Lynch Syndrome Criteria:

≥1 1st-degree relative with colorectal, endometrial, or gastric cancer diagnosed <50 years

≥1 1st- or 2nd-degree relative with synchronous or metachronous Lynch-associated malignancies at any age

≥2 1st- or 2nd-degree relatives with Lynch-associated cancers, including ≥1 diagnosed <50 years.

≥3 1st- or 2nd-degree relatives with Lynch-associated cancers regardless of age.

Genetic Testing Criteria

3. Prior Probability Model Thresholds

HBOC prediction models (Tyrer-Cuzick, BRCAPRO, CanRisk, etc.)

Clinically indicated if probability of a BRCA1/2 P/LP variant is >5%
(testing may be considered at 2.5%–5%)

Lynch Syndrome Prediction Models (PREMM5 etc.)

Recommended if model-predicted risk is ≥5% (for unaffected individuals without personal CRC/EC, ≥2.5% threshold can be considered based on clinical judgment)

Interpretation

Variant of Uncertain Significance(VUS)

Reclassification

80-90% of reclassified VUS are **DOWNGRADED** to benign/likely benign

- ✓ **Do NOT test family(cascade testing)** for VUS
- ✓ A VUS **MUST NOT be used to alter clinical management or guide risk-reducing surgery**

Interpretation

Negative result

True negative

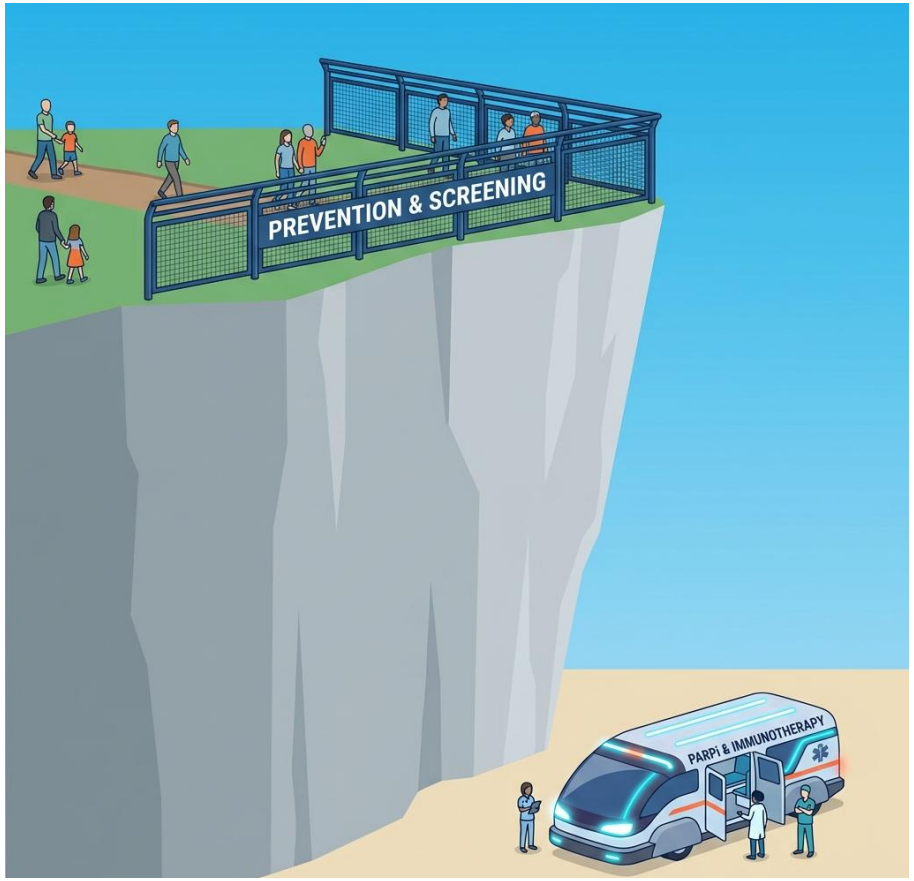
- Tested negative for a known familial pathogenic variant previously identified in the family
- Cancer risk reverts to near general population levels

Indeterminate negative

- Tested negative via MGPT, but no mutation has ever been identified in affected relatives
- High-risk screening must continue based on pedigree risk models
- Do not rule out hereditary cancer risk(missed, technical limits, unmapped genes)

Beyond Treatment

What is the current status of genetic screening and risk-reducing strategies prior to active treatment?





Principle of Management

Ovary & Fallopian tube

Screening limitation

Routine transvaginal ultrasound and serum CA125 do **NOT** reduce mortality

Standard of care : Risk-Reducing Salpingo-Oophorectomy(RRSO)

Timing : BRCA1 35-40y, BRCA2 40-45y, BRIP1, RAD51C/D 45-50y

SEE-FIM protocol(Sectioning and extensively examining the fimbriated end)

With/Without hysterectomy – benefit(?)

Ovary & Fallopian tube

Limitations of salpingectomy alone

- The efficacy of risk-reducing salpingectomy alone in reducing mortality among high-risk germline carriers remains unproven
- Should only be performed within clinical trial protocols

Chemoprevention & Postoperative hormone replacement therapy

Ovulation suppression

OCPs – Ovarian cancer risk reduction

Endometrial cancer

Most endometrial malignancy present with early clinical warning signs, particularly abnormal uterine bleeding (AUB) or postmenopausal bleeding

Patient education on immediate reporting and mandatory diagnostic endometrial biopsy upon symptom onset is the primary defense

Endometrial cancer

Endometrial biopsy

Screening biopsy every 1-2 years starting at age 30-35 can be considered

Routine transvaginal ultrasound is NOT recommended as a screening tool

Physiological variation

Endometrial cancer

Surgical prophylaxis(Risk-Reducing Hysterectomy)

Post-Childbearing intervention
Optimization of HRT regimens – Estrogen alone

Gene-specific surgical stratification

MLH1/MSH2 : starting around age 40
MSH6 : Hysterectomy at age 40; consider delayed BSO until age 45-50
PMS2 : delayed until age 50 or natural menopause

Progestin-mediated endometrial protection

OCs or LNG-IUD

Breast cancer

Screening

Initiated at age 25(or 5-10 years prior to the earliest familial breast cancer diagnosis)

Contrast-enhanced breast MRI

Superior sensitivity compared to mammography alone

Breast cancer

Surgical risk reduction(Risk-Reducing Mastectomy, RRM)

Restricted to High-Penetrance carriers : Lifetime breast cancer risk ≥ 40%

Avoidance in Moderate Penetrance

Histology and receptor-specific intervention

Selective estrogen receptor modulator(e.g., Tamoxifen) or aromatase inhibitor

For ER+ disease, not triple-negative breast cancer(BRCA1)



Management of HBOC genes

NCCN guideline(v 1.2027, 1.2026)

High penetrance HBOC

관리 장기	BRCA1	BRCA2	PALB2
유방 (선별)	25세 MRI / 30세+ 촬영술	25세 MRI / 30세+ 촬영술	30세 MRI + 촬영술
유방 (예방수술)	RRM 논의	RRM 논의	RRM 논의
난소 (RRSO)	**35–40세 권고**	40–45세 권고	45–50세 고려
췌장	50세 MRI·EUS	50세 MRI·EUS	50세 MRI·EUS
전립선 · 피부	40세 PSA 고려 / 피부검진	40세 PSA 권고 / 피부검진	40세 PSA 고려
약물 · 호르몬	OCs(난소) / Tamoxifen 제한적	OCs(난소) / Tamoxifen 우수(ER+)	내분비 예방 고려(ER+)

Moderate penetrance HBOC

관리 장기	RAD51C / D	BRIP1	ATM	CHEK2
유방 (선별)	40세 촬영술 + MRI	가족력 기반	30–35세 MRI / 40세 촬영	30–35세 MRI / 40세 촬영
유방 (예방수술)	RRM 미권고	RRM 미권고	RRM 미권고	RRM 미권고
난소 (RRSO)	45–50세 권고	45–50세 권고	일상적 수술 미권고	일상적 수술 미권고
췌장	미권고	미권고	50세 MRI · EUS (전체)	미권고
전립선	가족력 기반	가족력 기반	40세 PSA 고려	40세 PSA 고려

Lynch syndrome

관리 장기	MLH1 / MSH2 / EPCAM	MSH6	PMS2
자궁내막 (선별)	30–35세 내막 조직검사 (1–2년)	30–35세 내막 조직검사 (1–2년)	30–35세 내막 조직검사 (1–2년)
자궁·난소 (수술)	**40세 TH + BSO 고려**	**40세 TH / 45–50세 BSO**	50세(폐경 후) TH ± BSO
대장 (내시경)	**20–25세 시작 (1–2년 주기)**	30–35세 시작 (1–3년 주기)	30–35세 시작 (1–3년 주기)
위 · 소장	30–40세 내시경 (2–4년)	30–40세 위내시경 (2–4년)	일상적 감시 미권고
췌장 · 기타	췌장(가족력) / 피부(MSH2)	췌장(가족력) / 전립선 40세	일상적 감시 미권고
화학적 예방	Aspirin[1] / OCs · LNG-IUD	Aspirin / OCs · LNG-IUD	Aspirin / OCs · LNG-IUD

1. **Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial**

John Burn, Harsh Sheth, Faye Elliott*, Lynn Reed, Finlay Macrae, Jukka-Pekka Mecklin, Gabriela Möslein, Fiona E McRonald, Lucio Bertario, D Gareth Evans, Anne-Marie Gerdes, Judy W C Ho, Annika Lindblom, Patrick J Morrison, Jem Rashbass, Raj Ramesar, Toni Seppälä, Huw J W Thomas, Kirsi Pylvänäinen, Gillian M Borthwick, John C Mathers, D Timothy Bishop, on behalf of the CAPP2 Investigators*

Aspirin for cancer prevention in individuals with Lynch syndrome: first results from the CaPP3 multicentre, randomised, double-blind, non-inferiority trial

John Burn, Gillian M Borthwick, Faye Elliott, Finlay Macrae, Kai Ren Ong, Alison C Kraus, Nadir Arber, Jukka-Pekka Mecklin, Angel Alonso, Emma R Woodward, D Gareth Evans, Alex Murray, Katie Snape, Ruth E Cleaver, Adam Shaw, Huw J W Thomas, Ajith V Kumar, Dorothy Halliday, Lucy E Side, Rachel E Harrison, Rosemarie Davidson, Ruth Armstrong, Jackie Cook, Rachel Hart, Patrick J Morrison, Julian G Barwell, Alan Donaldson, Zoe Kemp, Jennie Murray, Zosia Miedzybrodzka, Caroline Pottinger, Jonathan Berg, Richard Gallon, D Timothy Bishop, on behalf of the CaPP3 co-investigators†

Case

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maternal aunt – Ovarian cancer at 52y

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Case

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C : Risk-reducing salpingectomy alone

D: Advise expedited childbearing followed by RRSO before age 40



2026년
대한부인종양학회
제31차 추계 심포지엄

2026.10. 23. (금) - 24. (토)

정부세종컨벤션센터 / 세종 코트야드 바이 메리어트

대한부인종양학회
Korean Society of Gynecologic Oncology