會議議程

時間: 2022 年 3 月 19 日

會議地點: 煙波飯店閣樓會議室

時間	議程	講師	座長
14:30-15:00	報到		
15:00-15:30	子宮頸韌帶保留子宮切除手術(CLSH)和微創手術檢體裝袋下切條取出法(CMM)	龐浸醛	丁大清
15:30-16:00	MTX for ectopic pregnancy:a possible legal claim	廖基元	丁大清
16:00-16:10	休息		
16:10-16:50	Evolution of 1L Ovarian Cancer Management in The Era of Precision Medicine: From Clinical Data to Real-World Practice	周宏學	丁大清
16:50-17:20	Why and How to Test for Homologous Recombination Deficiency in Ovarian Cancer	王映茹	廖基元
17:20-17:30	休息		
17:30-18:00	淺介口服避孕藥的演進	蔡啟智	廖基元
18:00-18:15	卵巢癌減積手術後熱化療(HIPEC)	陳盈希/龐浸醛	廖基元
18:15-18:30	重現 Okadayashi radical hysterectomy 步驟演示	陳姵辰/丁大清	廖基元
18:30	晚宴　用餐地點:煙波飯店 海宴 C 廳		

申請婦產科 B 類 3 學分

1110319花蓮婦產科學術&臨床個案分享會

題目1:精準微創手術--子宮頸韌帶保留子宮切除手術(CLSH)和微創手術檢體裝袋下切條取出法(CMM)

龐浸醛
花蓮慈濟醫院婦產部婦科主任
婦科微創手術中心主任

摘要

子宮全切除手術是全世界女性最常接受的婦科手術。文獻報告指出子宮全切除手術後會發生不同程度的骨盆底器官脫垂(POP)，發生率最高有到40%，包括陰道穹窿脫垂，膀胱脫垂等。流病學研究顯示子宮全切除手術的病人比沒有手術者在未來有更高的機率因為POP而需要再次接受骨盆底重建手術。這很可能跟子宮全切除手術時必須把女性骨盆底基本的支持系統--子宮頸周圍六條韌帶和兩側的子宮動靜脈切斷有關系；子宮動靜脈切斷會造成骨盆地部分筋膜或肌肉的血供至少是暫時性缺血甚至部分壞死，進一步造成骨盆底支持結構的不穩定，促進POP的發生。

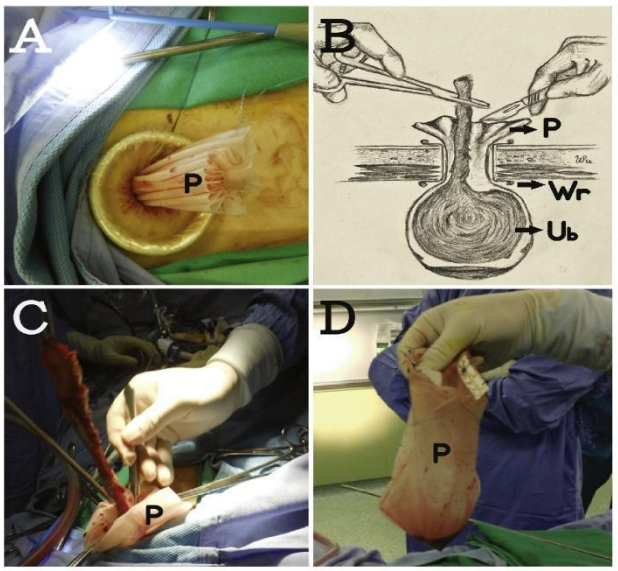
子宮次全切除手術固然能夠完整地保留了子宮頸韌帶，但是子宮頸保留下來日後有發生子宮頸癌的隱憂。此外，根據多項臨床試驗結果顯示5~24.8%次子宮次全切除手術的病人術後仍有點狀月經或週期性陰道炎的困擾，即便手術當時有對子宮頸內頸做電燒來破壞殘留內膜及子宮內頸腺體，其中約五分之一的病人後來還是需要再次手術將剩餘的子宮頸切除才能解決這些的困擾。

子宮頸韌帶保留子宮切除手術(Cervical Ligament Sparing Hysterectomy，CLSH)（圖1）就在這樣的背景下，於2014年被發展出來的精準微創手術。透過腹腔鏡進行次全切除手術後，進一步做子宮內頸錐狀切除;再經陰道進行子宮外頸錐狀切除。這樣，不但保留了女性骨盆底基本的支持系統--子宮頸的六條韌帶，周邊的神經和血管也得以保留。透過完全切除子宮頸腺體和s-c junction，術後也不再有月經和子宮頸癌。另外，因手術過程不需觸及子宮頸旁的輸尿管和膀胱，因此可避免這方面的併發症。CLSH可透過單一孔洞經肚臍完成，讓微創手術檢體取出的限制下降外，傷口癒合後也幾乎無疤。

微創手術後檢體取出一直都是一個重要的議題。過去在腹腔內使用碎瘤機（power morcellator）有散布潛在惡性子宮肉瘤的疑慮，或是造成寄生性肌瘤（parasitic myoma）、內膜異位症、腹膜炎、臟器受傷等併發症。慈濟婦科微創手術中心利用手術組織袋和wound retractor的協助下，發展出「裝袋下人工切條法（Contained Manual Morcellation，CMM）」，將檢體在腹腔內裝袋後，將袋口經牽開器傷口拉出，透過人工切條的方式取出檢體（圖2）。相對於傳統腹腔鏡碎瘤機，CMM讓檢體所有碎片和組織液皆留在袋內，可以避免檢體碎片遺留在腹腔內，造成潛在癌細胞擴散或者醫源性寄生性肌瘤等問題，因此對病人更加安全。

最後，值得一提的是CLSH和CMM在19屆亞太婦產科內視鏡醫學會（APAGE)發表時都雙雙獲獎。精準微創手術的精神包括只去除病灶、保留微創手術的優點和把併發症降到最低，CLSH和CMM就是很好的例子。本次報告將整理超過百例的CLSH和超過500例的CMM臨床經驗並以實際的手術影片和數據作分享和討論。

（圖1）

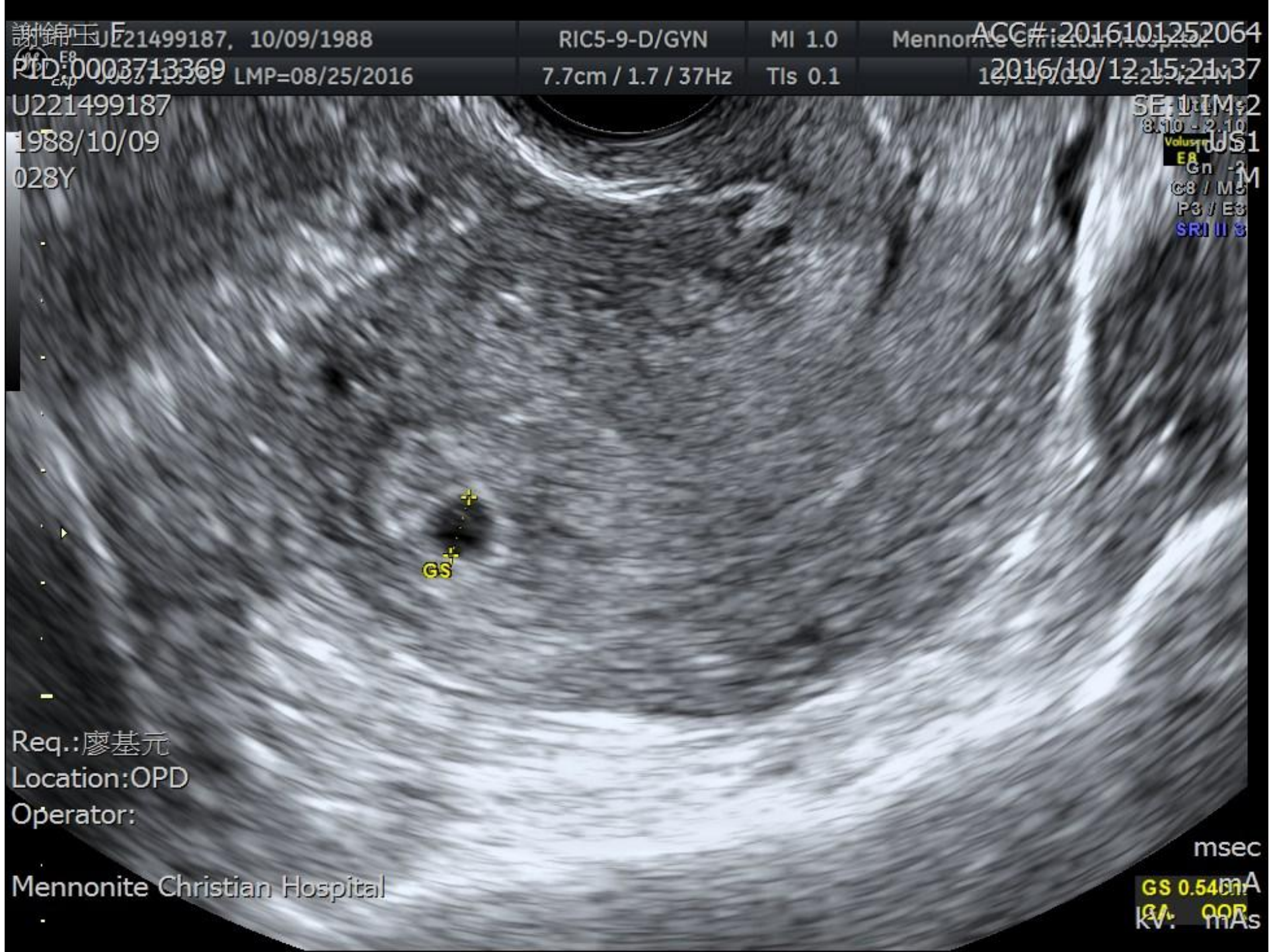


（圖2）

參考資料:
1. Two-phase laparoendoscopic single-site cervical ligament-sparing hysterectomy: An initial experience. Mun-Kun Hong, Tang-Yuan Chu, Jen-Huang Wang, Dah-Ching Ding.Ci Ji Yi Xue Za Zhi. Jul-Sep 2017;29(3):165-170. [PMID: 28974911]
2.Safety and efficacy of contained manual morcellation during laparoscopic or robotic gynecological surgery
Mun Kun Hong , Yu-Chi Wei , Tang-Yuan Chu , Jen-Hung Wang , Dah-Ching Ding .
Int J Gynaecol Obstet. 2020 Feb;148(2):168-173. doi: 10.1002/ijgo.13062. Epub 2019 Dec 10. [PMID: 31755560]
3.第19th 亞太腹腔鏡醫學會年會CLSH & CMM發表獲獎新聞:
https://hlm.tzuchi.com.tw/obsgyn/index.php/22-news-bulletin/1155-2019-03-12-08-06-25

MTX for ectopic pregnancy, a possible legal claim

- Case 1 ID 3713369
- LMP 1050825, 0926 urine HCG (+), sonar no IUP. 0929 B HCG 2800,
- Sonar neg, no IUP, Rx with MTX.
- 1012 6+6 wks , sonar sac.
- 1020 bleeding , sonar sac with yolk sac.
- Referred to Dr Huang for abortion.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Mennonite Christian Hospital
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1988/10/09
028Y
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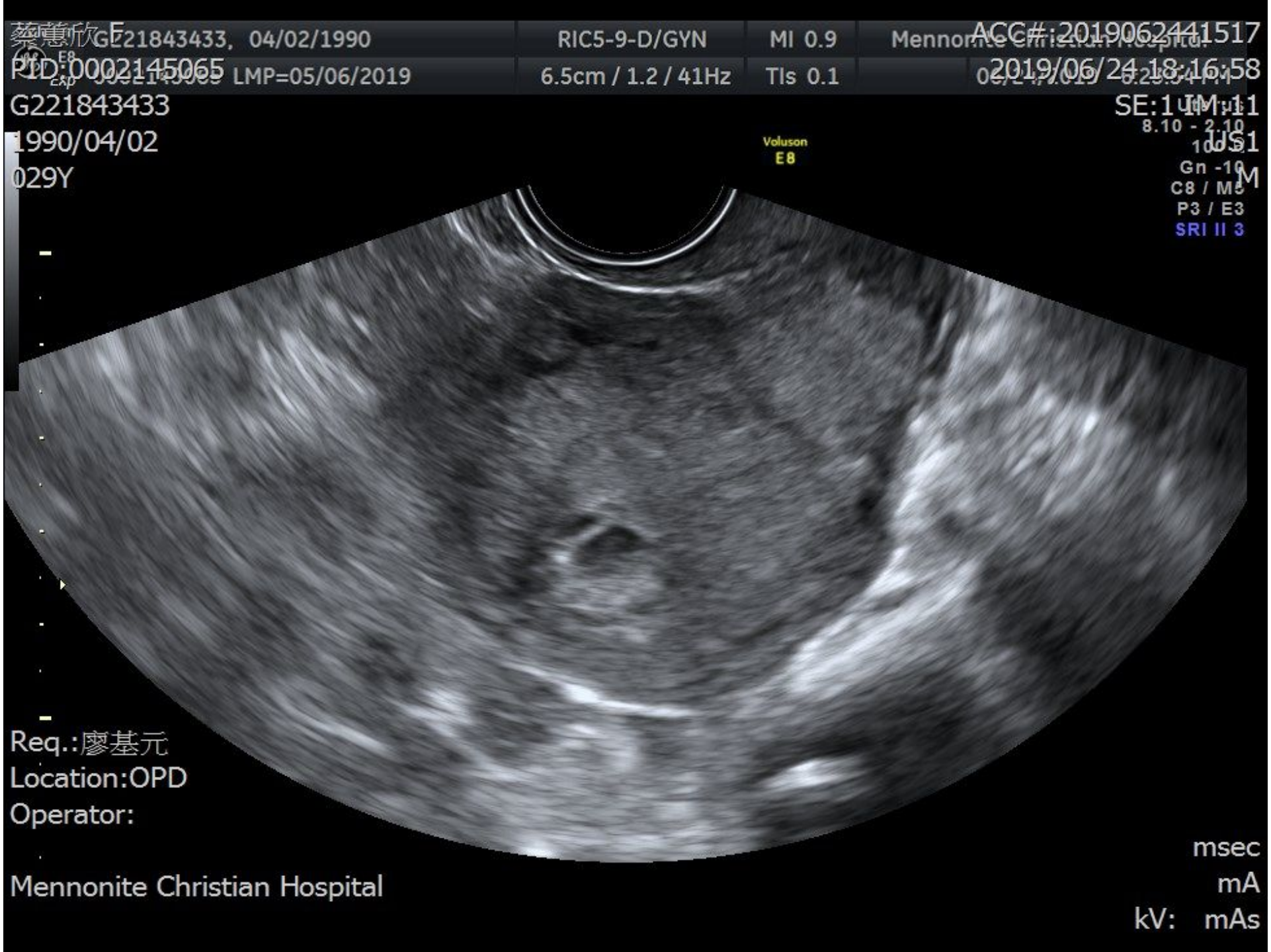
Operator:
Mennonite Christian Hospital
msec
mA
kV: mAs

Case 2

- 蔡女士 29y/o
- ID: 214506-5
- Imp: Ectopic pregnancy in myometrium

- Present Illness:
  This 29-year-old female, G8P2AA4SA1, soldier, a case of suspect ectopic pregnancy in Myometrium post laparoscopic + hysteroscopic + D&C was admitted via OPD. She was very well before and denied medical disease. She complained low abdominal pain and backache in early June, she visited to local Gyn clinic (彭文宗婦產科、李學智婦產科、黃港生婦產科) for help! Dr.彭及Dr.黃 told pregnancy but check sonogram no IUP. She visited to Hualien Tsu Chi hospital, 2019 06/17 (6 wks , LMP 0506) Gyn Dr check b-HCG: 6000 and accepted MTX treatment, 06/24 B-HCG: 9000 and accepted MTX treatment again.

- 0624 visited our clinic. She complained LLQ pain but no bleeding. Pelvic examination mild lifting pain. Physical examination: mild tenderness LLQ, no
- rebounding pain? Trans vaginal sonoram showed suspect left uterine gestational cavity sac ? IUP ? with flow. Option for follow or D&C, frozen if no villi do laparoscope or follow. After 0625 D&C → very minimal tissue found→ hysteroscopic exam → negative finding. > Laparoscope no ectopic pregnancy.
- SIS failure due to air.
- 0626 saline infusion sonogram proved intramyometrium ectopic pregnancy and tract could be traced.
- She was keep follow B HCG at out patient clinic.
- Past history.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1990/04/02
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Gn -10
C8 / M3
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SRI II 3
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Operator:
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mA
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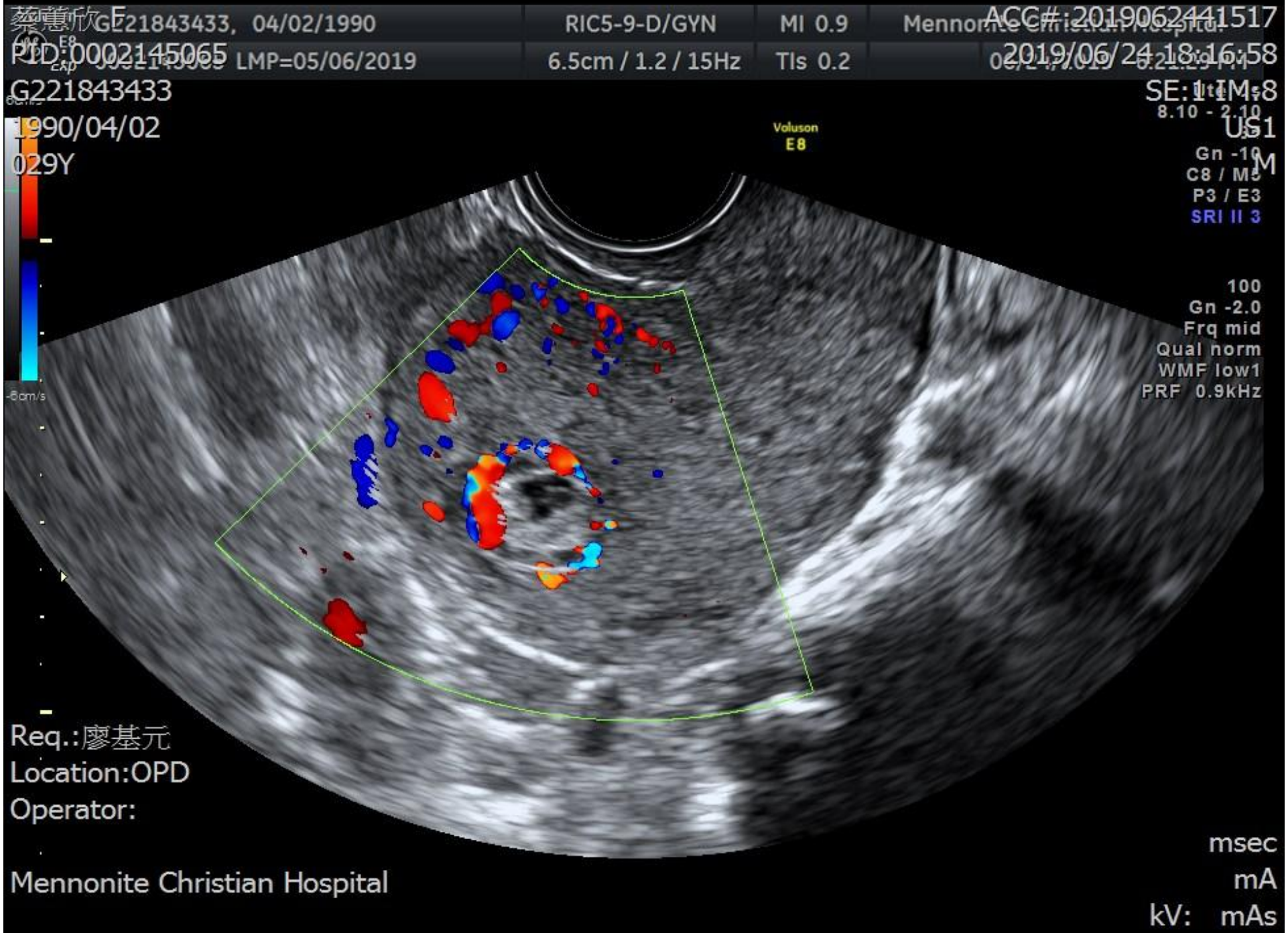
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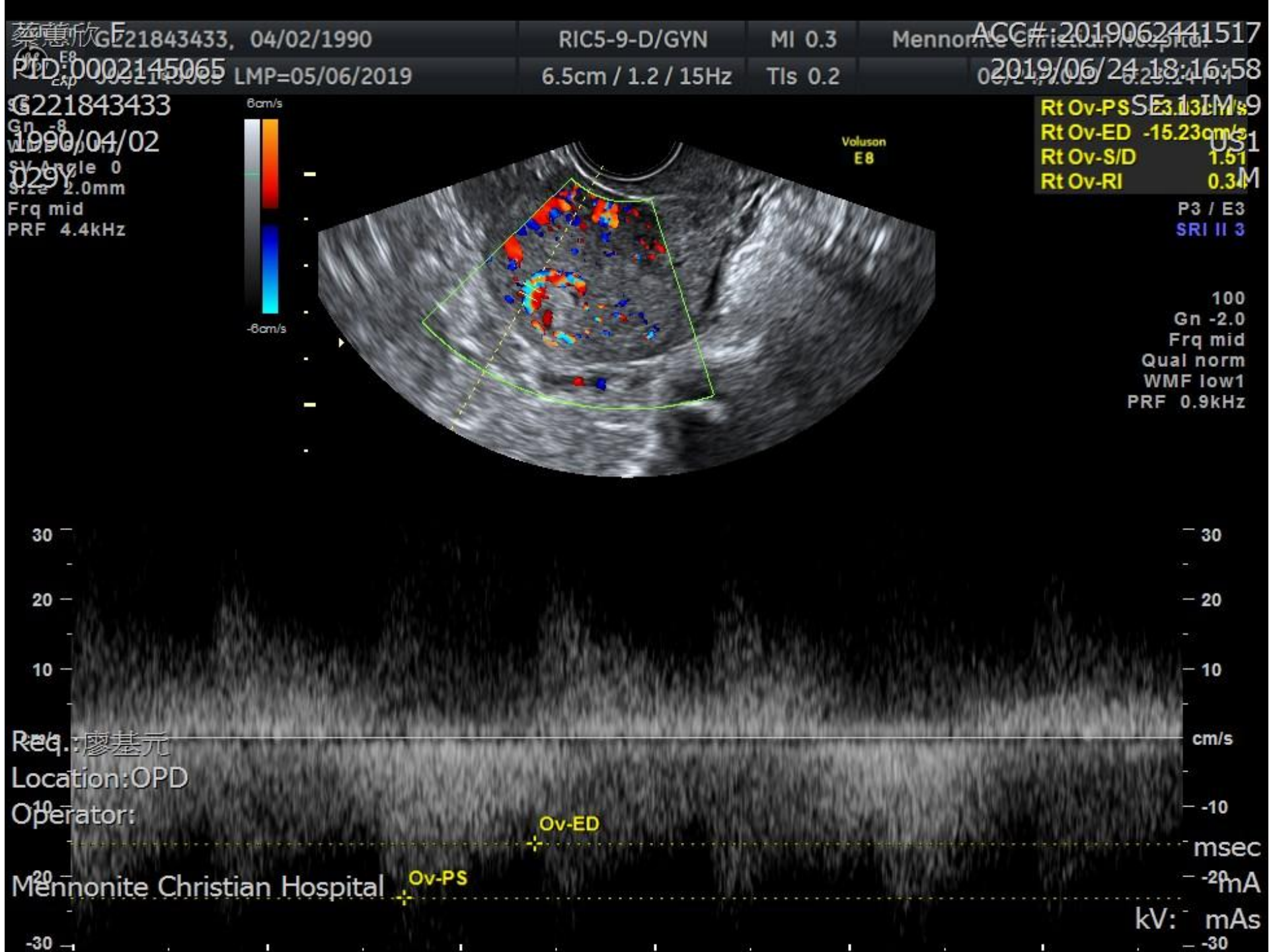
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6cm/s
-6cm/s
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E8
Rt Ov-PS 23.13cm/s
Rt Ov-ED -15.23cm/s
Rt Ov-S/D 1.51
Rt Ov-RI 0.34
SE:1 IM:9
US1
M
P3 / E3
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Qual norm
WMF low1
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30
20
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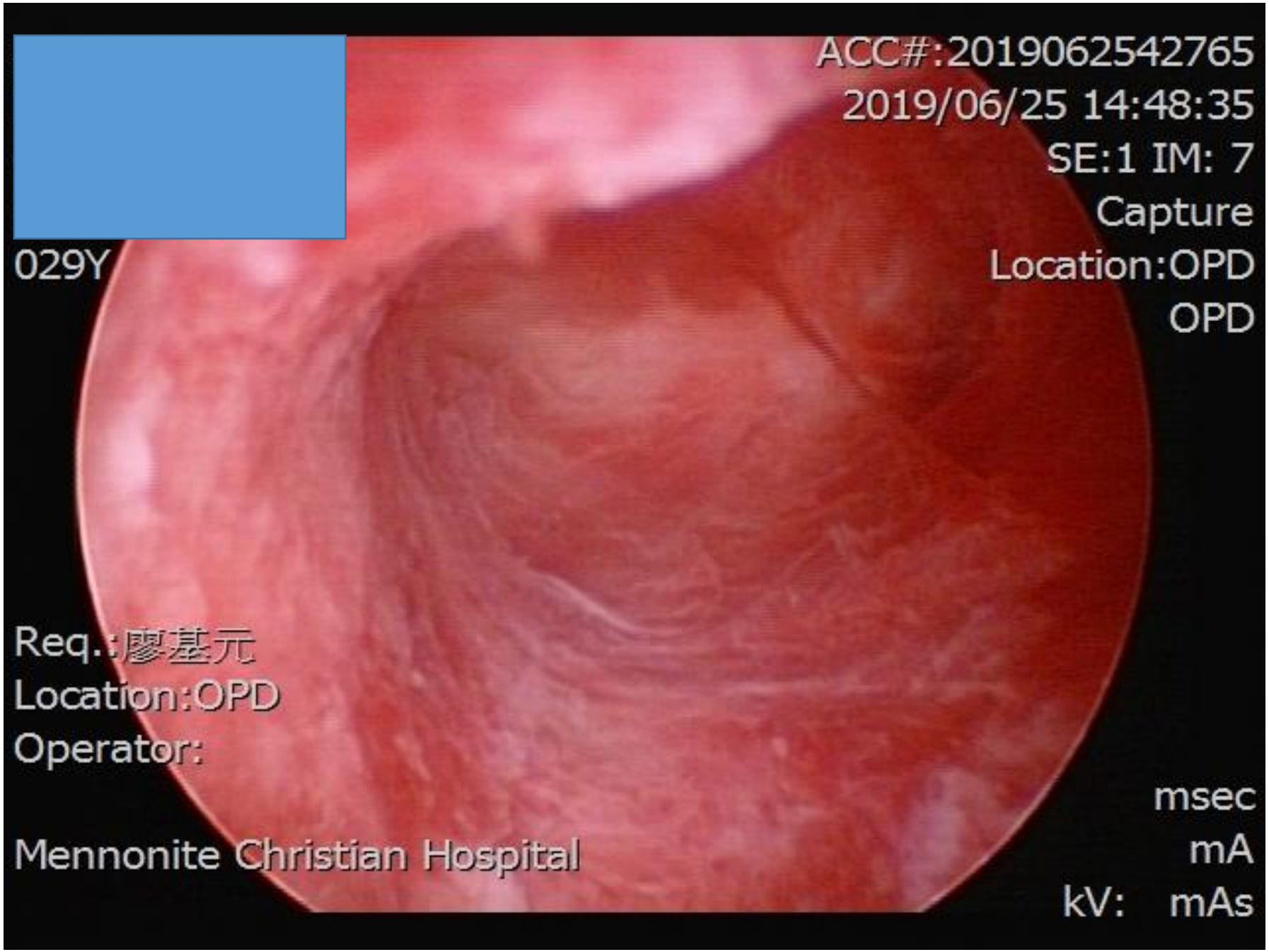
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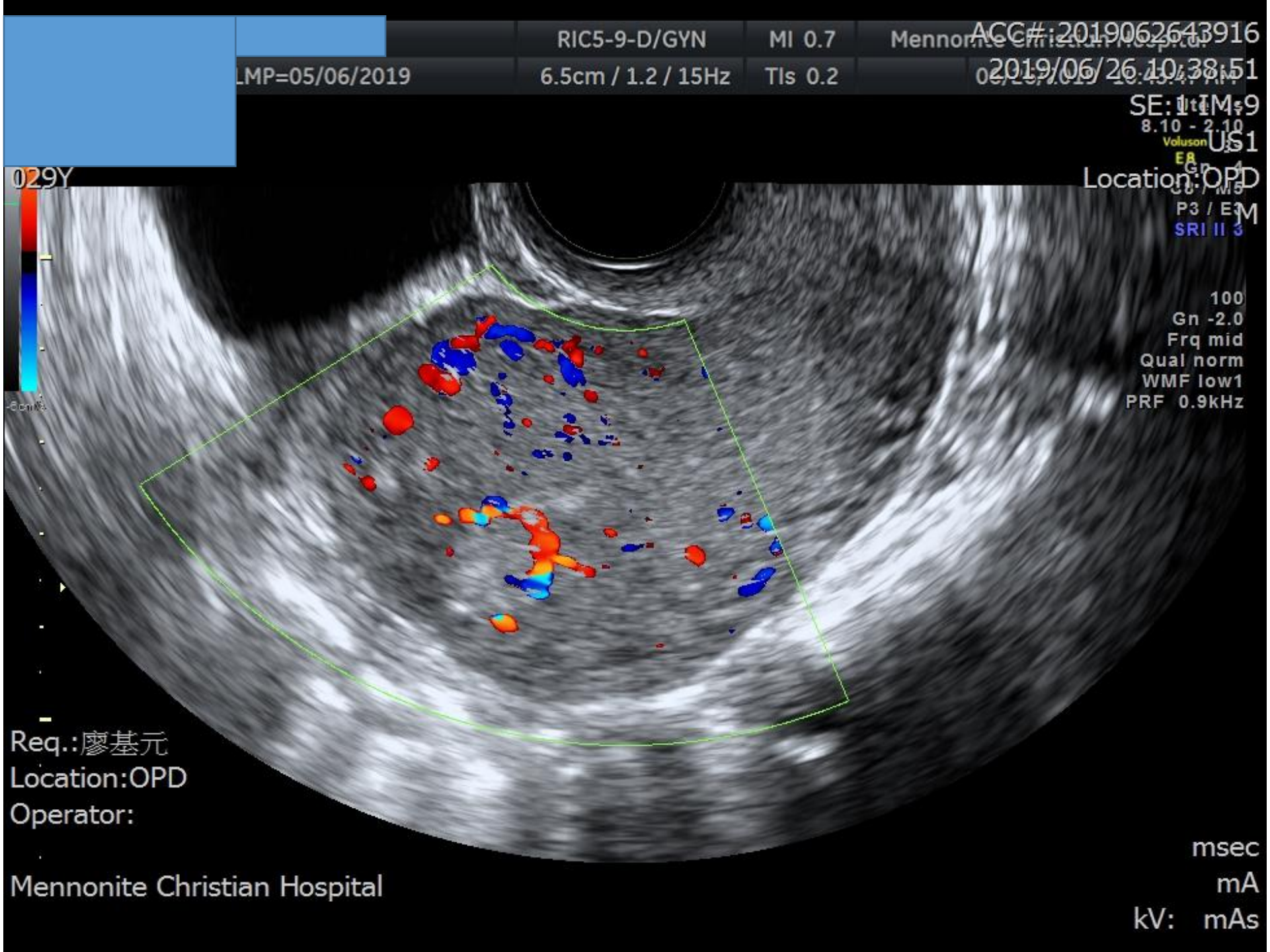
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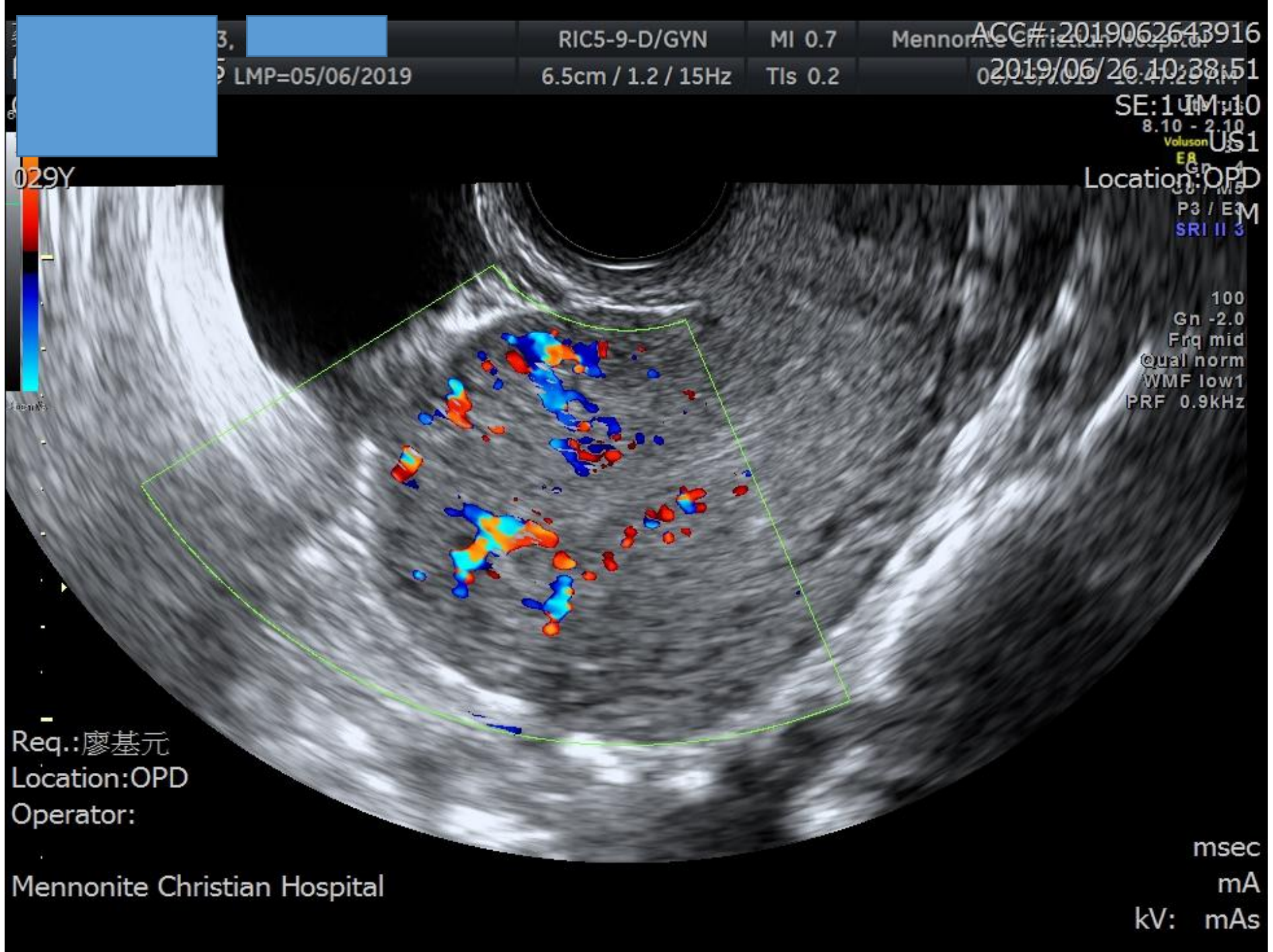
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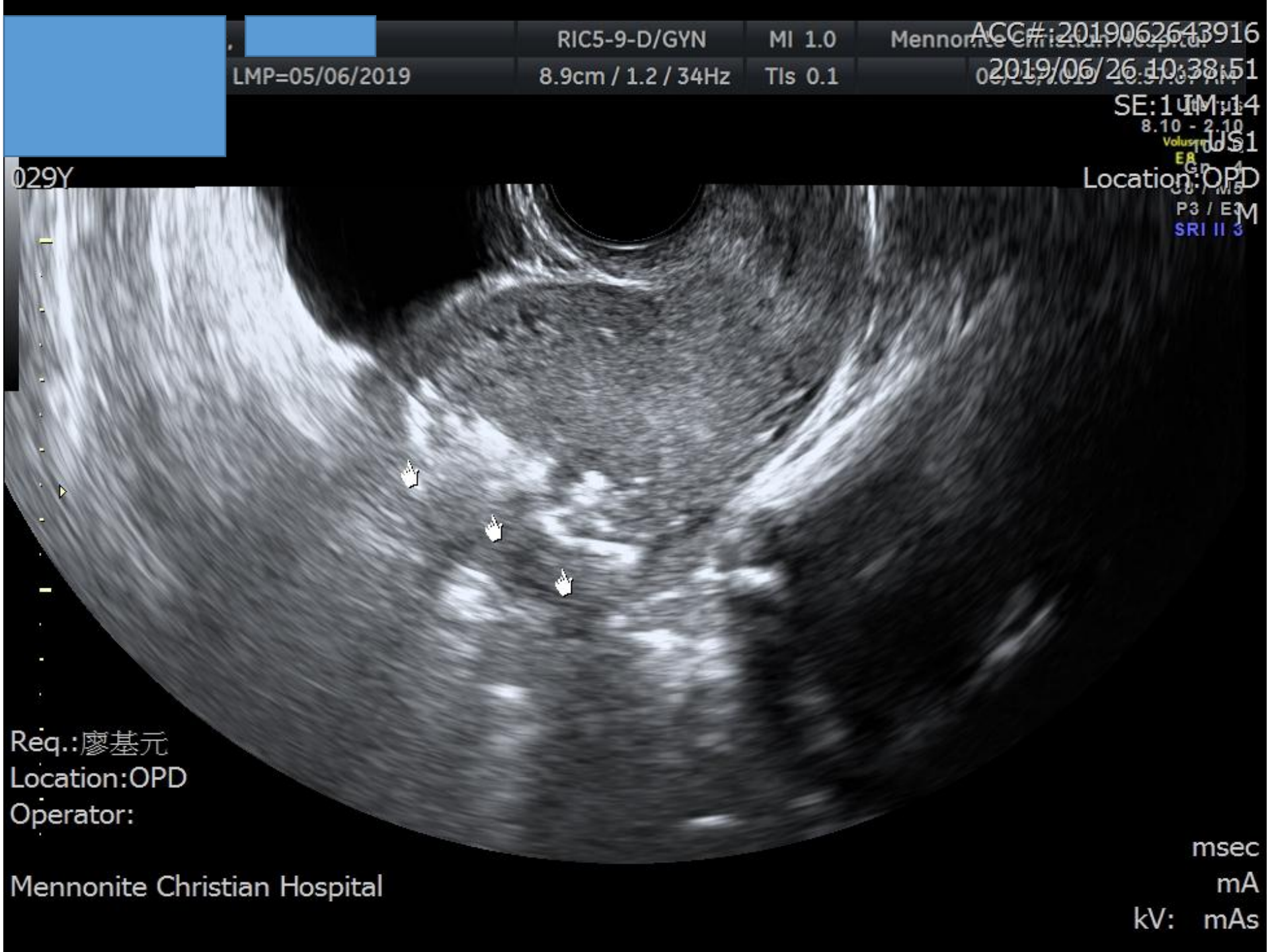
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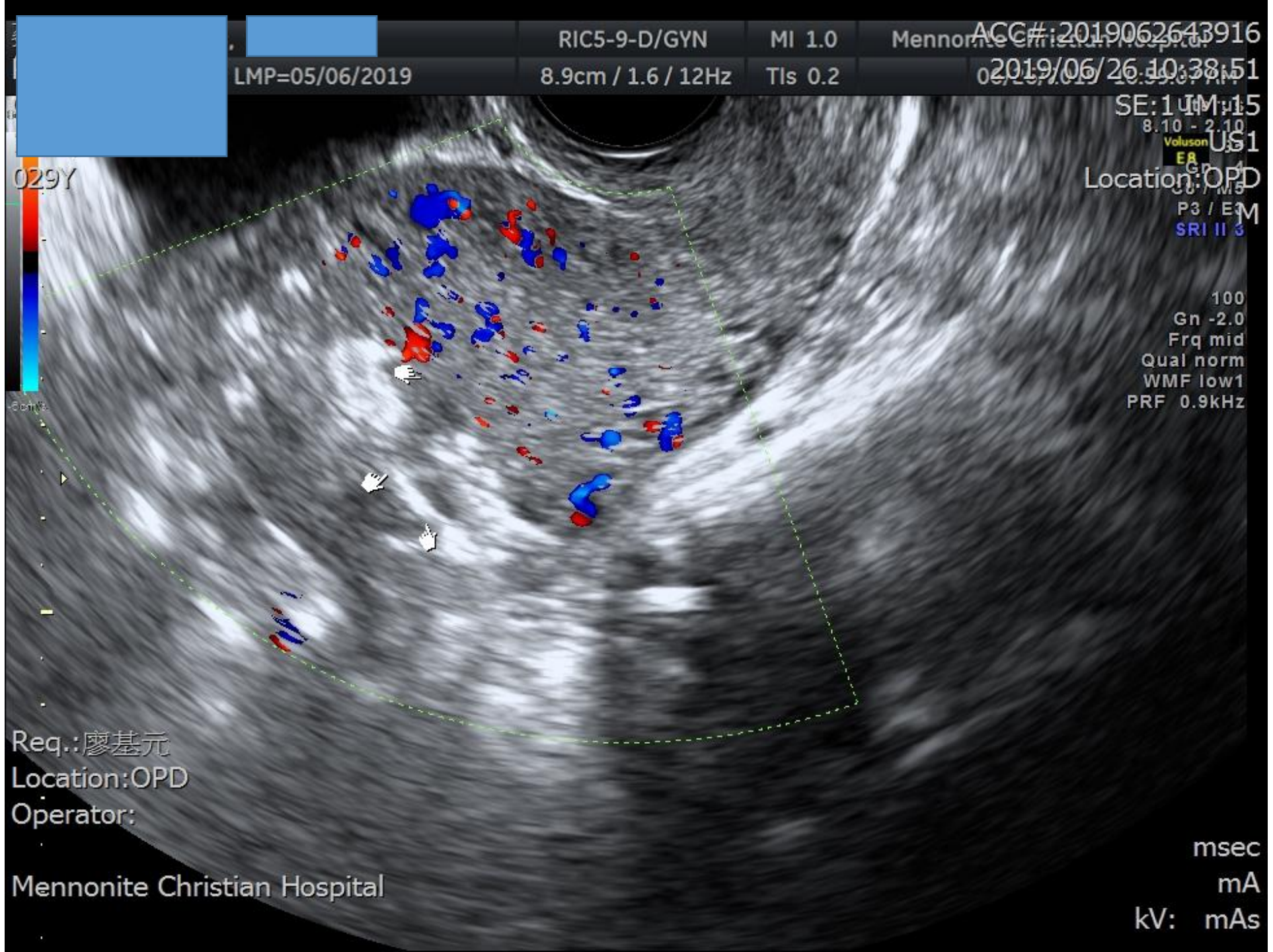
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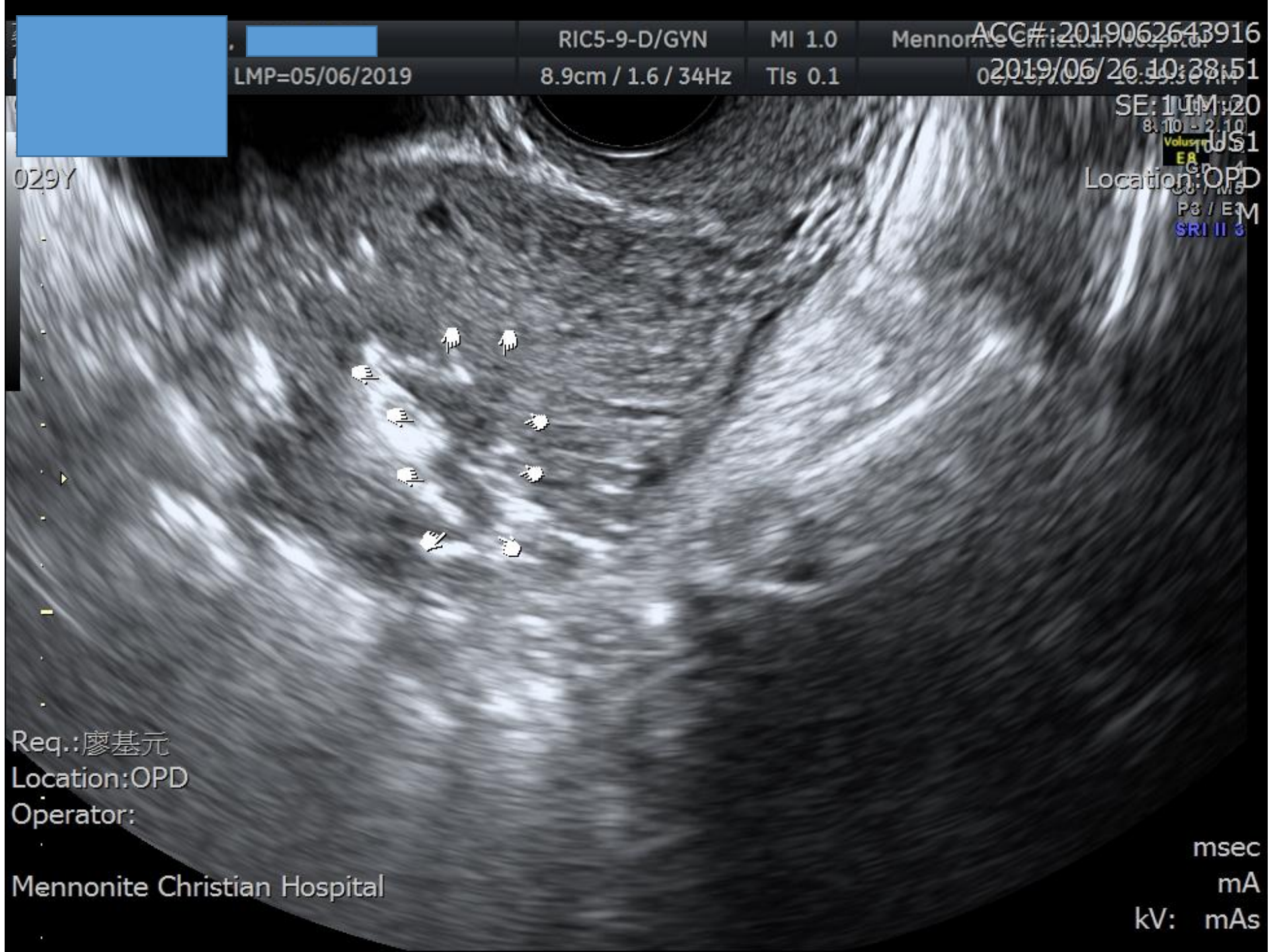
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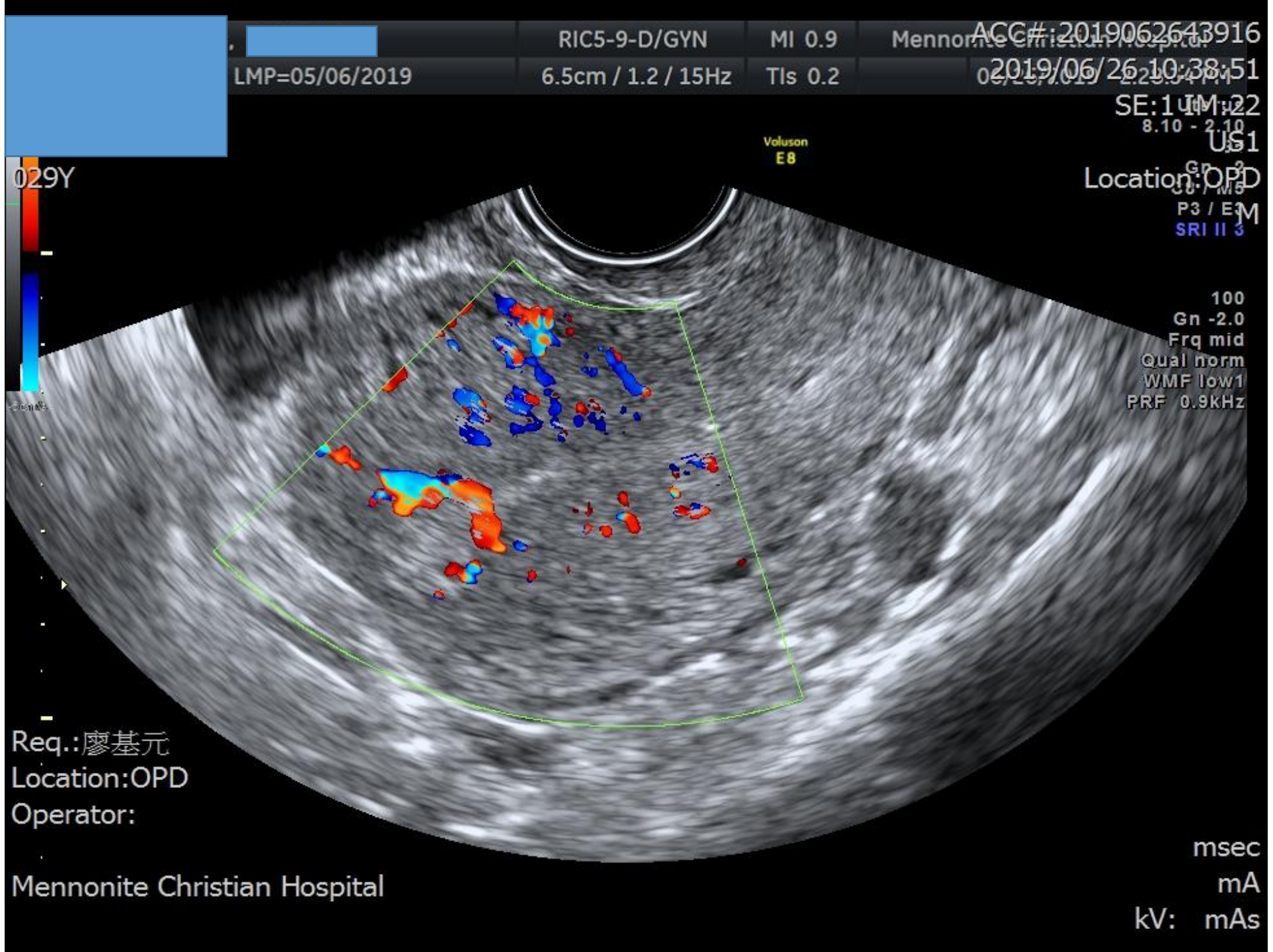
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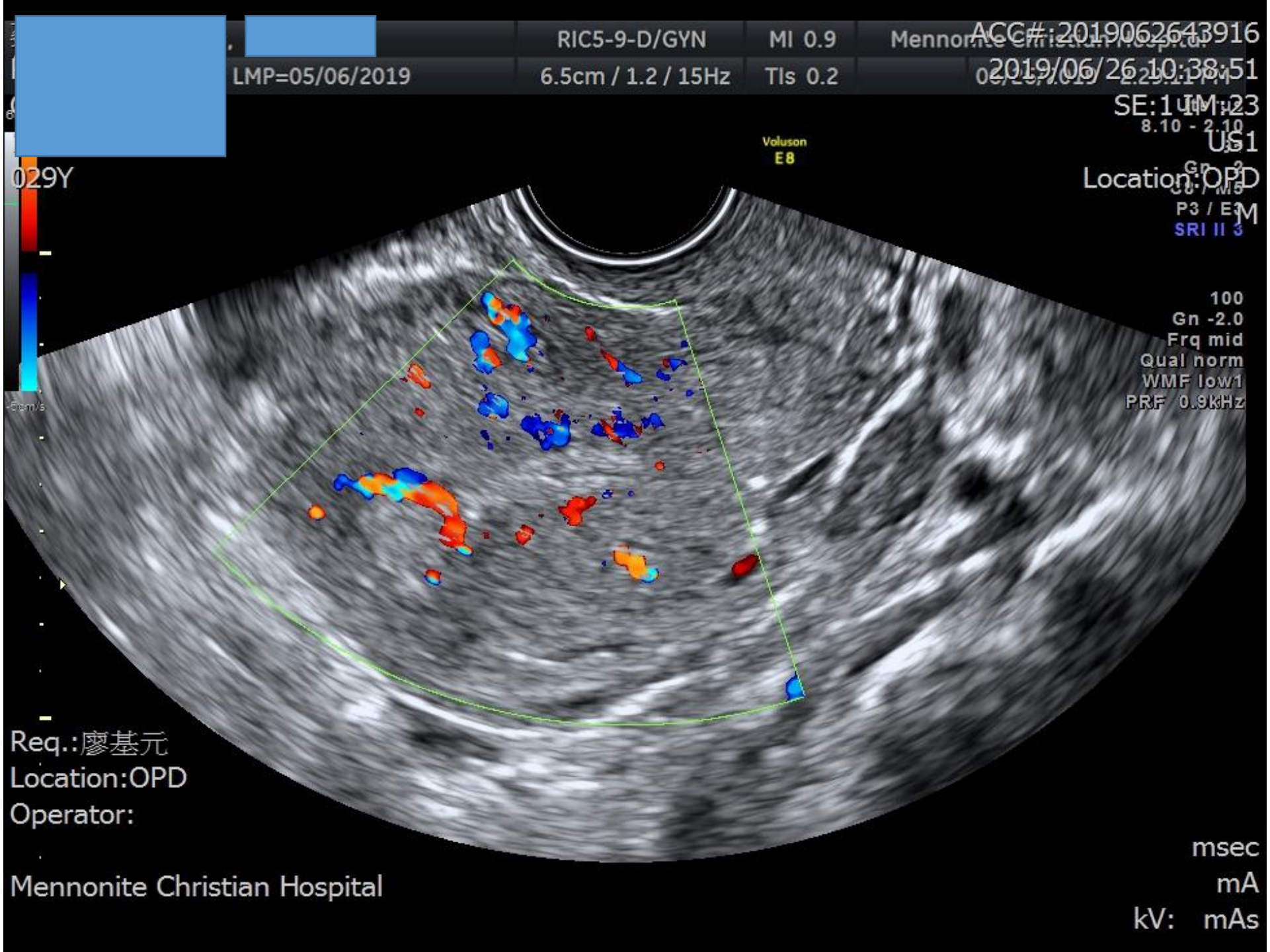
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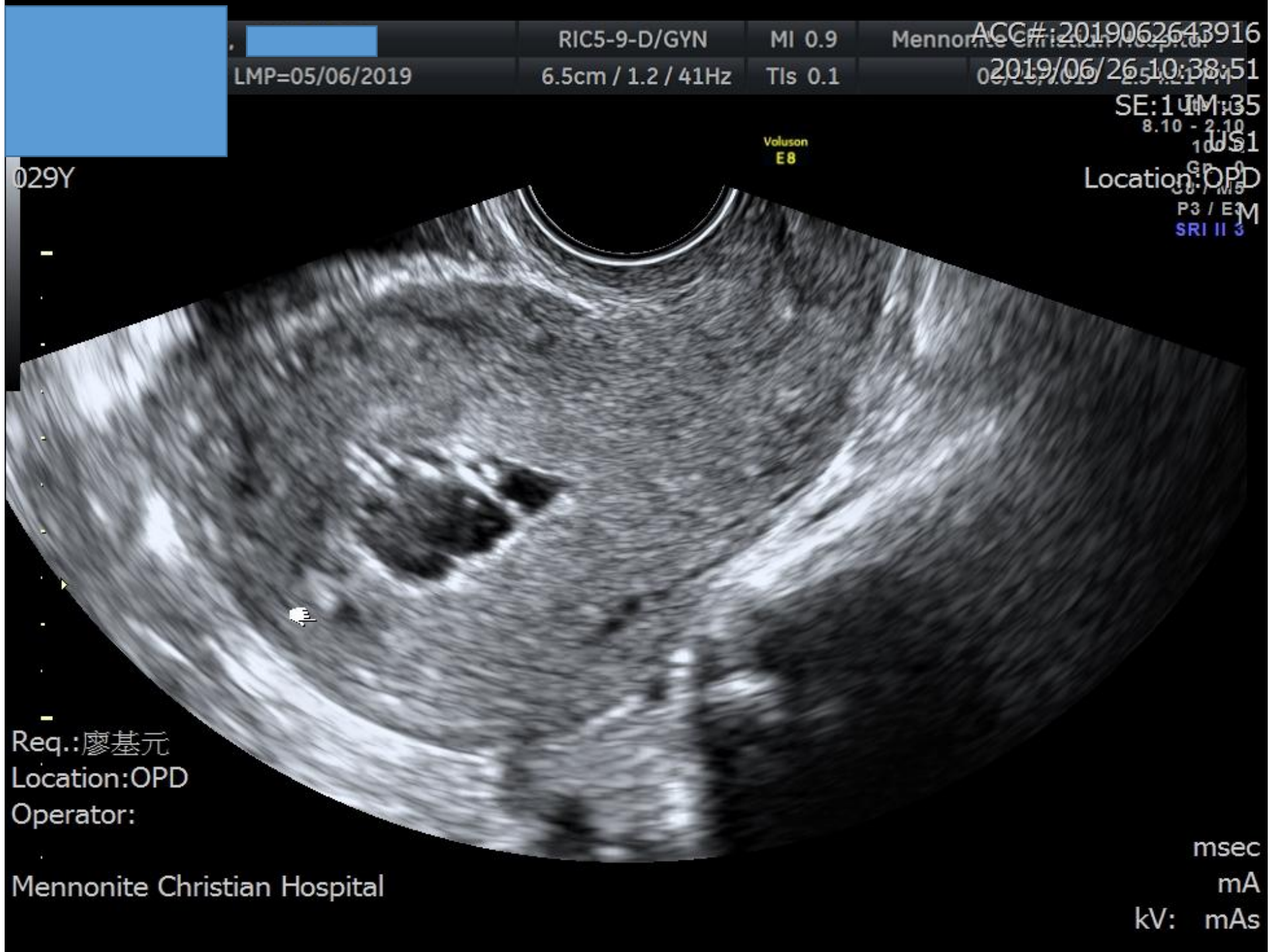
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msec
mA
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- 125004　　第四級外科病理Surgical pathology Level IV

- PATHOLOGICAL DIAGNOSIS:
- Uterus, endometrium, curettage --- gestational tissue
- PATHOLOGICAL GROSS FINDING:
- The specimen submitted consists of more than 10 tissue fragments measuring 3 gram in weight in aggregate, fixed in formalin.
-
- Grossly, they are brown and soft.
-
- All for section.
- PATHOLOGICAL MICOR FINDING:
- Microscopically, it shows a picture of gestational tissue with chorionic villi and cyto-/syncytiotrophoblast. Focally decidual endometrial stroma is included. No hydropic change or trophoblastic proliferation is discernible. Please follow up serum beta-HCG level clinically.

- **Methotrexate** administration often results in miscarriage, but in some instances women treated for a suspected ectopic **pregnancy** have been diagnosed with an ongoing **intrauterine pregnancy**. ... Wrongful treatment with **methotrexate** has become a common reason for medical liability.2013年11月1日

- **hCG discriminatory zone** — The discriminatory zone is the serum hCG level above which a gestational sac should be visualized by TVUS if an IUP is present. In most institutions, the discriminatory zone is a serum hCG level of 2000 international units/L. However, results and discriminatory zone vary by laboratory and institution, and some data suggest that an IUP may not be visible until a higher level is reached (3510 international units/L).

- Setting the discriminatory zone at 3510 international units/L minimizes the risk of interfering with a viable IUP, if present, but increases the risk of delaying diagnosis of an ectopic pregnancy. However, even in women with an hCG >3510 international units/L, if she is clinically stable, it is often prudent to get a follow-up ultrasound to exclude a viable IUP rather than treat for ectopic pregnancy. Management of women with ectopic pregnancy depends upon several factors and it is important to emphasize that a patient should not be treated for an ectopic pregnancy based upon a single assessment with ultrasound and hCG. If an IUP has not been confirmed, the hCG is between 2000 and 3510 international units/L, the patient is stable, and the pregnancy is desired, the patient may be followed with close surveillance until the hCG is at least 3510 international units/L. However, if an ectopic pregnancy seems likely and the pregnancy is not desired, treatment may be given if the hCG is >2000 international units/L, the serial hCG results are consistent with an abnormal pregnancy, and the ultrasound shows no IUP. Importantly, if there are concerns about rupture of a fallopian tube or other structure by an ectopic gestation, urgent treatment is required.

- The reported sensitivity and specificity of TVUS for the detection of an ectopic pregnancy at a serum hCG of >1500 international units/L are 15.2 and 93.4 percent, respectively, and for an hCG level of >2000 international units/L,sensitivity and specificity are 10.9 and 95.2 percent, respectively [21]. However, in order to not administer methotrexate inadvertently, a decision to treat for ectopic pregnancy should not be based solely on a single hCG value.
-

- It is important to note that there is a variation in the level of hCG across pregnancies for each gestational age and the discriminatory levels are not always reliable. In one study, 185 of 188 (98 percent) IUPs in women with hCG above 1500 international units/L were visualized [22]. However, in a study of 651 women with first trimester bleeding or pain, among viable IUPs, a gestational sac was seen at differing hCG levels in the following proportion of pregnancies: 1500 milli-international units/mL (80 percent of had a gestational sac visualized), 2000 milli-international units/mL (91 percent), and 3510 milli-international units/mL (99 percent) [20].
- Other causes for variation of the discriminatory zone are that it is dependent upon the skill of the ultrasonographer, the quality of the ultrasound equipment, the presence of physical factors (eg, fibroids, multiple gestation, obesity), and the laboratory characteristics of the hCG assay used.

- In a study of 20 patients in the first 40 days of pregnancy, the hCG concentration rose by at least 66 percent every 48 hours in 85 percent of viable IUPs; only 15 percent of viable pregnancies had a rate of rise less than this threshold [25].
- ●Two studies that included more than 1000 women with symptomatic early pregnancies found that pregnancies with an hCG rise of ≥35 percent in two days should be considered potential IUPs. In one study, 99.9 percent of IUPs had an hCG rise of ≥35 percent every two days [26]. The other study found that diagnosis of IUP by use of the criterion of an hCG rise of ≥35 percent every two days had a sensitivity of 92 percent and specificity of 94 percent [27

- The most common protocol is to measure the hCG every two days. In our practice, we find that measurement every 72 hours is more practical than every 48 hours, and allowing 72 hours for doubling helps to avoid misclassifying those viable pregnancies with slower than average doubling times. Yet, in practice, management is usually based on clinical findings and by TVUS, with little emphasis on hCG doubling time.
-

hCG below the discriminatory zone

- The most common protocol is to measure the hCG every two days. In our practice, we find that measurement every 72 hours is more practical than every 48 hours, and allowing 72 hours for doubling helps to avoid misclassifying those viable pregnancies with slower than average doubling times. Yet, in practice, management is usually based on clinical findings and by TVUS, with little emphasis on hCG doubling time.
-

- **hCG is rising normally** (increasing by ≥35 percent in 48 hours OR doubling in 72 hours) – The patient should be evaluated with TVUS when the hCG reaches 3500 international units/L. At that time, an IUP or ectopic pregnancy can be diagnosed by TVUS.
- •**hCG is rising, but NOT normally** – The lack of a normal rise in hCG across three measurements (the initial serum quantitative hCG and two additional serial measurements) is consistent with an abnormal pregnancy (an ectopic gestation or IUP that will ultimately abort). The hCG level may be rising slowly or may plateau at or very close to the previous level. The clinician can be reasonably certain that a normal IUP is not present. The number of serial measurements to use to make the diagnosis has not been well studied. Some data suggest that use of three serial measurements is more effective than two measurements [32].
- In patients with an abnormal rise in hCG, the TVUS should be repeated or diagnostic uterine aspiration performed. If there are findings that confirm an IUP, an ectopic pregnancy is excluded and the patient should be managed as a failed pregnancy. If an extraovarian adnexal mass consistent with an ectopic pregnancy is visualized, then medical or surgical treatment is administered for a presumed ectopic pregnancy. If an extraovarian adnexal mass is not visualized, some clinicians administer methotrexate and others perform aspiration to exclude an IUP and thereby avoid medical therapy of nonviable IUP [33].
  (See 'Aspiration' below.)
- •**hCG is decreasing** – A decreasing hCG is most consistent with a failed pregnancy (eg, spontaneous abortion, tubal abortion, spontaneously resolving ectopic pregnancy). To follow up with these patients, weekly hCG concentrations should be measured until the result is undetectable.

hCG above the discriminatory zone

- For women with a quantitative serum hCG above the discriminatory zone, the results of TVUS guide management. If TVUS does not reveal an IUP and shows a complex extraovarian adnexal mass, an extrauterine pregnancy is almost certain. Treatment of ectopic pregnancy should be instituted. If the serum hCG level is ≥3500 milli-international units/mL and no IUP is visible on TVUS, it is almost certain that the pregnancy is extrauterine.
- The diagnosis of ectopic pregnancy is less certain if no complex extraovarian adnexal mass can be visualized, since there is variability in the level of expertise among ultrasonographers. Furthermore, a serum hCG >2000 international units/L without visualization of intrauterine or extrauterine pathology may represent a multiple gestation, since there is no proven discriminatory level for multiple gestations. For these reasons, our next step in this clinical scenario is to repeat the TVUS examination and hCG concentration two days later. If an IUP is still not observed on TVUS, then the pregnancy is abnormal.
-

Aspiration

- The intrauterine location of a pregnancy is diagnosed with certainty if trophoblastic tissue is obtained by uterine curettage. Obviously, the use of curettage as a diagnostic tool is limited by the potential for disruption of a viable pregnancy. Moreover, the sensitivity of curettage in finding chorionic villi is only 70 percent [37]. Pipelle endometrial biopsy is even less sensitive than curettage for detection of villi; sensitivities reported in two small series were 30 and 60 percent [38,39]. If curettage is performed, serum hCG levels can be followed post-curettage if histopathology does not confirm the clinical impression. When an IUP has been evacuated, hCG levels should drop by at least 15 percent the day after evacuation [33].
- Some experts have recommended performing aspiration only on women with both an hCG concentration below the discriminatory zone and a low doubling rate [40,41]. Approximately 30 percent of these patients have a nonviable intrauterine gestation, and the remainder have an ectopic pregnancy [41,42]. Knowing the results of aspiration avoids unnecessary methotrexate treatment of the 30 percent of patients without ectopic pregnancy. The positive predictive value is high if chorionic villi are found [43].
- A decision analysis comparing the cost/complication rates in patients who undergo diagnostic aspiration before administration of methotrexate with those who do not have a aspiration concluded there was no significant benefit of one approach over the other [42]. However, the authors' preference was to perform aspiration in these patients to be more certain of the diagnosis, and felt this information was useful prognostically (eg, risk of recurrence) and for future decision-making.
- In contrast, we and others believe it is more practical and less invasive to continue observation or administer one dose of methotrexate than to perform aspiration [44,45]. The side effects of one dose of methotrexate are negligible. In addition, aspiration carries a risk of intrauterine adhesion formation

Medical Malpractice

- If you were mistakenly prescribed Methotrexate on a daily dose, or your pharmacist filled your Methotrexate prescription incorrectly, **you may have a legal claim**.
- ISMP has identified methotrexate as a **high-alert medication**[11] in both hospital and community settings, even when used for nononcological purposes, such as RA. As with all high-alert medications, there is a heightened risk of significant patient harm when this drug is used in error.

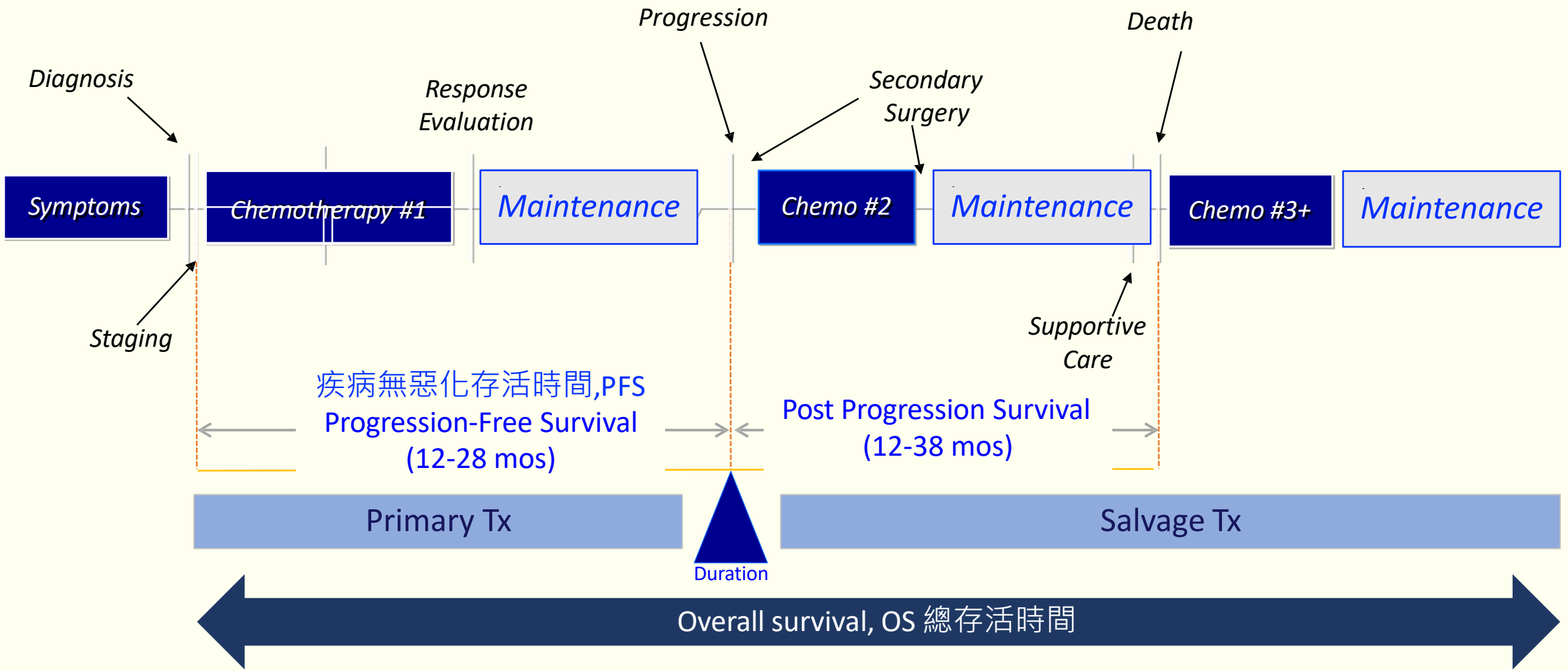
Evolution of 1L Ovarian Cancer Management in The Era of Precision Medicine: From Clinical Data to Real-World Practice

林口長庚紀念醫院婦癌科
周宏學 醫師

TW-17900-LYN-26/11/2021

卵巢癌隨著復發次數增加終將產生抗藥性，使用維持療法(maintenance therapy)延長存活時間為治療趨勢

卵巢癌的治療：手術加化學治療，但是復發性高(70%)

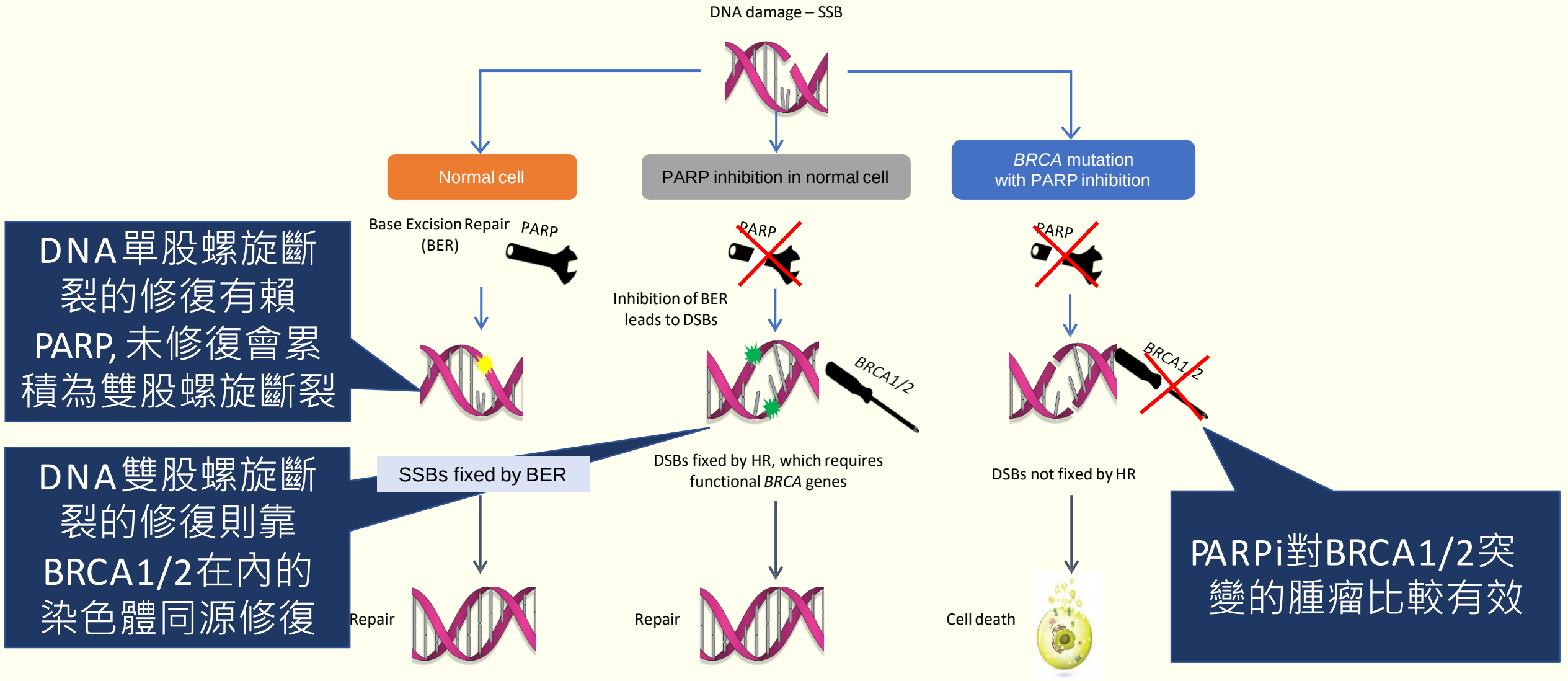


Switch Maintenance Tx
替換性維持療法

Synthetic Lethality 加成殺傷力

BRCA mutant cancers are selectively sensitive to PARP inhibition

當BRCA mutation而無法救援時，抑制PARP才能殺死癌細胞



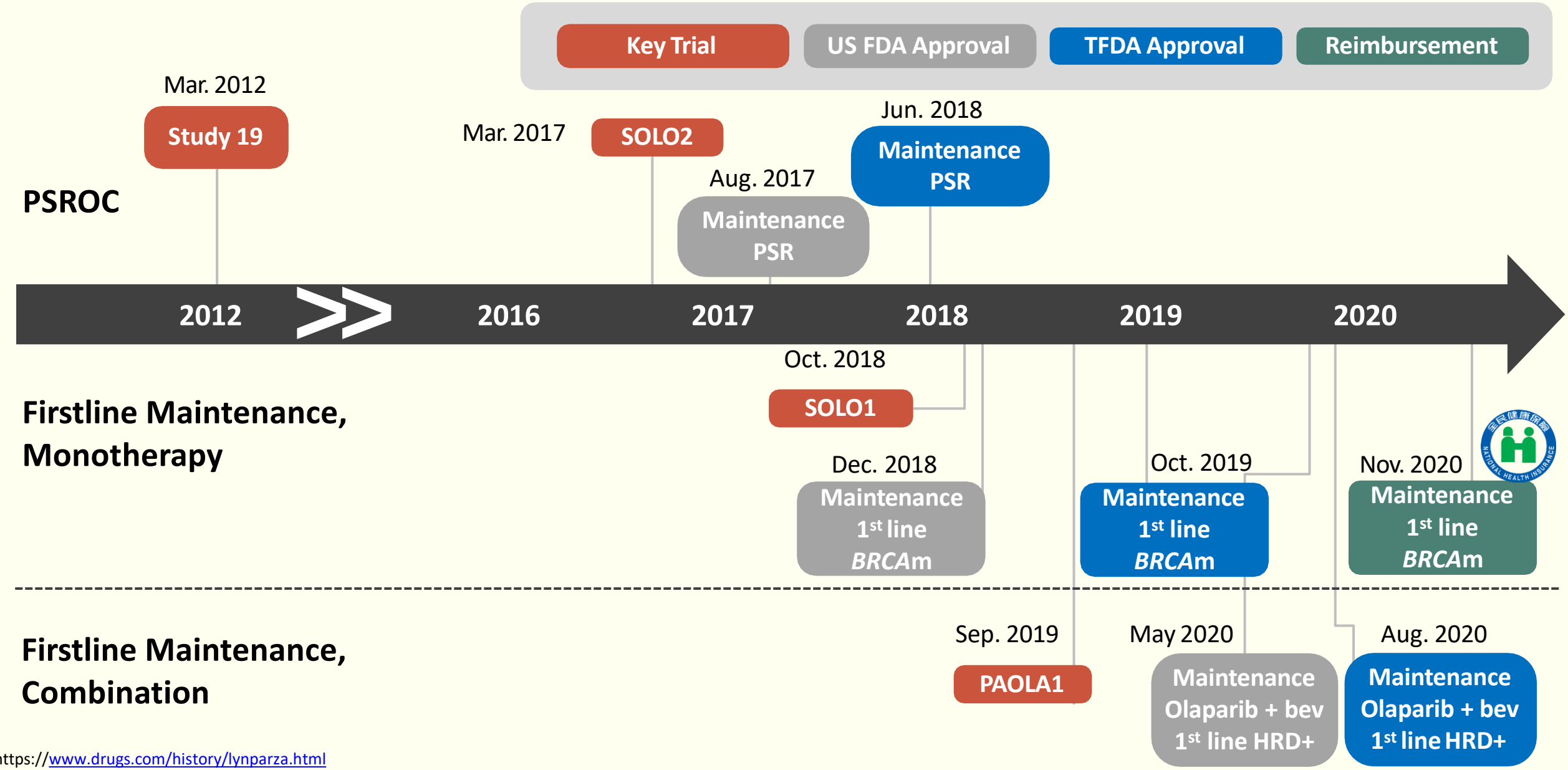
DNA單股螺旋斷裂的修復有賴PARP, 未修復會累積為雙股螺旋斷裂

DNA雙股螺旋斷裂的修復則靠BRCA1/2在內的染色體同源修復

PARPi對BRCA1/2突變的腫瘤比較有效

Ellisen LW. *Cancer Cell.* 2011;19:165–167; McLornan DP et al. *N Engl J Med.* 2014;371:1725–1735.

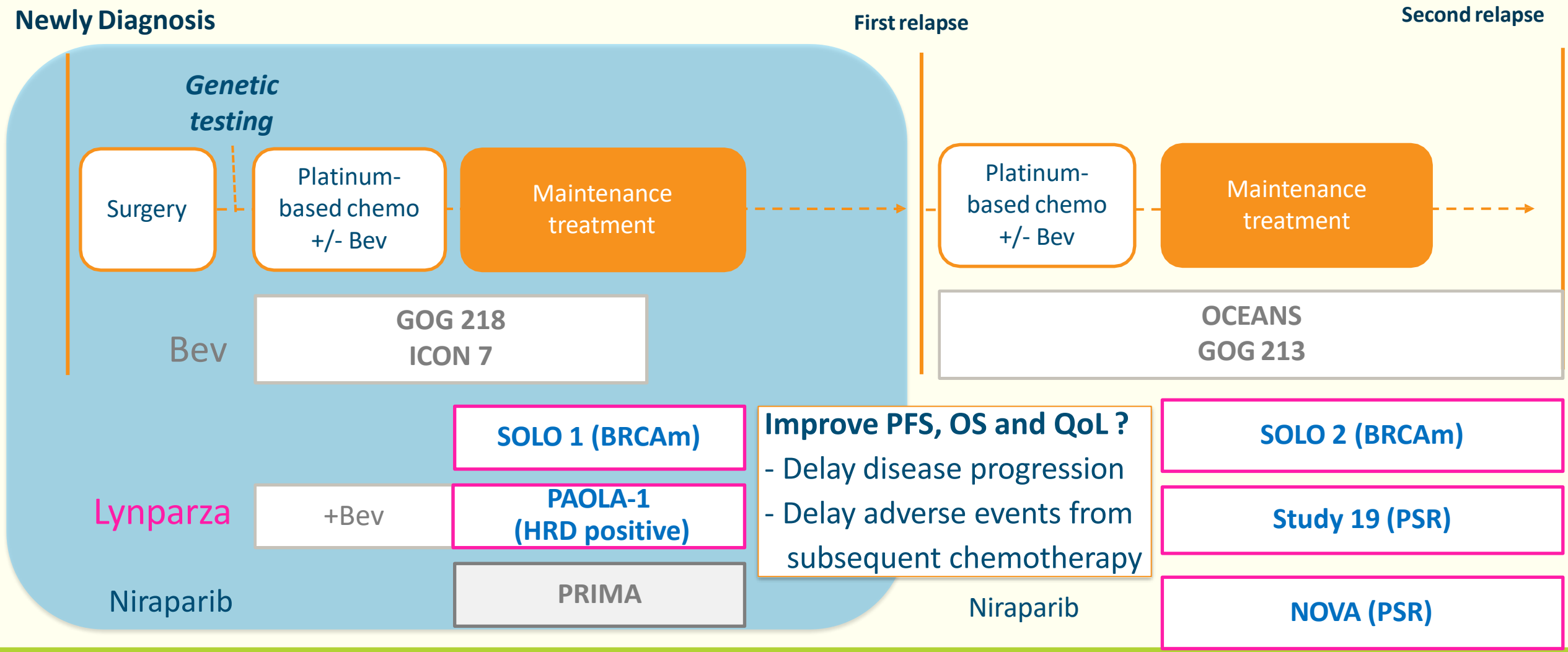
Lynparza Timeline in OC : Key Data, Approval, and Reimbursement



https://www.drugs.com/history/lynparza.html
https://www.fda.gov.tw/TC/siteContent.aspx?sid=9926 ; https://www.fda.gov.tw/TC/siteContent.aspx?sid=9927

Current strategies for targeted treatment of newly-diagnosed high-grade serous epithelial ovarian cancer in Taiwan

Lynparza™ olaparib tablets 150 mg



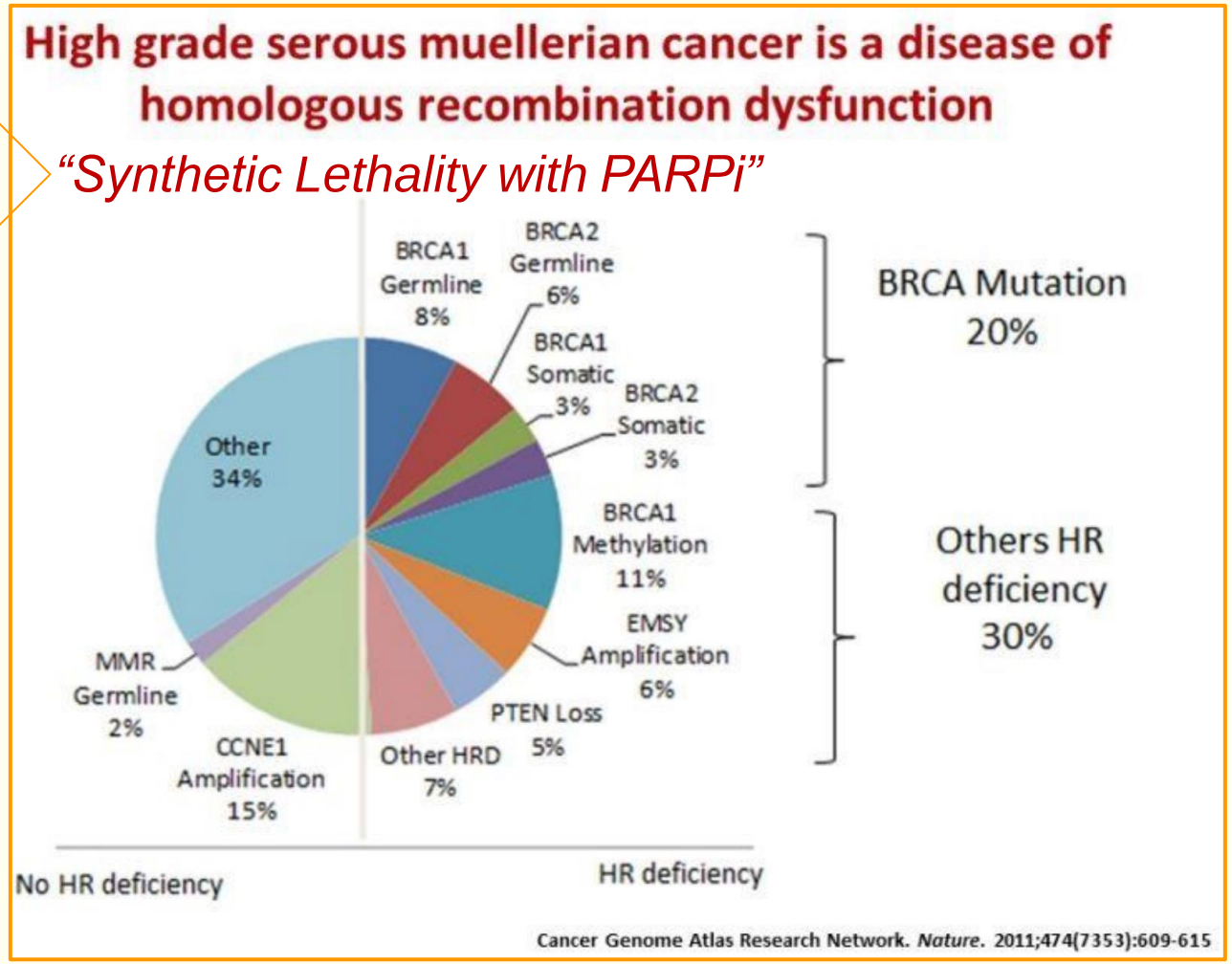
Bev=bevacizumab
Chemo=chemotherapy
PSR=platinum sensitive relapse

Olaparib is only indicated for the dosage of tablets in Taiwan, please refer to the TFDA approved package insert for the full information.

台灣卵巢癌組織分類%和國外略有不同，漿液性卵巢癌大約佔45%

組織分類	%
漿液性卵巢癌	44.6
清細胞卵巢癌	18.5
子宮內膜樣卵巢癌	15.4
黏液性卵巢癌	9.2
其他上皮癌	8.5
混合細胞腺癌	3.8
合計 (全部)	100

"Anti-angiogenesis with Bevacizumab"



GOG218: Final Overall Survival of a Randomized Trial of Bevacizumab for Primary Treatment of Ovarian Cancer

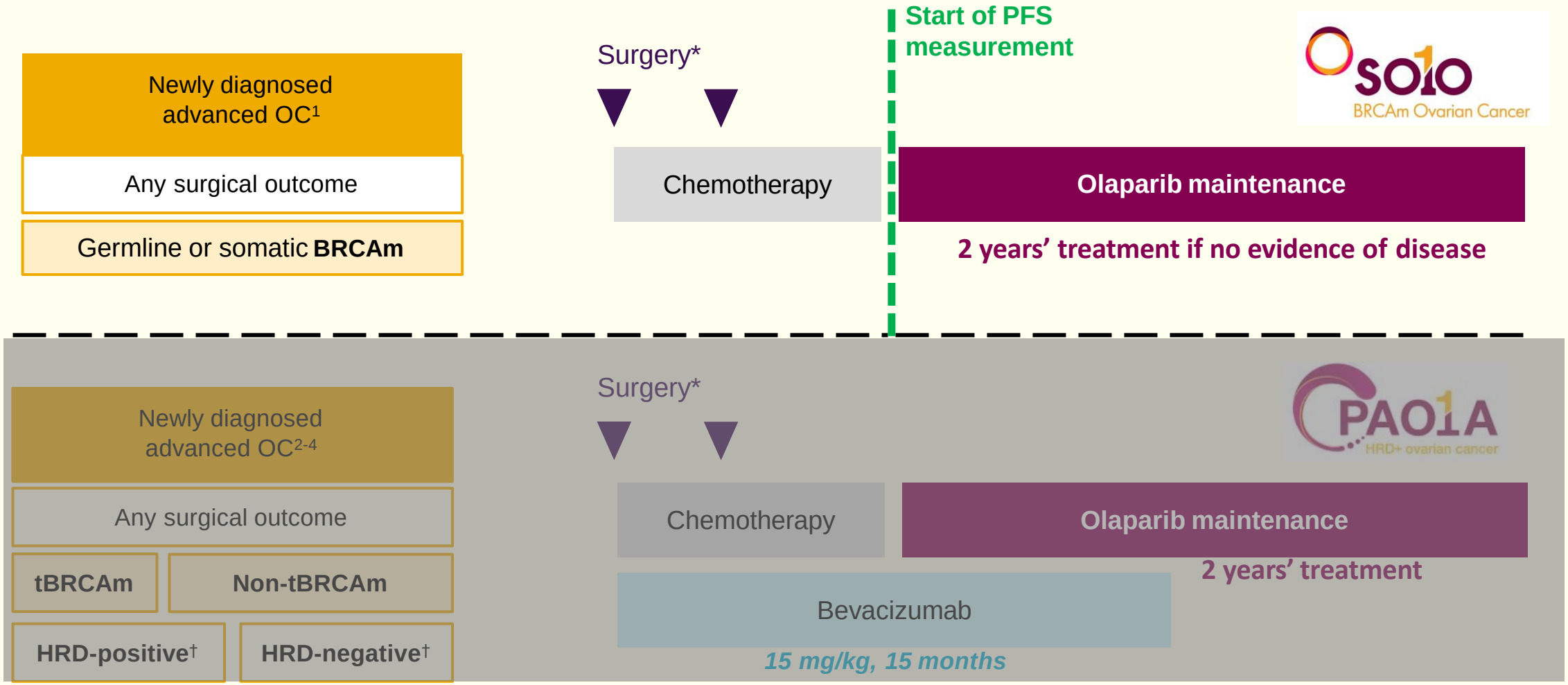
"Results: BRCA1/2, HRR, and CD31 were not predictive of bevacizumab activity."

CONCLUSION: No survival differences were observed for patients who received bevacizumab compared with chemotherapy alone.

In the Final lines of Paper: "After primary resection, patients without contraindications to anti-angiogenesis therapy may consider postoperative chemotherapy with bevacizumab, during which time germline and (if necessary) somatic BRCA1/2 testing can be performed. Patients with BRCA1/2 mutated carcinoma can be transitioned to maintenance olaparib, whereas those without mutations may remain on maintenance bevacizumab."

Monk. J Clin Oncol 2019, 37:2317-2328

Olaparib maintenance treatment has been investigated in newly diagnosed advanced OC in two Phase III studies



*Surgery may be upfront or interval debulking

†HRD-positive determined by tBRCAm or Myriad myChoice CDx genomic instability score ≥42.
HRD-negative determined by non-tBRCAm and Myriad myChoice CDx genomic instability score <42

BRCAm=mutation in *BRCA1/2*; CDx=companion diagnostic test; HRD=homologous recombination deficient; OC=ovarian cancer; tBRCAm=tumour BRCA mutation

1. Moore K et al. N Engl J Med. 2018;379(26):2495-2505; 2. Study NCT02477644. Available at https://clinicaltrials.gov/ct2/show/NCT02477644. Last accessed December 2019;
3. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 4. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428 Supplementary appendix.

SOLO-1 Is The First Phase III Trial To Investigate Maintenance Therapy With A PARP Inhibitor In Newly Diagnosed Ovarian Cancer

SOLO-1 is a global randomised multicentre placebo controlled Phase III study

- Newly diagnosed, FIGO stage III–IV, high-grade serous or endometrioid ovarian, primary peritoneal or fallopian tube cancer
- Germline or somatic *BRCA*m
- ECOG performance status 0–1
- Cytoreductive surgery*
- In clinical complete response or partial response after platinum-based chemotherapy

Stratified by response to platinum-based chemotherapy

2:1 randomisation

Olaparib 300 mg bid (N=260)

Placebo (N=131)

- Study treatment continued until disease progression
- Patients with no evidence of disease at 2 years stopped treatment
- Patients with a partial response at 2 years could continue treatment

2 years' treatment if no evidence of disease

Primary endpoint

- Investigator-assessed PFS (modified RECIST 1.1)

Secondary endpoints

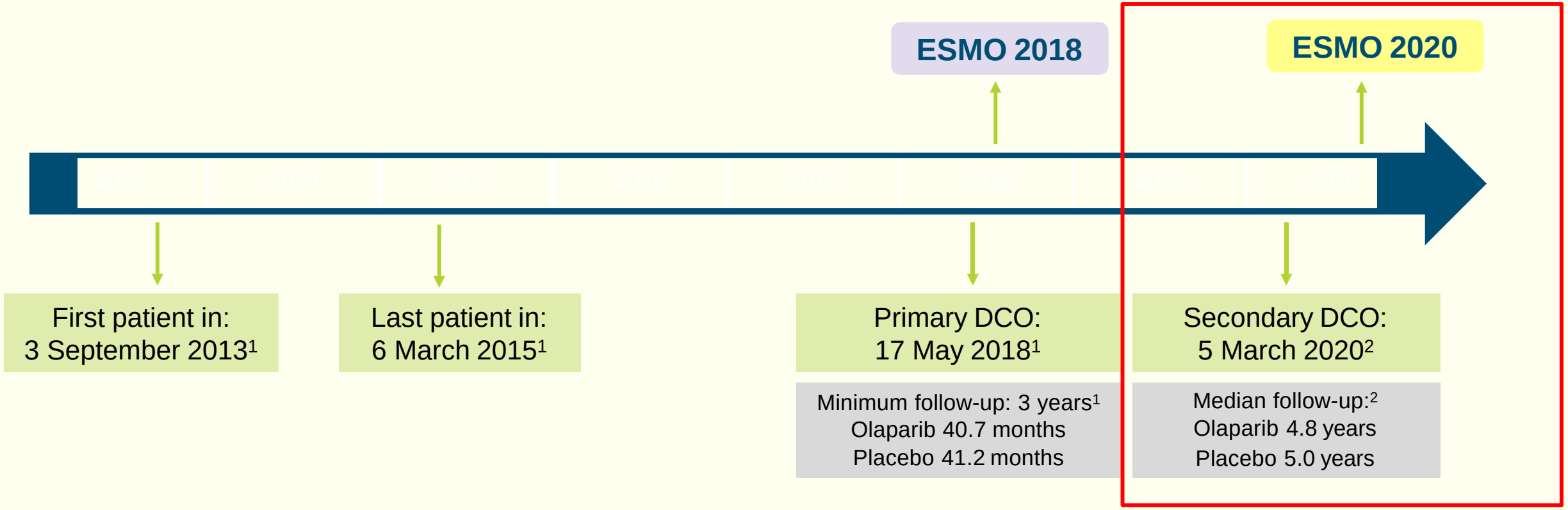
- PFS using BICR
- PFS2
- Overall survival
- Time from randomisation to first subsequent therapy or death (TFST)
- Time from randomisation to second subsequent therapy or death (TSST)
- HRQoL (FACT-O TOI score)

*Upfront or interval attempt at optimal cytoreductive surgery for stage III disease and either biopsy and/or upfront or interval cytoreductive surgery for stage IV disease

BICR = blinded independent central review; ECOG = Eastern Cooperative Oncology Group; FACT-O = Functional Assessment of Cancer Therapy – Ovarian Cancer; FIGO = International Federation of Gynecology and Obstetrics; HRQoL = health-related quality of life; PFS = progression-free survival; PFS2 = time to second progression or death; RECIST = Response Evaluation Criteria in Solid Tumours; TOI = Trial Outcome Index; PARP = poly (ADP-ribose) polymerase; *BRCA*m = *BRCA* gene mutation

https://clinicaltrials.gov/ct2/show/NCT01844986 (accessed October 2018)

Study Timeline



SOLO-1: 5-year follow-up

DCO=data cutoff

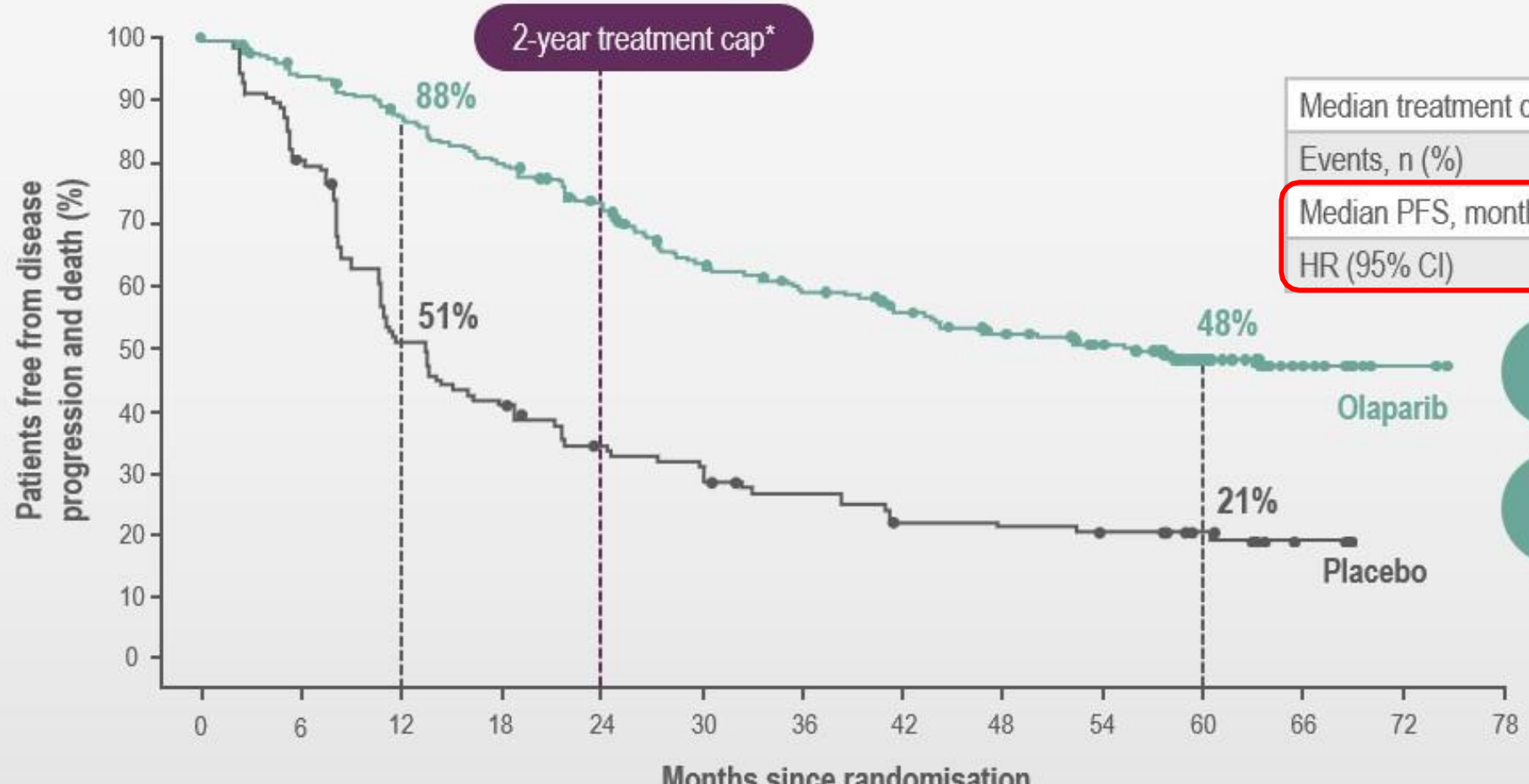
1. Moore K, et al. Presented at ESMO Annual Congress 2018; 19–23 October 2018; Munich, Germany. Presentation #LBA7_PR;
2. Banerjee S, et al. Presented at ESMO Virtual Congress 2020. 19-21 September. Abstract #811MO

5-year follow up Data cut-off March 2020

SOLO-1 (ESMO 2020 update)

Lynparza™ olaparib tablets 150 mg

PFS BENEFIT OF OLAPARIB MX WAS SUSTAINED BEYOND THE END OF TREATMENT



	Olaparib (n=260)	Placebo (n=131)
Median treatment duration, months	24.6	13.9
Events, n (%)	118 (45)	100 (76)
Median PFS, months	56.0	13.8
HR (95% CI)	0.33 (0.25–0.43)	

Median PFS difference for olaparib vs placebo: 42.2 months

48% of patients in the olaparib arm were progression-free at 5 years

No. at risk														
Olaparib:	260	229	212	194	173	140	129	115	101	91	58	30	2	0
Placebo:	131	103	65	53	41	38	30	24	23	22	16	3	0	

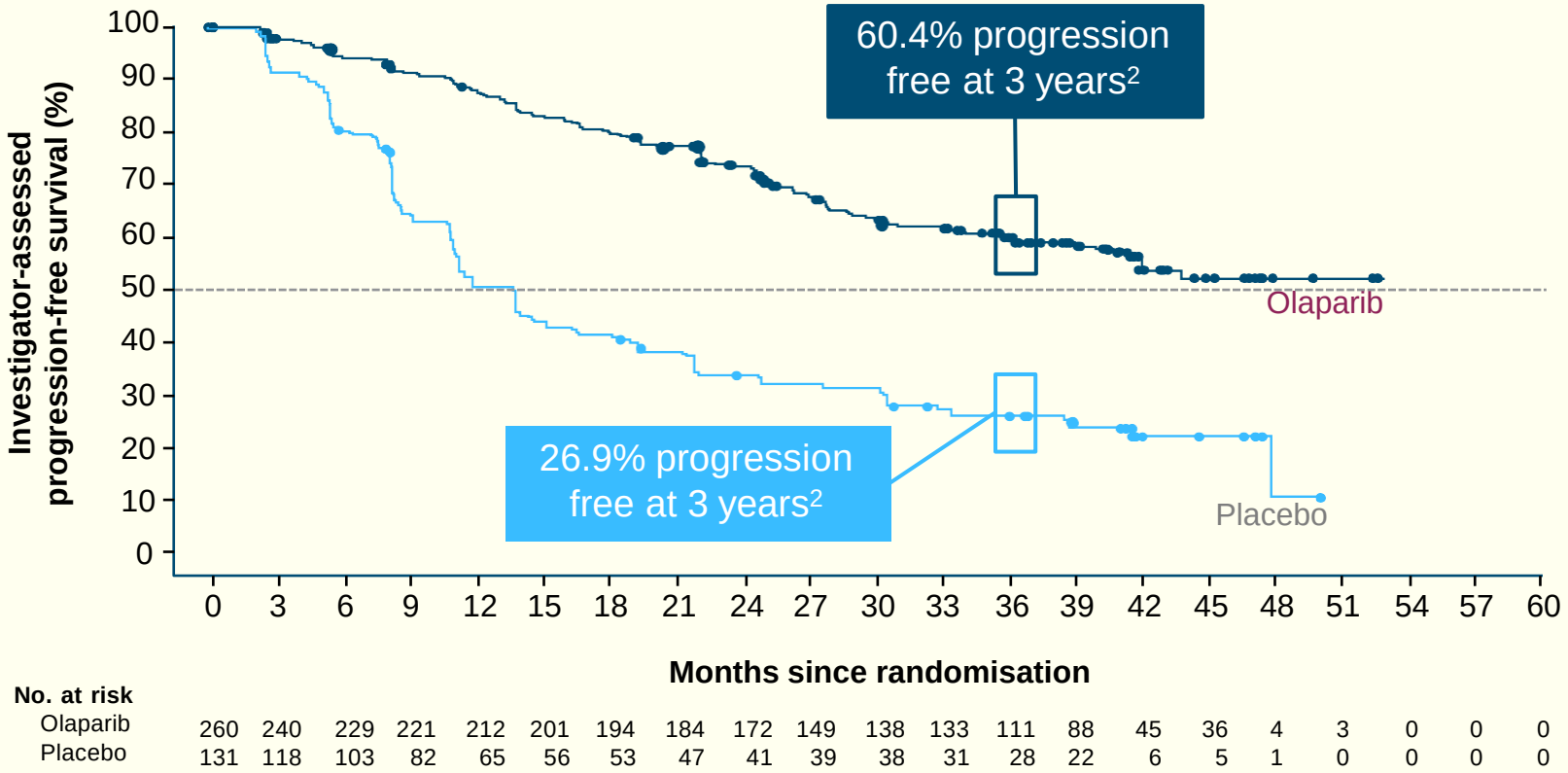
Median follow-up for PFS:

Olaparib	Placebo
4.8 years	5.0 years

*Patients who had no evidence of disease at 2 years stopped receiving the trial intervention; patients who had a PR at 2 years were permitted to continue receiving the trial intervention in a blinded manner; 13 patients (all in the olaparib arm) continued study treatment past 2 years
Investigator assessed by modified RECIST v1.1.; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival
Banerjee S, et al. Presented at ESMO 2020 Virtual Congress

第三/四期卵巢癌第一線化療後 服用標靶治療(PARPi)2年復發/死亡減少70%

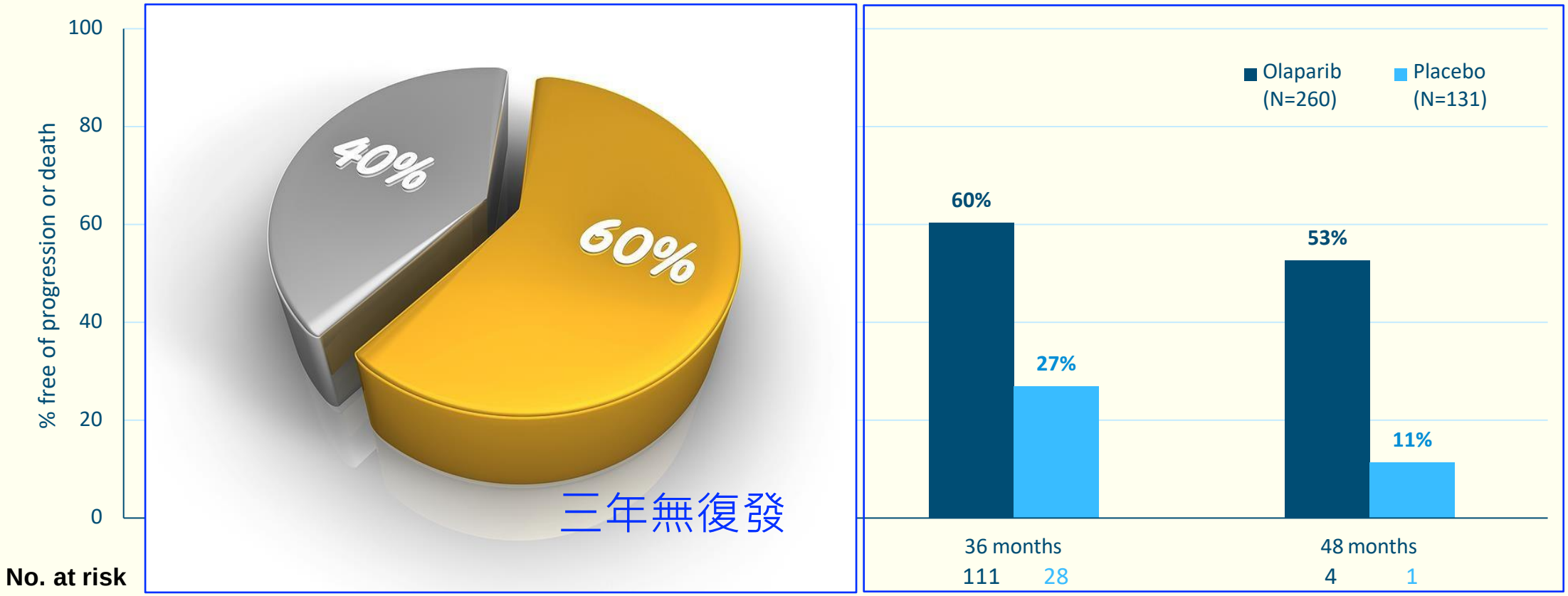
Lynparza™ olaparib tablets 150 mg



- DCO: May 2018; Median FU: olaparib, 40.7 months placebo, 41.2 months
- Analysis was performed after 198 progression events had occurred (in 50.6% of patients)
- PFS = progression-free survival; DCO = data cut-off; HR = hazard ratio; CI = confidence interval
- 1. Moore K et al. N. Engl. J. Med. 2018;379:2495-2505;; 2. Moore K et al. Oral presentation LBA7_PR, ESMO (2018)

AstraZeneca

到第三年，標靶治療(PARPi)病人仍然有60%無復發



*Based on Kaplan-Meier estimates
DCO: May 2018; Median FU: olaparib, 40.7 months placebo, 41.2 months
DCO = data cut-off
Moore K et al. N. Engl. J. Med. 2018;379:2495–2505; 2. Moore K et al. N. Engl. J. Med. 2018;379:2495–2505 [supplementary appendix]

5-year follow up Data cut-off March 2020

Secondary efficacy outcomes* support the observed PFS benefit

The PFS2 & TSST

PFS2	Overall		Patients in CR at baseline	
	Olaparib (n=260)	Placebo (n=131)	Olaparib (n=189)	Placebo (n=101)
Events, n (%)	80 (31)	61 (47)	49 (26)	45 (45)
Event free at 5 years, %	64	41	68	44
Median, months	NR	42.1	NR	52.9
	HR 0.46 (95% CI 0.33–0.65)		HR 0.48 (95% CI 0.32–0.71)	

TSST	Overall		Patients in CR at baseline	
	Olaparib (n=260)	Placebo (n=131)	Olaparib (n=189)	Placebo (n=101)
Events, n (%)	95 (37)	77 (59)	64 (34)	56 (55)
Event free at 5 years, %	62	36	65	39
Median, months	NR	40.7	NR	47.7
	HR 0.46 (95% CI 0.34–0.63)		HR 0.50 (95% CI 0.35–0.72)	

TSST : **time of randomisation** to **second subsequent therapy or death**

*Measured from randomization. AE, adverse event, AML, acute myeloid leukaemia; CR, complete response; MDS, myelodysplastic syndrome. DOC: 5 March 2020

Population-adjusted indirect treatment comparison of PAOLA-1 & SOLO-1

A comparison of olaparib ± bevacizumab, bevacizumab monotherapy, and placebo maintenance therapies in 1L BRCAm ovarian cancer

Should I combine olaparib with bevacizumab to treat BRCA mutation patients?

There’s no olaparib single arm in PAOLA-1 study

Population-adjusted ITC methodology

SOLO-1 and PAOLA-1 did not have a common comparator arm or patient population. Therefore the study results are not directly comparable without adjustment of the populations

Population-adjusted ITC can estimate the relative treatment effect when comparing studies which do not have common comparator arm

A **propensity score weighting technique** was used to minimise differences in observable characteristics between the trial populations

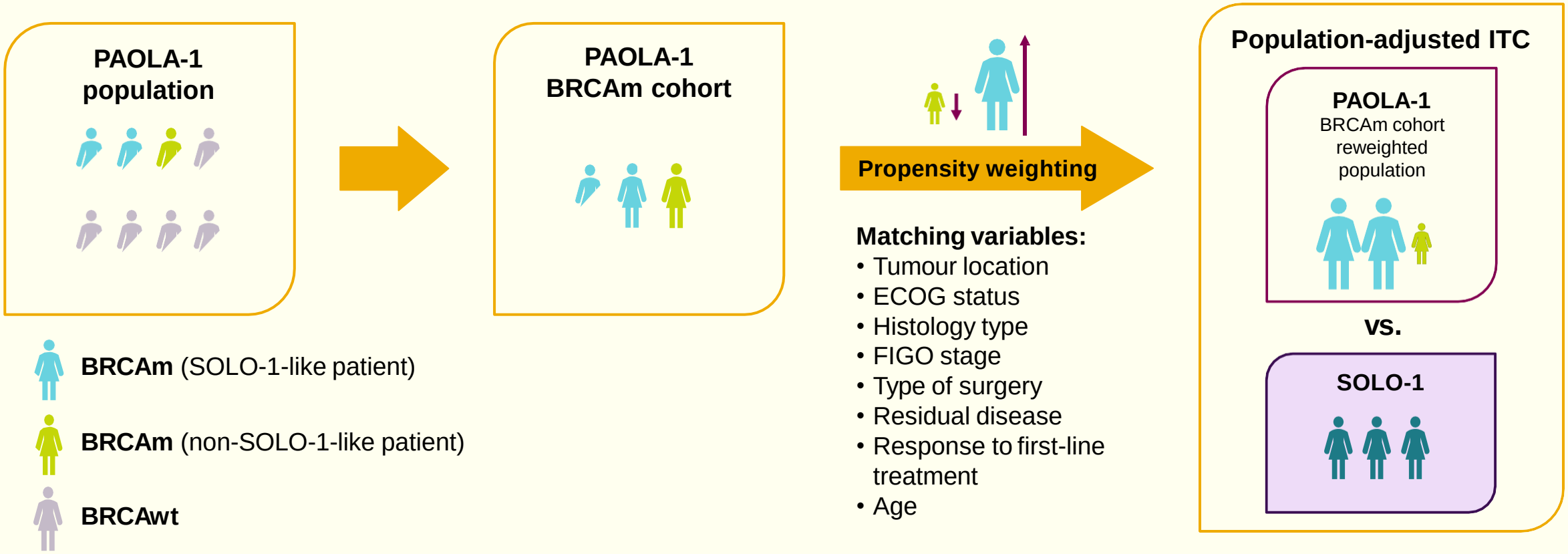
Weighted cox regression and Kaplan-Meier analyses were used to compare efficacy by investigator-assessed PFS (RECIST v1.1)

All analyses were performed in patients with complete baseline data.
BRCAm=mutation in *BRCA1/2*; ITC=indirect treatment comparison; PFS=progression-free survival; RECIST=Response Evaluation Criteria in Solid Tumors

1. Vergote I, et al. Presented at SGO Annual Conference 2020

Propensity score weighting

The PAOLA-1 BRCAm cohort was adjusted to match the SOLO-1 patient population using a propensity score weighting method



*Icon size to denote weights. The olaparib arm of SOLO-1 was selected as the target population as it represents the current standard of care for patients with newly diagnosed advanced ovarian cancer and a BRCAm All analyses were performed in patients with complete baseline data. Although this ITC analysis is based on accepted methodology, it was not possible to address all differences in baseline characteristics as the analysis was non-randomised

BRCAm=*BRCA1* or *BRCA2* mutation; ECOG=Eastern Cooperative Oncology Group; FIGO=International Federation of Gynecology and Obstetric; ITC=indirect treatment comparison

1. Vergote I, et al. Presented at SGO Annual Conference 2020

Patient baseline characteristics prior to population adjustment

Prior to population adjustment, patients in PAOLA-1 had a greater disease burden than those in SOLO-1

Characteristic	PAOLA-1 (BRCAm subset) n=222		SOLO-1 n=380	
	Olaparib + bevacizumab (n=151)	Placebo + bevacizumab (n=71)	Olaparib (n=254)	Placebo (n=126)
Tumour location ovary, %	85	92	85	86
ECOG PS 1, %	25	24	23	19
FIGO Stage IV, %	28	31	14	18
Surgery*				
Interval, %	43	38	37	34
Residual disease, %	32	30	22	23
PR to first-line, %	15	17	26	21
Age				
Mean, years	57.0	55.0	53.6	53.4
≥65 years, %	22	15	13	15

target

*Patients who did not have surgery were excluded from this population-adjusted indirect treatment comparison

The analyses were performed on the SOLO-1 data and the subset of patients in PAOLA-1 that had confirmed tBRCA mutations. All analyses were performed in patients with complete data on matching variables.

Ten patients from the original PAOLA-1 olaparib plus bevacizumab cohort, nine patients from the original PAOLA-1 placebo plus bevacizumab cohort, six patients from the original SOLO-1 olaparib cohort and five patients from the original SOLO-1 placebo cohort had missing values for matching variables; therefore, they were excluded. The implications of removing those with missing data was assessed.

Although this indirect treatment analysis is based on accepted methodology, it was not possible to address all differences in baseline characteristics as the analysis is non-randomized.

In SOLO-1, median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. In PAOLA-1, median follow-up was up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm]

BRCAm=*BRCA1* or *BRCA2* mutation; ECOG PS=Eastern Cooperative Oncology Group performance status; FIGO=Federation of Gynecology and Obstetrics; PR=partial response; PS=performance status

1. Vergote I, et al. Presented at SGO Annual Conference 2020

Patient baseline characteristics after weighting

After weighting, baseline characteristics for the PAOLA-1 BRCAm subset were comparable to those for SOLO-1 patients

Characteristic	PAOLA-1 (BRCAm subset) n=222		SOLO-1 n=380	
	Olaparib + bevacizumab* (n=151) ESS 110.8	Placebo + bevacizumab* (n=71) ESS 54.7	Olaparib (n=254)	Placebo (n=126)
Tumour location ovary, %	84	88	85	86
ECOG PS 1, %	23	29	23	19
FIGO Stage IV, %	14	16	14	18
Surgery†				
Interval, %	40	37	37	34
Residual disease, %	26	22	22	23
PR to first-line, %	19	17	26	21
Age				
Mean, years	54.3	53.9	53.6	53.4
≥65 years, %	16	13	13	15

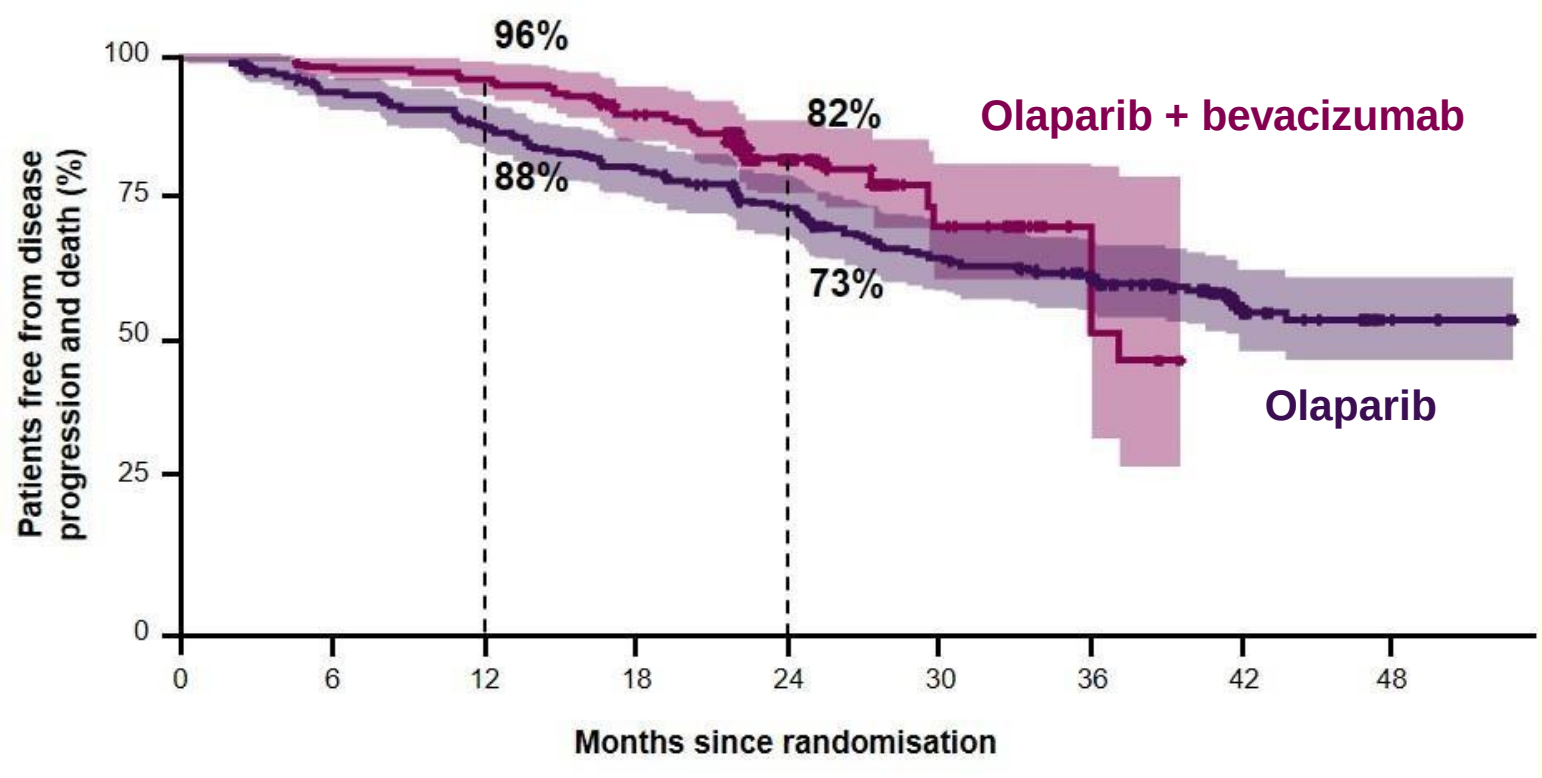
target

*Values are weight adjusted to match baseline characteristics to the olaparib arm of the SOLO-1 trial. †The values for patients who did not have surgery were not weight adjusted
All analyses were performed in patients with complete data on matching variables. The analyses were performed on the SOLO-1 data and the subset of patients in PAOLA-1 that had confirmed BRCA mutations
A sensitivity analysis was conducted to assess the impact of the difference in first-line outcome. This sensitivity analysis found that the different complete response rates across arms had little impact on the hazard ratios estimated from the weighted Cox proportional hazards models
ESS represents the approximate number of independent non-weighted individuals that would be required to give an estimate with the same precision as the weighted sample
BRCAm=*BRCA1* or *BRCA2* mutation; ECOG PS=Eastern Cooperative Oncology Group performance status; ESS=effective sample size; FIGO=Federation of Gynecology and Obstetrics; PR=partial response; PS=performance status

1. Vergote I, et al. Presented at SGO Annual Conference 2020

Olaparib + bevacizumab vs. olaparib maintenance monotherapy

Patients receiving olaparib + bevacizumab combination therapy may reduce the risk of disease progression at 24 months compared with those receiving olaparib maintenance monotherapy



	PAOLA-1 BRCAm subset	SOLO-1
	Olaparib + bevacizumab* n=151	**Olaparib n=254**
Patients progression-free at 12 months, %	96	88
Patients progression-free at 24 months, %	82	73
	HR 0.71 (95% CI 0.45–1.09)†	

*These results are based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (interval vs. upfront), residual disease status after surgery, response to first-line treatment and age to SOLO-1. †Confidence intervals generated via bootstrapping

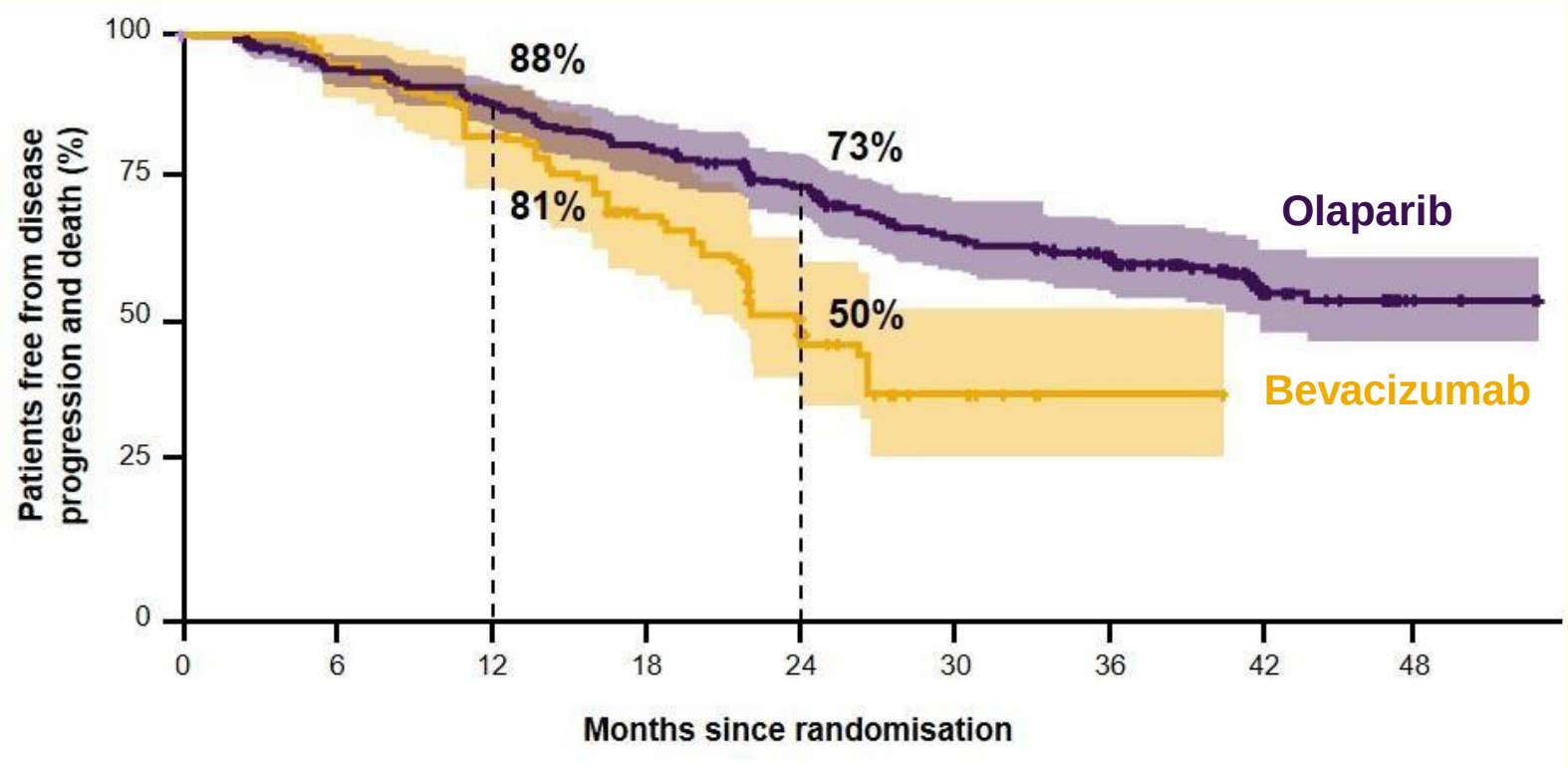
In SOLO-1 median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. In PAOLA-1 median follow up was up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm

BRCAm=*BRCA1* or *BRCA2* mutation; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; FIGO=Federation of Gynecology and Obstetrics; HR=hazard ratio; PFS=progression-free survival

1. Vergote I, et al. Presented at SGO Annual Conference 2020

Olaparib monotherapy vs. bevacizumab monotherapy

Patients receiving olaparib maintenance monotherapy were observed a 52% reduction in the risk of disease progression at 24 months compared with those receiving bevacizumab monotherapy



	PAOLA-1 BRCAm subset	SOLO-1
	Placebo + bevacizumab* n=71	Olaparib n=254
Patients progression-free at 12 months, %	81	88
Patients progression-free at 24 months, %	50	73
	HR 0.48 (95% CI 0.30–0.75)†	

*These results are based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (interval vs. upfront), residual disease status after surgery, response to first-line treatment and age to SOLO-1. †Confidence intervals generated via bootstrapping

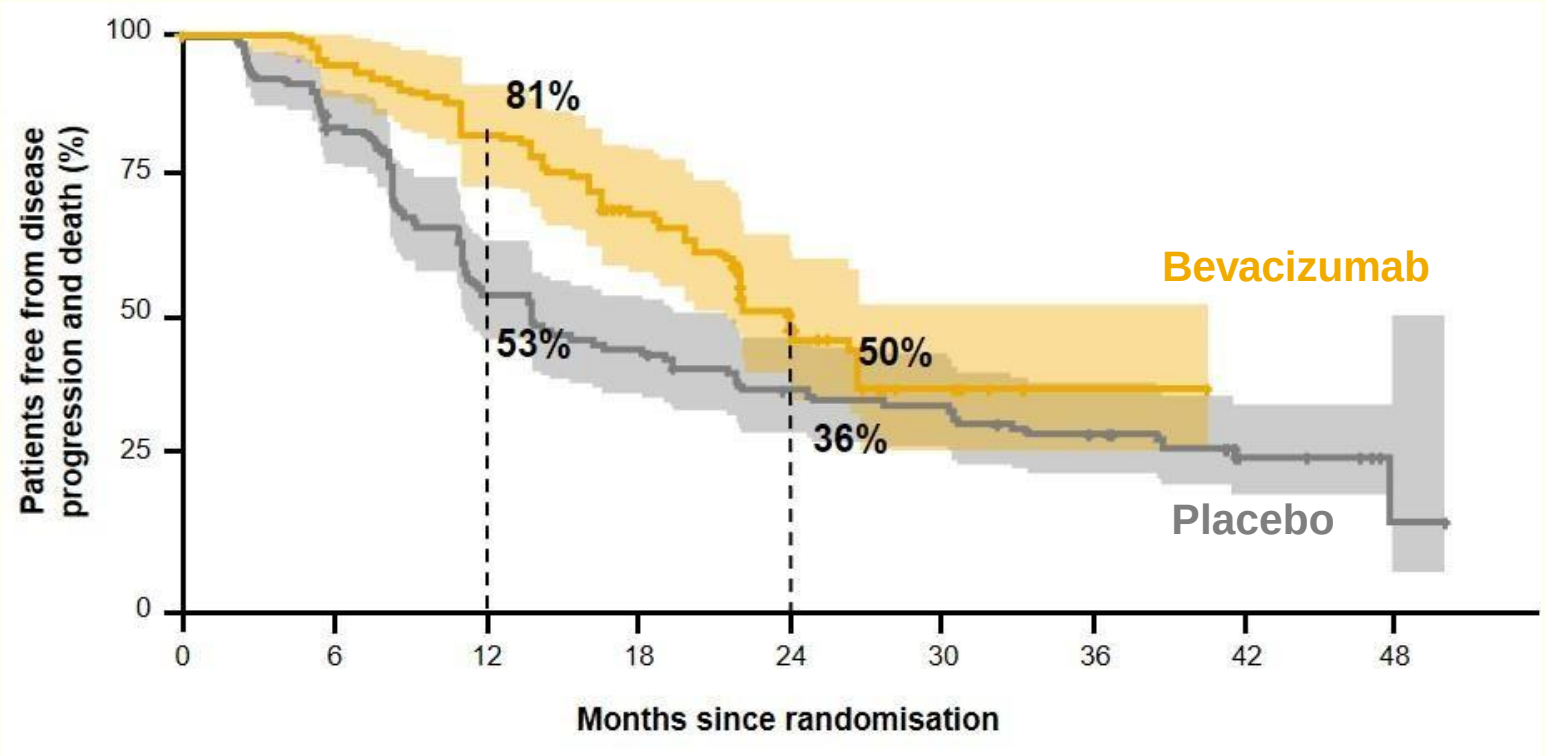
In SOLO-1 median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. In PAOLA-1 median follow up was up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; FIGO=Federation of Gynecology and Obstetrics; HR=hazard ratio

1. Vergote I, et al. Presented at SGO Annual Conference 2020

Bevacizumab monotherapy vs. placebo

Patients receiving bevacizumab maintenance therapy were observed a 35% reduction in the risk of disease progression at 24 months compared with those receiving no active treatment



	PAOLA-1 BRCAm subset	SOLO-1
	Placebo + bevacizumab* n=71	Placebo n=126
Patients progression-free at 12 months, %	81	53
Patients progression-free at 24 months, %	50	36
	HR 0.65 (95% CI 0.43–0.95)†	

*These results are based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (interval vs. upfront), residual disease status after surgery, response to first-line treatment and age to SOLO-1. †Confidence intervals generated via bootstrapping

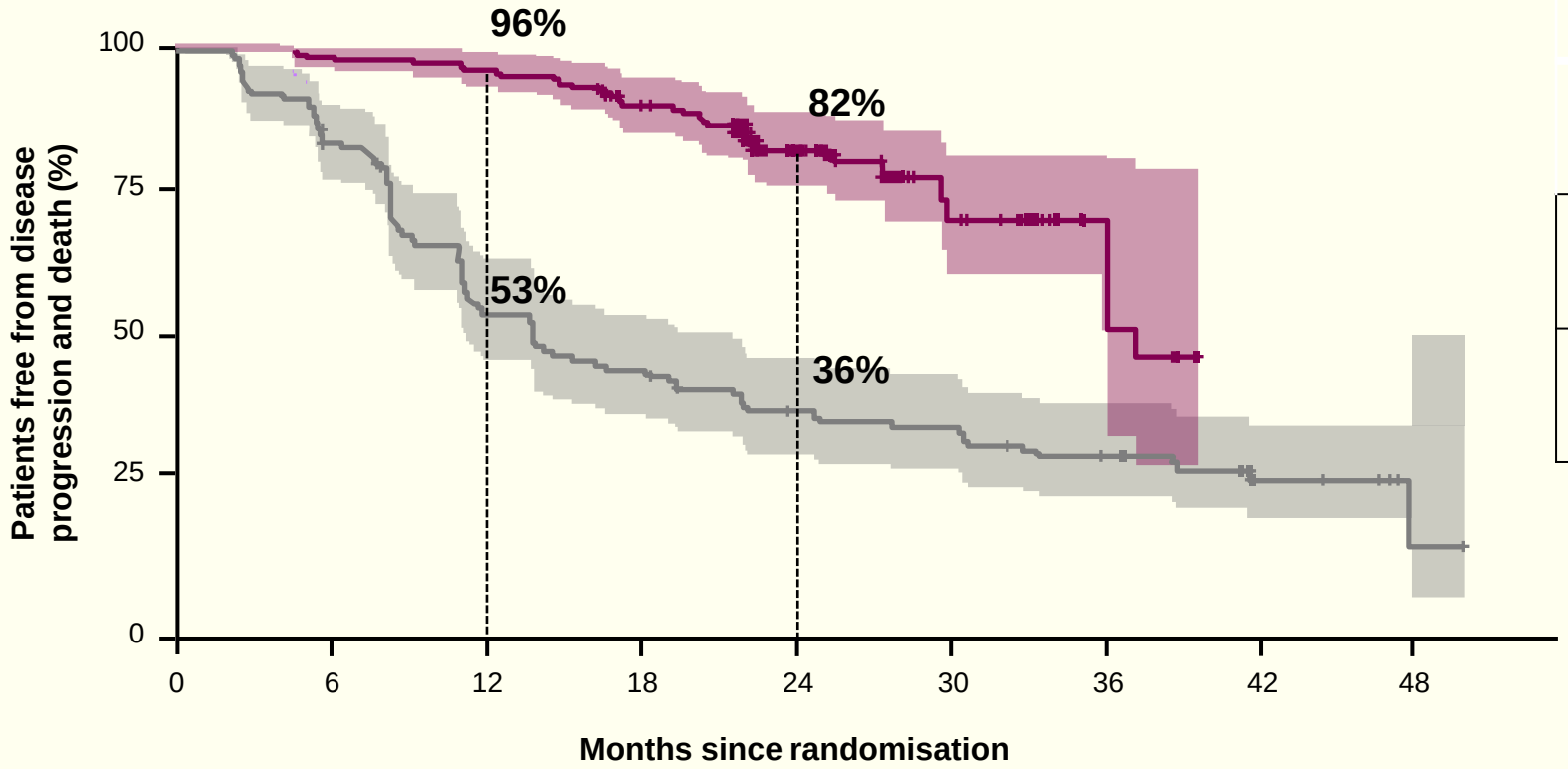
In SOLO-1 median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. In PAOLA-1 median follow up was up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm

CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; FIGO=Federation of Gynecology and Obstetrics; HR=hazard ratio

1. Vergote I, et al. Presented at SGO Annual Conference 2020

Olaparib + bevacizumab vs. placebo

Patients receiving olaparib and bevacizumab combination maintenance therapy were observed a 77% reduction in the risk of disease progression at 24 months compared with those receiving placebo



	PAOLA-1 BRCAm subset	SOLO-1
	Olaparib + bevacizumab* n=151	**Placebo n=126**
Patients progression-free at 12 months, %	96	53
Patients progression-free at 24 months, %	82	36
	HR 0.23 (95% CI 0.14–0.34)†	

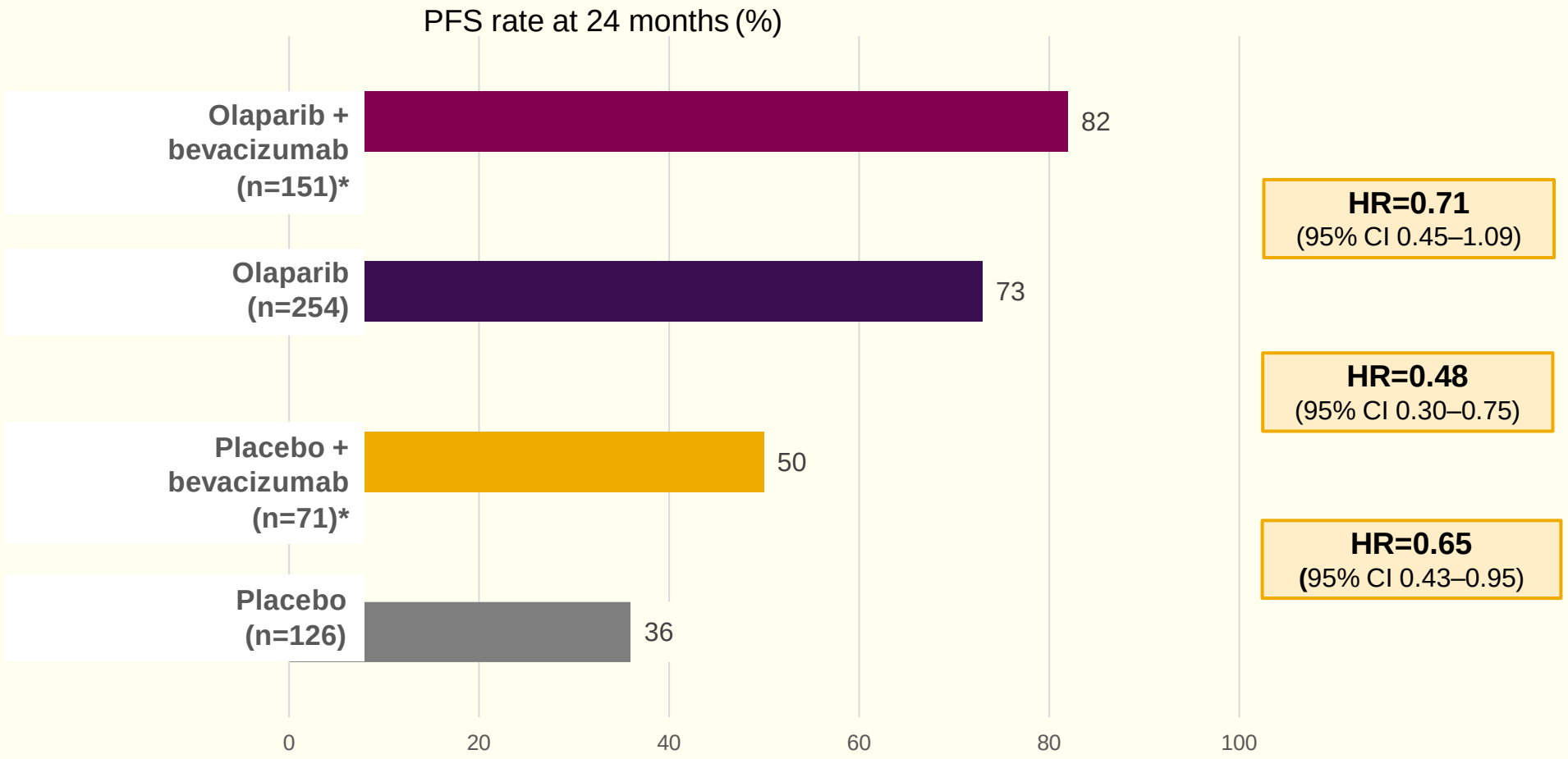
*These results are based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (interval vs. upfront), residual disease status after surgery, response to first-line treatment and age to SOLO-1. †Confidence intervals generated via bootstrapping

In SOLO-1 median follow-up was 40.7 months in the olaparib arm and 41.2 months in the placebo arm. In PAOLA-1 median follow up was up was 22.7 months in the olaparib + bevacizumab arm and 24.0 months in the placebo + bevacizumab arm

BRCAm=*BRCA1* or *BRCA2* mutation; CI=confidence interval; ECOG=Eastern Cooperative Oncology Group; FIGO=Federation of Gynecology and Obstetrics; HR=hazard ratio

1. Vergote I, et al. Presented at SGO Annual Conference 2020

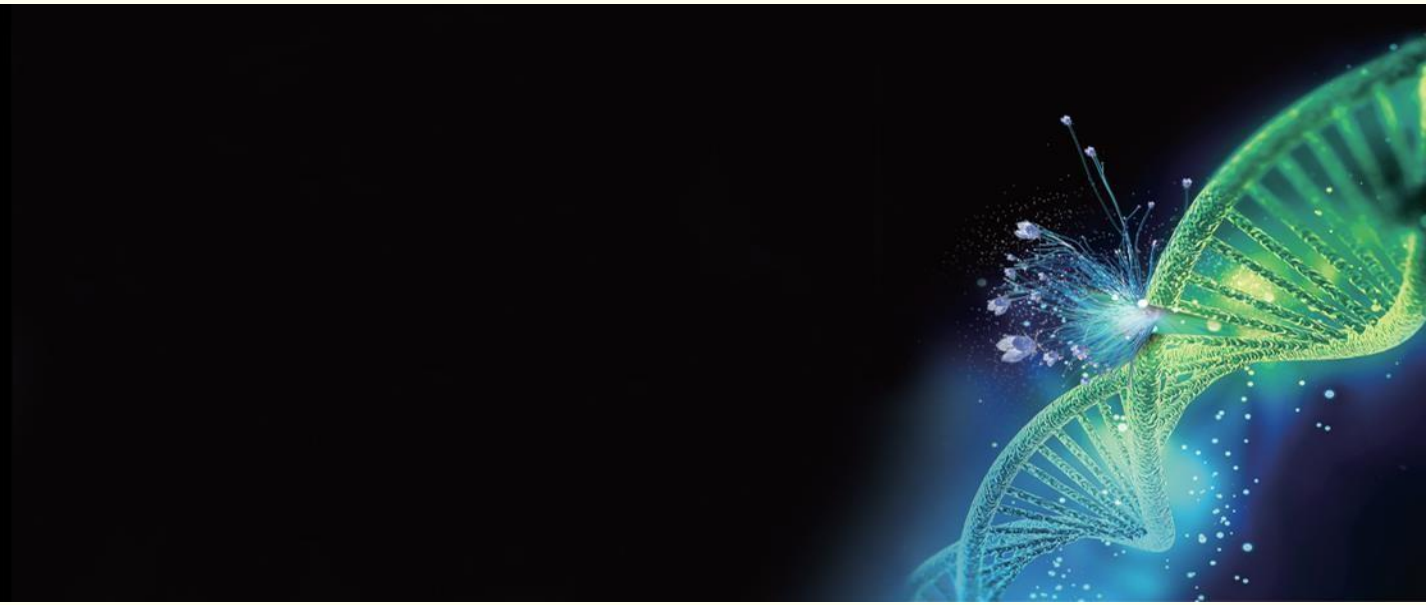
The PFS rate at 24 months seems to be greatest with olaparib + bevacizumab combination therapy in BRCAm



* Results based on weighted outcomes after matching tumour location status, ECOG status, FIGO stage, type of surgery (interval versus initial), residual disease status after surgery (yes or no), response to first-line treatment and age to SOLO-1
BRCAm=mutation in BRCA1/2; PFS=progression free survival

1. Vergote I, et al. SGO Annual Meeting 2020

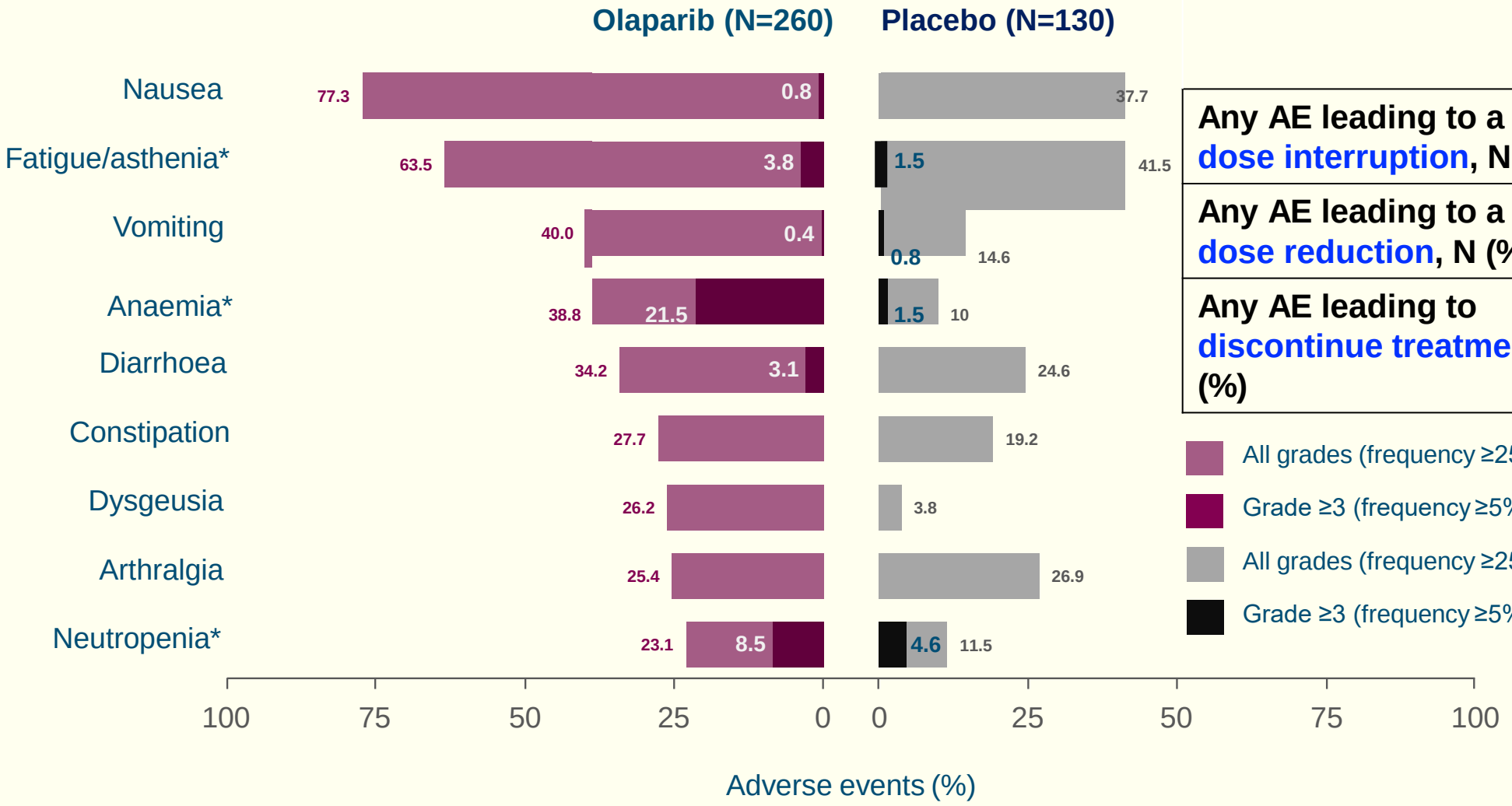
Safety



The Adverse Events and Toxicity

The Most Common AEs Reported In Patients On Olaparib In SOLO-1 Were Gastrointestinal Disturbances, Fatigue And Anaemia

Lynparza™ olaparib tablets 150 mg



	Olaparib (N=260)	Placebo (N=130)
Any AE leading to a dose interruption, N (%)	135 (52)	22 (17)
Any AE leading to a dose reduction, N (%)	74 (28)	4 (3)
Any AE leading to discontinue treatment, N (%)	30 (12)	3 (2)

大約:
1/2需要調整
1/4需要降劑量
1/8需要停藥

*Grouped term
AE = adverse event

1. Moore K et al. Oral presentation LBA7_PR, ESMO (2018)

SOLO-1: Few Pts discontinued olaparib for haematologic AEs

Lynparza™ olaparib tablets 150 mg

23% of pts in the olaparib gr and 2% in the placebo gr received at least one blood transfusion

Haematologic AEs	Anaemia†		Neutropenia†		Thrombocytopenia†	
	Olaparib	Placebo	Olaparib	Placebo	Olaparib	Placebo
Patients with event (all grades), n (%)	101 (39)	13 (10)	60 (23)	15 (12)	29 (11)	5 (4)
Management, n (%)*						
Supportive treatment	72 (71)	4 (31)	11 (18)	2 (13)	2 (7)	1 (20)
Dose interruption	58 (57)	1 (8)	30 (50)	5 (33)	6 (21)	0 (0)
Dose reduction	44 (44)	1 (8)	10 (17)	1 (7)	4 (14)	0 (0)
Discontinuation	6 (6)	0 (0)	1 (2)	0 (0)	1 (3)	0 (0)
Outcome, n (%)*						
Recovered/resolved	84 (83)	11 (85)	53 (88)	14 (93)	21 (72)	4 (80)
Recovered/resolved with sequelae	2 (2)	0 (0)	0 (0)	0 (0)	2 (7)	0 (0)
Recovering/resolving	5 (5)	0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Not recovered/resolved	10 (10)	2 (15)	6 (10)	1 (7)	6 (21)	1 (20)
Patients with grade ≥3 events, n (%)	56 (22)	2 (2)	22 (9)	6 (5)	2 (1)	2 (2)

*Percentages were calculated from the number of patients with that event; †Grouped-term events.
AE=adverse event

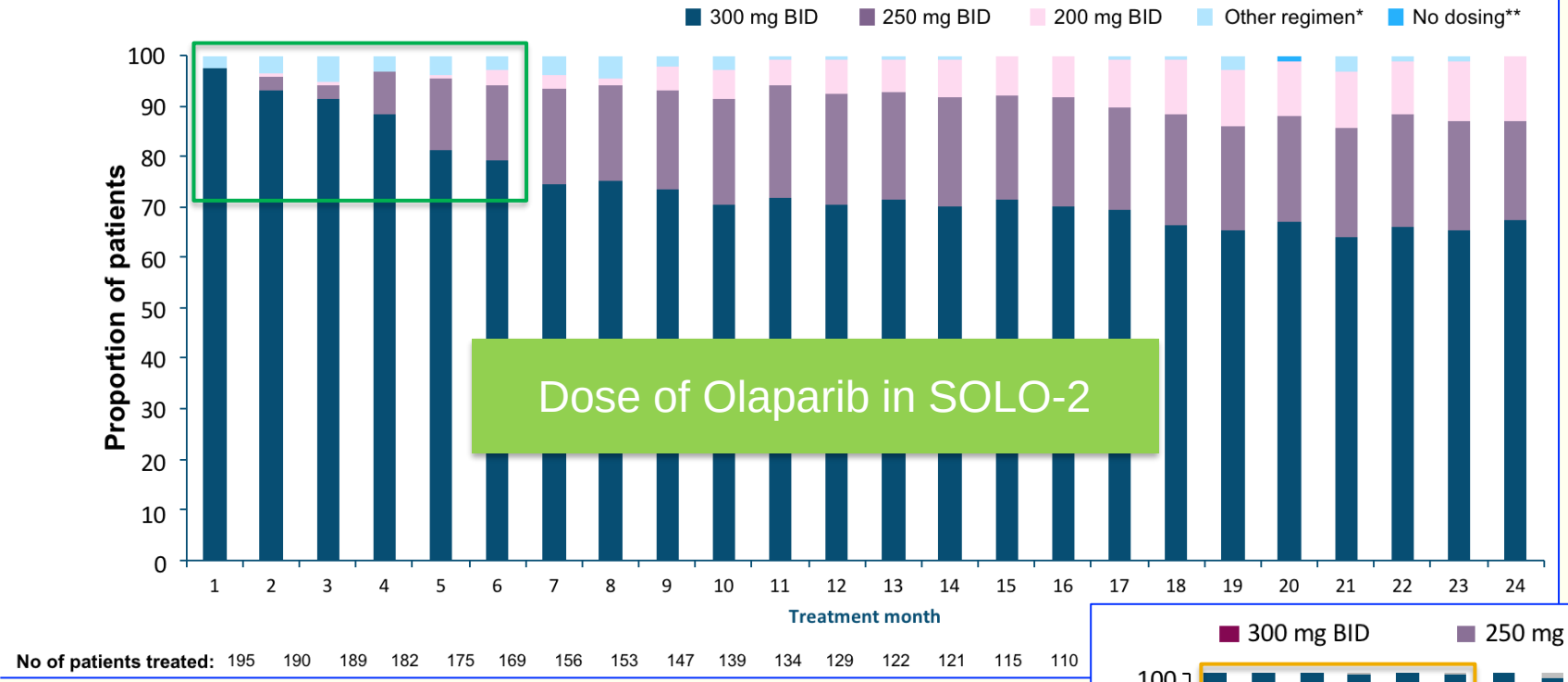
Colombo N, et al. Presented at 2019 ASCO Annual Meeting; May 31–Jun 4, 2019; Chicago, IL. Poster #5539

SOLO-1 & SOLO-2 & PAOLA-1 Trials:
Anaemia was the most common haematological AE

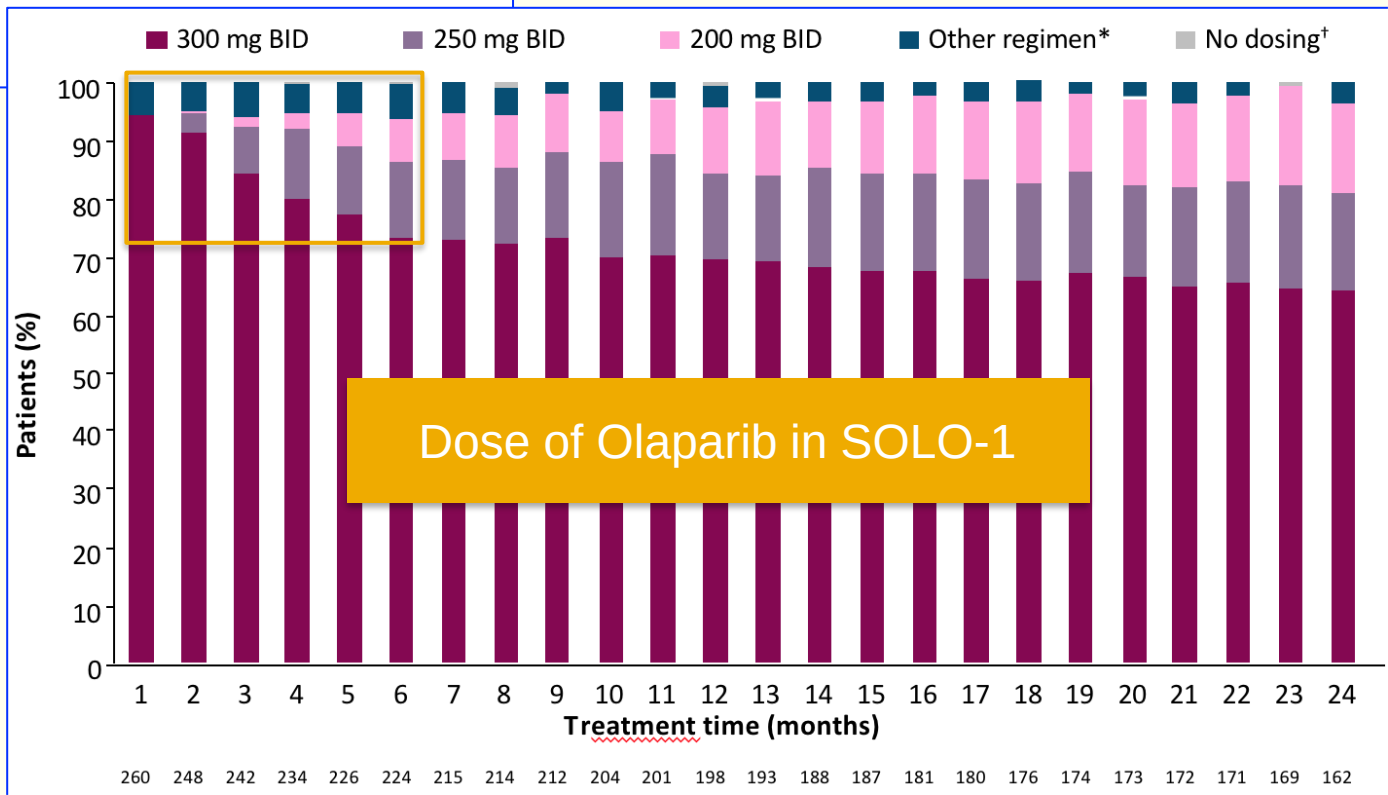
There was only a small increase in the occurrence of haematological AEs at the final DCO compared to the primary DCO

	SOLO-1				SOLO-2				PAOLA-1			
	Olaparib 300 mg BID (n=260) %		Placebo (n=130) %		Olaparib 300 mg BID (n=195) %		Placebo (n=99) %		Olaparib + Beva (N=533)%		Beva (N=267)%	
	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3	Any	Grade ≥3
Anemia	39	22	10	2	46	21	10	2	41	17	10	<1
Neutropenia	23	9	12	5	24	7	6	4	18	6	16	3
Thrombocytopenia	11	1	4	2	16	2	4	1	8	2	3	<1

DCO 3 February 2020
*Grouped term.
AE=adverse event; BID=twice daily; DCO=data cut-off
Poveda A, et al. Presented at ASCO 2020. Abstract #6002



Dose reduction occurred mainly in initial 6 months



MDS/AML of SOLO-1 & SOLO-2 Trials: AEs Of Special Interest Were In Line With Rates Seen In Previous Trials Of Olaparib[1,2]

Lynparza™ olaparib tablets 150 mg

	SOLO-1		SOLO-2	
	Olaparib N=260 (%)	Placebo N=130 (%)	Olaparib N=195 (%)	Placebo N=99 (%)
MDS/AML,* N (%)	3 (1)	0	16 (8)	4 (4)
New primary malignancies,† N (%)	5 (2)	3 (2)	8 (4)	2 (2)
Pneumonitis/ILD, N (%)	5 (2)	0	3 (2)	0 (0)

*The three cases of MDS/AML occurred 1.7–5.7 months after stopping olaparib (duration of olaparib therapy of 14.3–24.9 months); †Including breast cancer (n=3), head and neck cancer (n=1) and thyroid cancer (n=1) in the olaparib group and breast cancer (n=3) in the placebo group
AML = acute myeloid leukaemia; MDS = myelodysplastic syndrome; ILD = interstitial lung disease

1. Moore K et al. N. Engl. J. Med. 2018;379:2495-2505; 2. Moore K et al. N. Engl. J. Med. 2018;379:2495-2505 [supplementary appendix].

Incidence of MDS/AML in Olaparib Trials Across Cancer Types

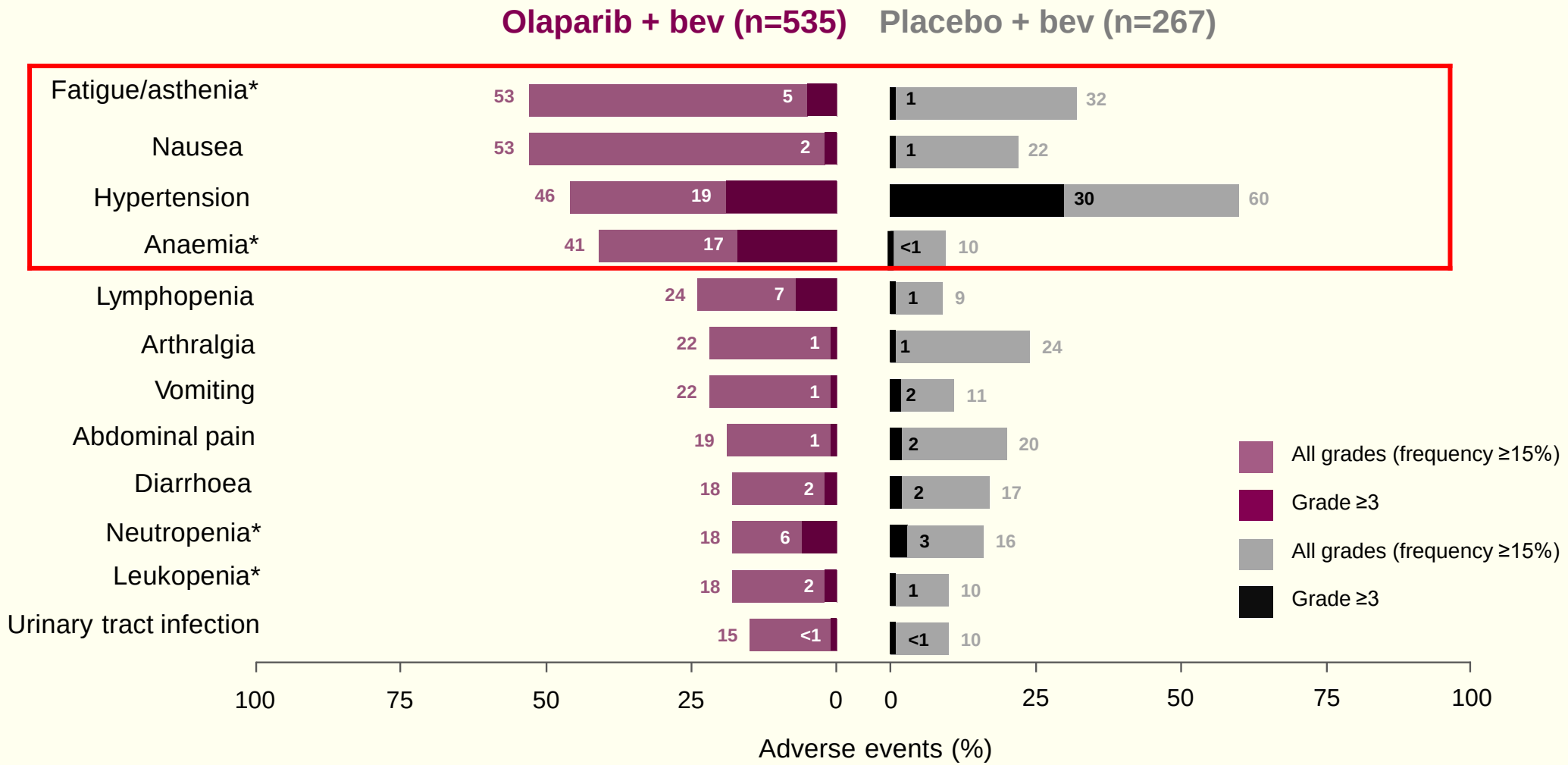
Trial	Setting	Median follow-up (months)	AML/MDS rate in PARPi arm n/N (%)	AML/MDS rate in comparator arm, n/N (%)	Comparator arm
Ovarian cancer					
SOLO-2[2]	PSR OC maintenance, BRCAm	22 (primary DCO)	4/195 (2)	4/99 (4)	Placebo
		66 in the olaparib arm, 65 in the placebo arm (final DCO)	16/195 (8)	4/99 (4)	
Study 19[5]	PSR OC maintenance	78	2/136 (1)	1/128 (1)	Placebo
PAOLA-1[6]	Newly diagnosed OC maintenance, in combination with bevacizumab	36	6/535 (1)	4/267 (1)	Bevacizumab
SOLO-1[1]	Newly diagnosed OC maintenance, BRCAm	58 in the olaparib arm, 60 in the placebo arm	3/260 (1)	0/130 (0)	Placebo
Other tumour types					
OlympiAD[3]	HER2- gBRCAm mBC	25 in the olaparib arm, 26 in the TPC arm	0/205 (0)	0/91 (0)	TPC:capecitabine, eribulin or vinorelbine
POLO[4]	1L mPC	9 in the olaparib arm, 4 in the placebo arm	0/91 (0)	0/60 (0)	Placebo

Olaparib is only indicated for the dosage of tablets in Taiwan, please refer to the TFDA approved package insert for the full information.

Please note that as head-to-head studies we are not conducted between these products, it is inappropriate to draw any comparisons and/or make any conclusions as the study design, demographics.

1. Banerjee S, Moore K, Colombo N, et al. Maintenance olaparib for patients with newly diagnosed advanced ovarian cancer and a BRCA mutation: 5-year follow-up from SOLO1. Abstract #811MO. Presented at the: ESMO Virtual Congress 2020; 19-21 September.
2. Korach J, Turner S, Milenkova T, et al. Incidence of myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) in patients (pts) with a germline (g) BRCA mutation (m) and platinum-sensitive relapsed ovarian cancer (PSR OC) receiving maintenance olaparib in SOLO2: Impact of prior lines of platinum therapy. Abstract #5548. Presented at the: ASCO Annual Meeting 2018; 1-5 June; Chicago, US.
3. Robson M, Tung N, Conte P, et al. OlympiAD final overall survival and tolerability results: Olaparib versus chemotherapy treatment of physician's choice in patients with a germline BRCA mutation and HER2-negative metastatic breast cancer. *Ann Oncol*. 2019;30(4):558-566.
4. Golan T, Hammel P, Reni M, et al. Maintenance Olaparib for Germline BRCA-Mutated Metastatic Pancreatic Cancer. N Engl J Med. 2019;381(4):317-327.
5. Friedlander M, Matulonis U, Gourley C, et al. Long-term efficacy, tolerability and overall survival in patients with platinum-sensitive, recurrent high-grade serous ovarian cancer treated with maintenance olaparib capsules following response to chemotherapy. *Br J Cancer*. 2018;119(9):1075-1085.
6. Ray-Coquard I, et al.. Olaparib plus Bevacizumab as First-Line Maintenance in Ovarian Cancer. N Engl J Med. 2019;381:2416-2428
7. Ledermann JA, Harter P, Gourley C, et al. Overall survival in patients with platinum-sensitive recurrent serous ovarian cancer receiving olaparib maintenance monotherapy: an updated analysis from a randomised, placebo-controlled, double-blind, phase 2 trial. Lancet Oncol. 2016;17(11):1579-1589

The AE profile of olaparib in PAOLA-1 was consistent with previous trials of olaparib



*Grouped terms. All grade thrombocytopenia (grouped term) occurred in 8% of patients in the olaparib group, and 3% of patients in the placebo group, grade ≥3 thrombocytopenia occurred in 2% of patients in the olaparib group and <1% of patients in the placebo group
AE=adverse event

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428.

Dose interruptions and reductions due to AEs were more common in PRIMA than in PAOLA-1 and SOLO-1[1-4]

n (%)	PAOLA-1[1,2] Olaparib + bevacizumab (n=535)	SOLO-1[3] Olaparib (n=260)	PRIMA[4] Niraparib (n=484)
All grade AEs	531 (99)	256 (98)	478 (99)
Grade ≥3 AEs	303 (57)	102 (39)	341 (70)
SAEs	167 (31)	(21)	156 (32)
Deaths	1 (<1)	0	2 (<1)
Dose interruptions due to AEs	291 (54)	135 (52)	385 (80)
Dose reductions due to AEs	220 (41)	74 (28)	343 (71)
Discontinuations due to AEs	109 (20)	30 (12)	58 (12)

In the absence of head to head studies, cross-trial comparisons cannot be made as trials differ in design, size, time period of recruitment, location of study sites etc.
AE=adverse event; SAE=serious adverse event

1. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428; 2. Ray-Coquard I, et al. N Engl J Med. 2019;381:Supplementary Appendix; 3. Moore K, et al. N Engl J Med. 2018;379:2495–2505;
4. Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391-2402

Haematological AEs of 3 Trials of PARPi in First Line Maintenance Treatment

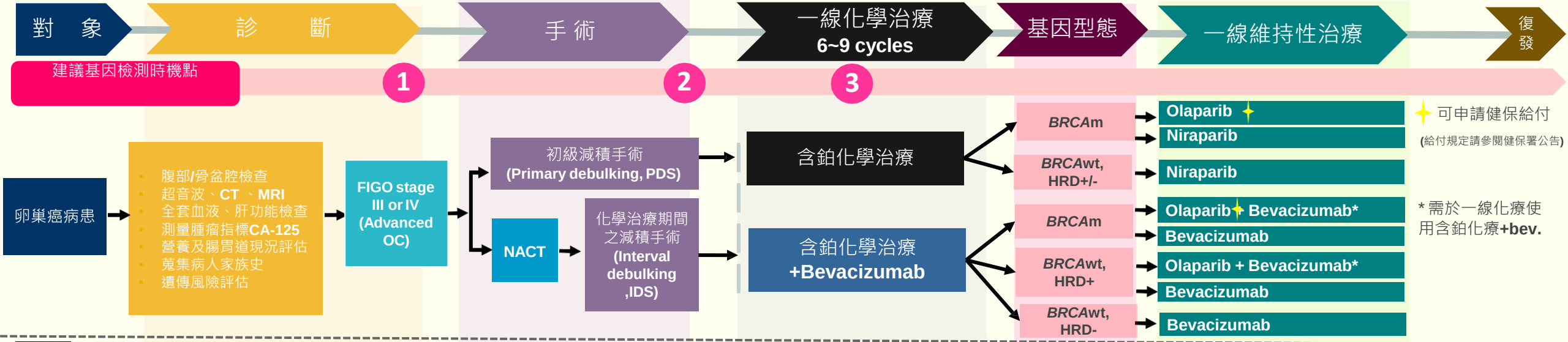
Grade ≥3 AEs, %	PRIMA[1]			PAOLA-1[2]		SOLO-1[3]	
	Niraparib fixed dose (n=315)	Niraparib modified dose (n=169)	Placebo (both) (n=244)	Bevacizumab + olaparib (n=535)	Bevacizumab + placebo (n=267)	Olaparib (n=260)	Placebo (n=131)
Any	76	60	19	57	51	39	18
Anamia	36	22	2	17	<1	22	2
Neutropenia	24	15	1	6	3	9	5
Thrombocytopenia	48	21	<1	2	<1	1	2
Hypertension	7	5	1	19	30	NR	NR

One case of MDS was reported in PRIMA, in the fixed dose niraparib group[4]

In the absence of head to head studies, cr … **etc**
Data by niraparib dosing group for non-ha e…
*Excluding patients who discontinued because of disease progression
AE=adverse event; MDS=myelodysplastic syndrome; NR=not reported

1. Mirza M et al. Presented at ASCO Virtual Conference 2020, 29-31 May. Abstract #6050; 2. Ray-Coquard I, et al. N Engl J Med. 2019;381:2416-2428;
3. Moore K, et al. N Engl J Med. 2018;379:2495–2505; 4. Gonzalez-Martin A, et al. N Engl J Med. 2019;381:2391-2402

新診斷之晚期上皮卵巢癌、輸卵管腫瘤及原發性腹膜癌病患基因檢測流程建議



基因檢測的時機點與治療策略

檢體來源

血液樣本: 進行遺傳性 *BRCA*基因檢測 (germline *BRCA* testing)

- 腫瘤組織切片: 預先針對基因檢測檢體進行採檢
- 手術開刀取得腫瘤組織檢體: 需留意檢體量及品質

檢測類別

- **Germline *BRCA* Testing:** 確認是否具有遺傳性***BRCA* 1/2**基因突變
- **Tissue *BRCA* Testing:** 確認是否具有***BRCA* 1/2**基因突變 ∮
- **HRD Testing:** 同時確認是否具有***BRCA* 1/2**基因突變∮以及基因體不穩定**(genomic instability)**ǂ

∮包含遺傳性與自發性

ǂ NCCN (V.3.2021): In the absence of a BRCA ½ mutation, HRD testing may also be considered, as it may provide information about the magnitude of benefit of PARP inhibitor maintenance therapy following first-line chemotherapy (category 2B).

檢測時機

★檢測報告結果所需時間: ***BRCA***基因檢測 **2**週 **/ HRD**基因檢測 **2-4**週 ★**Olaparib**健保申請: **2** 週

1 手術前

確認 *BRCA*及HRD status，及早擬定完整術後治療策略(包含化學治療& 維持性治療)，可避免等待時間延誤治療時機。

對於需進行術前輔助性化療(NACT)接續IDS的病患，為避免後續檢體不足問題，應在一開始進行基因檢測卻保有足夠完整的基因資訊，以訂定後續治療策略。

2 手術後，一線化學治療前

確認 *BRCA*及HRD status，及早擬定完整術後治療策略(包含化學治療& 維持性治療)，可避免等待時間延誤治療時機。

特別考量*

對於需進行術前輔助性化療*(NACT)*接續*IDS*的病患，須留意一開始要採集足夠且良好品質的檢體

3 含鉑化學治療療程中 (3~4 cycle)

可根據病患對於含鉑化學治療之反應**(CA-125**濃度下降**or**影像學的緩解)，以溝通接續進行基因檢測，進而為後續維持治療進行準備。

特別考量*

1. 需注意時檢測**&**健保申請所需時間，避免因等待時間而延誤治療
2. 須留意一開始要有足夠且良好品質的檢體

PDS: Primary debulking surgery
IDS: Interval debulking surgery
NACT: Neoadjuvant chemotherapy
BRCA: Breast cancer susceptibility gene
HRD: Homologous recombination deficiency
NCCN: National Comprehensive Cancer Network

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed August 23, 2021. 2. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V.2.2021. ©National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed June 3, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 3. Pennington KP, et al. *Clin Cancer Res.* 2014;20(3):764-775. 4. Konstantinopoulos PA, et al. J Clin Oncol. 2020;38(11):1222-1245. 5. SGO website. http://www.sgo.org/clinical-practice/guidelines/genetic-testing-for-ovarian-cancer/. Accessed June 3, 2021. 6. Colombo N, Ledermann JA, on behalf of the ESMO Guidelines Committee, Updated treatment recommendations for newly diagnosed epithelial ovarian carcinoma from the ESMO Clinical Practice Guidelines, Annals of Oncology (2021)

關於卵巢癌基因檢測的3W1H

WHY TEST

基因檢測可幫助了解晚期上皮卵巢癌、輸卵管腫瘤及原發性腹膜癌病患的基因變異類型，針對個人化制定策略 **(**含化療療程及維持性治療**)**，以達到精準化醫療之目標。

WHOM TO TEST

根據各卵巢癌國際指標性治療指引最新版 **(NCCN, ASCO, ESMO*,SGO)**建議針對所有診斷為上皮卵巢癌之婦女皆應進行遺傳性或**/**和組織性**BRCA**基因檢測。

而**HRD**基因檢測可進一步提供病患基因不穩定**(genomic instability)**相關資訊，做為治療決策參考，可建議病患進行。

HOW TO TEST

檢體	檢測種類	卵巢癌陽性比例[6, 9]
	遺傳性 **BRCA** 基因檢測 **(germline BRCA testing)**	**≈13~15%**
	組織 **BRCA** 基因檢測 **(tissue BRCA testing)**	**≈20%**
	HRD基因檢測，含**BRCA**基因檢測 **(HRD genomic instability test)**	**≈50%**

WHEN TO TEST

基因檢測的時機點會影響治療策略擬定，以下針對不同基因檢測的時機點與治療策略提供建議指引參考。

*ESMO Guideline (2021 July update) recommends all patients with high-grade OC should be tested for *BRCA1/2*mutation (germline/somatic) at diagnosis.

NCCN=National Comprehensive Cancer Network; ASCO=American Society of Clinical Oncology; ESMO: European Society for Medical Oncology; SGO=Society of Gynecologic Oncology; BRCA1=breast cancer susceptibility gene 1; BRCA2=breast cancer susceptibility gene 2; HRD=homologous recombination deficiency.

1. Frey MK, et al. *Gynecol Oncol Res Pract.* 2017;4:4. 2. Watkins JA, et al. *Breast Cancer Res.* 2014;16(3):211. 3. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Ovarian Cancer Including Fallopian Tube Cancer and Primary Peritoneal Cancer V.2.2021. © National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed August 23, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. NCCN makes no warranties of any kind whatsoever regarding their content, use or application and disclaims any responsibility for their application or use in any way. 4. Pennington KP, et al. *Clin Cancer Res.* 2014;20(3):764- 775. 5. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic V.2.2021. ©National Comprehensive Cancer Network, Inc. 2021. All rights reserved. Accessed June 3, 2021. To view the most recent and complete version of the guideline, go online to NCCN.org. 6. Konstantinopoulos PA, et al. J Clin Oncol. 2020;38(11):1222-1245. 7. SGO website. http://www.sgo.org/clinical-practice/guidelines/genetic-testing-for-ovarian-cancer/. Accessed June 3, 2021. 8. Colombo N, Ledermann JA, on behalf of the ESMO Guidelines Committee, Updated treatment recommendations for newly diagnosed epithelial ovarian carcinoma from the ESMO Clinical Practice Guidelines, Annals of Oncology (2021). 9. Konstantinopoulos PA, et al. Cancer Discov 2015;5:1137–1154.

Lynparza 適應症及健保給付

TFDA 核准適應症

晚期高度惡性上皮卵巢癌、輸卵管腫瘤或原發性腹膜癌，且具遺傳性或體細胞BRCA1/2（germline or somatic BRCA1/2）致病性或疑似致病性突變，對第一線含鉑化療有反應（完全反應或部分反應）之成年病人作為維持治療。

對先前含鉑藥物敏感且復發之高度惡性上皮卵巢、輸卵管腫瘤或原發性腹膜癌，在復發後對含鉑化療有反應（完全反應或部分反應）之成人病人，作為維持治療。

Lynparza 併用 bevacizumab 可用於晚期高度惡性上皮卵巢癌、輸卵管腫瘤或原發性腹膜癌，且對第一線含鉑化療合併bevacizumab有反應有完全反應或部分反應之成年病人，做為維持治療。且其癌症帶有下列任一定義的DNA同源修復系統缺失(homologous recombination deficiency, HRD)：致病性或疑似致病性 BRCA 突變，及/或基因體不穩定(genomic instability)

Lynparza單一療法可用於治療曾接受前導性、術後輔助性或轉移性化療，且具遺傳性BRCA1/2（germline BRCA1/2）致病性或疑 似致病性突變的HER2（-）轉移性乳癌成人病人。針對荷爾蒙受體陽性的乳癌病人，本品應在曾經接受過荷爾蒙治療、或不適合使 用荷爾蒙治療之狀況下使用。

Lynparza 單一療法之維持治療，可用於遺傳性 BRCA 突變且經第一線含鉑化療至少 16 週後疾病未惡化之轉移性胰腺癌成年病人。

用於去勢療法無效的轉移性攝護腺癌(metastatic castration-resistant prostate cancer，mCRPC)，且具BRCA1/2 (遺傳性及/或體細胞)致病性或疑似致病性突變、先前曾接受新荷爾蒙藥物(novel hormonal agents)治療後惡化之成人病人。

Lynparza™ olaparib tablets 150 mg 卵巢癌健保給付條文

Olaparib (Lynparza)：

1.高度惡性上皮卵巢、輸卵管或原發性腹膜癌：

檢附病理報告，給付條文並無限定細胞型態

(1) 單獨使用於具下列所有條件的病患做為維持治療，限用兩年：

A.對第一線含鉑化療有治療反應後使用。

對第一線含鉑化療有達到CR或PR ❼　影像學報告，CA125

B.具生殖細胞或體細胞BRCA 1/2致病性或疑似致病性突變。

檢附BRCA mutation基因檢測報告，
給付條文並未限制基因檢測公司，
也沒有限定血液檢測或組織檢測

C.FIGO (International Federation of Gynecology and Obstetrics) Stage Ⅲor Ⅳ disease。

檢附病理報告，確認FIGO staging

(2) 須經事前審查核准後使用，每次申請事前審查之療程以六個月為限，再次申請必須提出客觀證據（如：影像學）證實無惡化，才可繼續使用。

✓ **4x30x6 = 720**

小撇步: 提早在藥物用完前安排影像學檢查(如CT)及血液學檢測(CA-125)，以利後續申請藥物銜接治療

影像學無惡化: Stable disease / no recurrence

2. 三陰性乳癌：(略)

3.每日最多使用4 粒

Take-Home Message

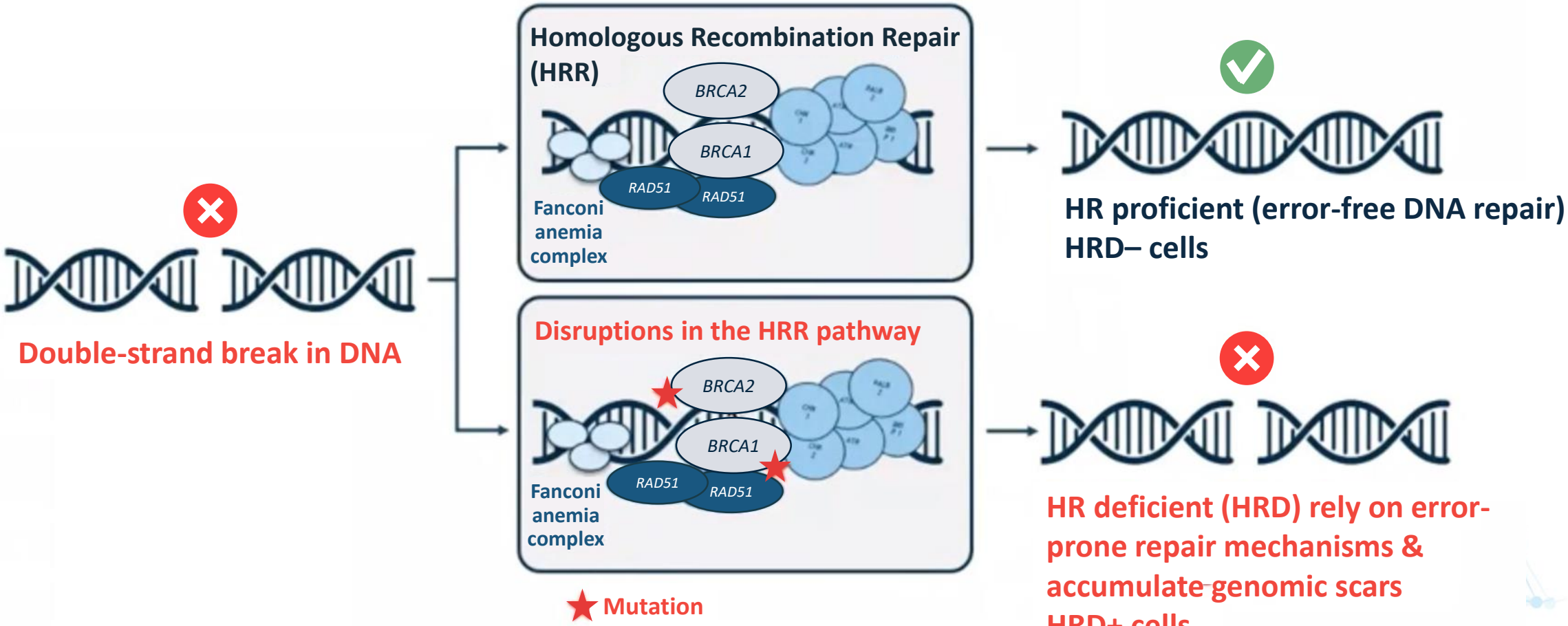
- SOLO1: For stage III/IV HGSC, Olaparib is the most powerful maintenance therapy after 1st-line chemotherapy (CR or PR)
- PAOLA-1:
  - Adding Olaparib to Bevacizumab prolonged PFS over Bevacizumab alone
- Population-based analysis from SOLO1 & PAOLA-1
  - PFS benefit is similar between Olaparib & Bevacizumab+Olaparib
  - However, Head-to-Head comparison is needed for more solid evidence
- Bevacizumab had no boundary of histology type, neither *BRCA*m biomarker
- Early check-up of BRCA/HRD status help select maintenance therapy
- Real-world data in CGMH Linkou good tolerance to Olaparib 600 mg/D

Thank You for Your Attention!

SOFIVA HRD Status

SOFIVA Genomics

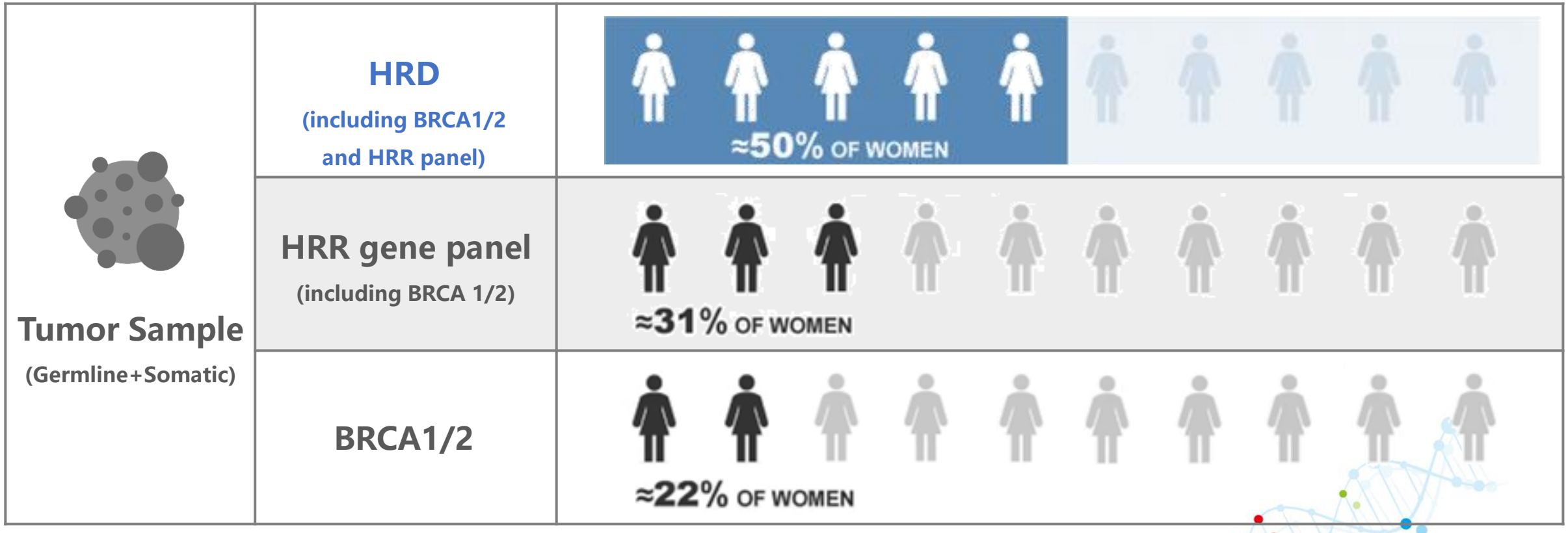
What is Homologous Recombination Deficiency (HRD)?



SOFIVA GENOMICS

Why Use Two Strategies to Detect HRD?

✓ **The goal is to identify as many patients as possible that will benefit from PARP inhibitor**



SOFIVA GENOMICS

Summary of Efficacy in Randomised Phase III Trials of PARPis in the Front-Line Ovarian Cancer Setting

Trial	Maintenance			
	PRIMA/ENGOT-OV26 niraparib ($N = 733$)[23]		PAOLA-1/ENGOT-OV25 olaparib + bevacizumab ($N = 806$)[22]	
Median duration of follow-up, months (PARPi vs control)	14		23 vs 24	
All comers	**($N = 733$)**		**($N = 806$)**	
PFS HR (95% CI)	**0.62 (0.50–0.76)**		**0.59 (0.49–0.72)**	
Median PFS, months (PARPi vs control)[b]	**13.8 vs 8.2**		**22.1 vs 16.6**	
BRCA mutated	($N = 223$)		($N = 237$)	
PFS HR (95% CI)	0.40 (0.27–0.62)	30%	0.31 (0.20–0.47)	29%
Median PFS, months (PARPi vs control)[b]	22.1 vs 10.9		37.2 vs 21.7	
HRD test positive	**($N = 373$)**		($N = 387$)	
PFS HR (95% CI)	**0.43 (0.31–0.59)**	51%	0.33 (0.25–0.45)	48%
Median PFS, months (PARPi vs control)[b]	**21.9 vs 10.4**		37.2 vs 17.7	
HRD test positive non-*BRCA* mutated	($N = 150$)		($N = 152$)	
PFS HR (95% CI)	0.50 (0.31–0.83)	20%	0.43 (0.28–0.66)	19%
Median PFS, months (PARPi vs control)[b]	19.6 vs 8.2		28.1 vs 16.6	
HRD test negative (proficient)	($N = 249$)		($N = 277$)	
PFS HR (95% CI)	0.68 (0.49–0.94)		1.00 (0.75–1.35)	
Median PFS, months (PARPi vs control)[b]	8.1 vs 5.4		16.6 vs 16.2	

OFIVA GENOMICS

Ann Oncol. 2020 Sep;31(9):1148-1159.

Summary of Efficacy in Randomised Phase III Trials of PARPis in the Front-Line Ovarian Cancer Setting

Table 1 Biomarker Testing for Patient Selection

Olaparib

Indication	Biomarker
First-line maintenance treatment of germline or somatic *BRCA*m advanced ovarian cancer*	*BRCA1*m, *BRCA2*m
First-line maintenance treatment of HRD-positive advanced ovarian cancer in combination with bevacizumab*	*BRCA1*m, *BRCA2*m and/or genomic instability
Maintenance treatment of recurrent ovarian cancer	No requirement for biomarker testing
Advanced g*BRCA*m ovarian cancer	*gBRCA1*m, *gBRCA2*m

T-OV26 niraparib		PAOLA-1/ENGOT-OV25 olaparib + bevacizumab ($N = 806$)[22]	
		23 vs 24	
.76)		**($N = 806$)** **0.59 (0.49–0.72)** **22.1 vs 16.6**	
.62)	30%	($N = 237$) 0.31 (0.20–0.47) 37.2 vs 21.7	29%
.59)	51%	($N = 387$) 0.33 (0.25–0.45) 37.2 vs 17.7	48%
.83)	20%	($N = 152$) 0.43 (0.28–0.66) 28.1 vs 16.6	19%
.94)		($N = 277$) 1.00 (0.75–1.35) 16.6 vs 16.2	

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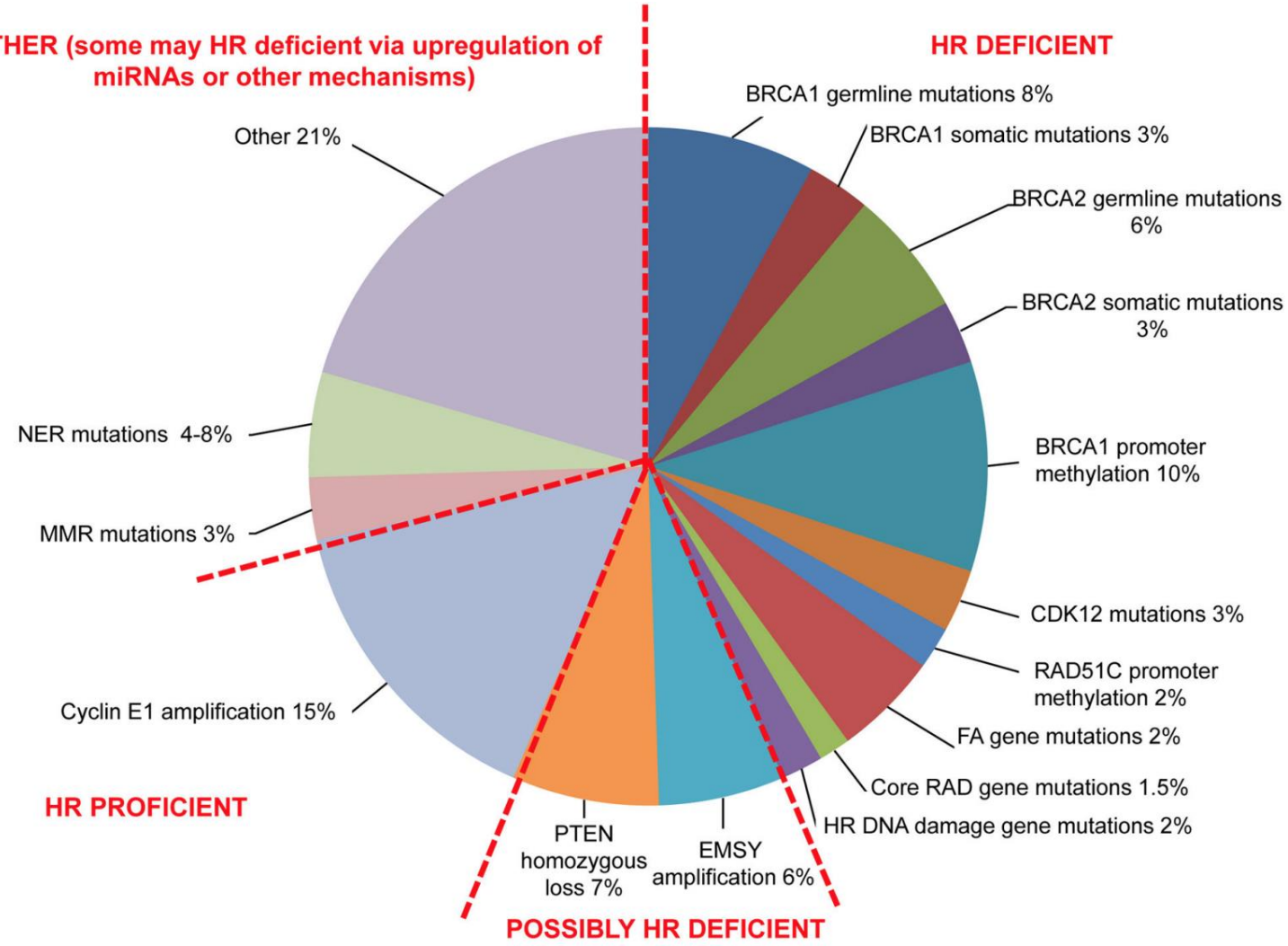
Ann Oncol. 2020 Sep;31(9):1148-1159.

Approximately 50% of HGSOC Have Alterations in HRR Genes



HRD

HRR Gene Mutations

Entire Genomic Landscape

SOFIVA GENOMICS

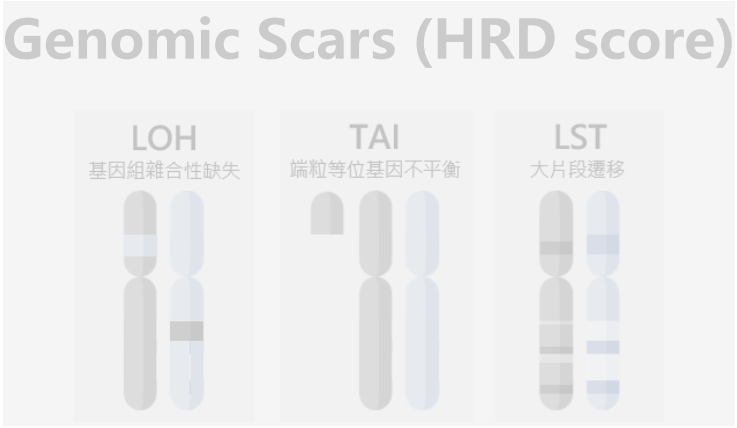
Cancer Discov. 2015;5:1137-1154.

Detection of Homologous Recombination Deficiency (HRD)

HRD

Inability to repair DNA

Genomic Instability



Effect

Genomic Integrity Index

Low-pass WGS

Access accumulated DNA damage

SOFIVA HRD Status – Test of Content

CAUSE	EFFECT

28 HRR gene variants (including *BRCA1/2*) **+ Genomic integrity index = HRD status**

Targeted Sequencing + **Low-Pass WGS** + **Deep Learning**

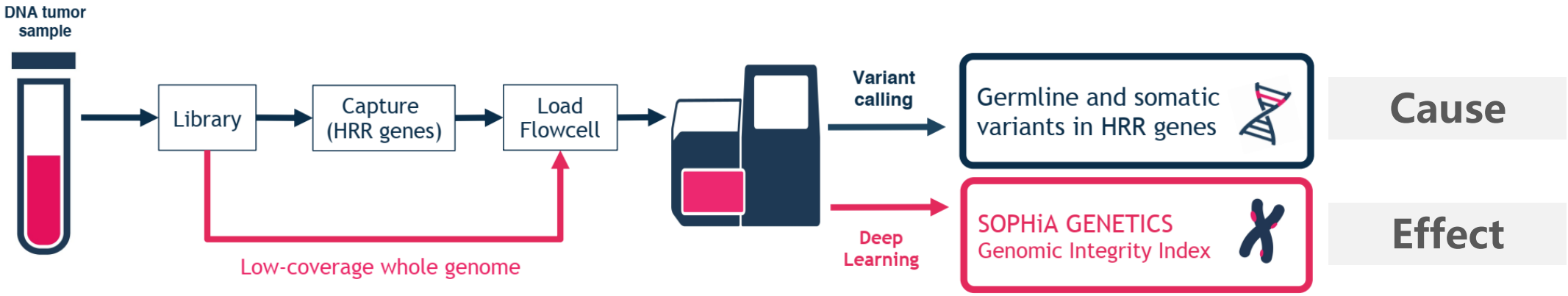
- **MLPA: *BRCA1/2***
- **Sanger sequencing**

✓ Combines the sequencing of HRR genes and measures Genomic Integrity in a single assay

✓ Fully exploits the information provided by low-pass WGS

✓ Cost-effective

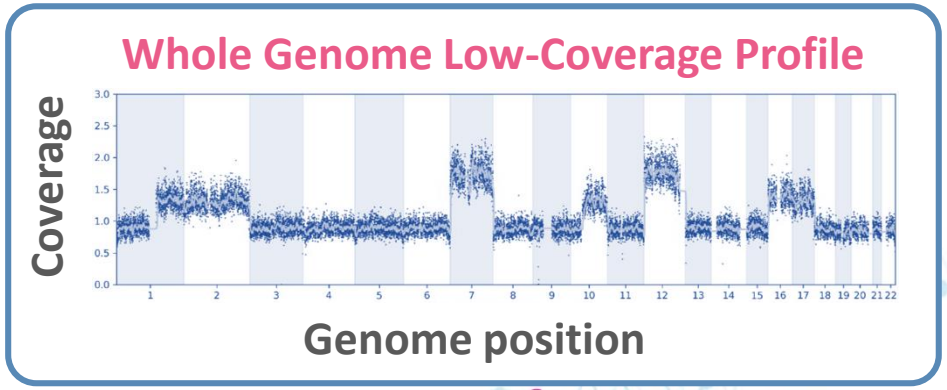
SOFIVA HRD Status – Test of Content



HRR gene variants + Genomic integrity index = HRD status

HRR Gene List

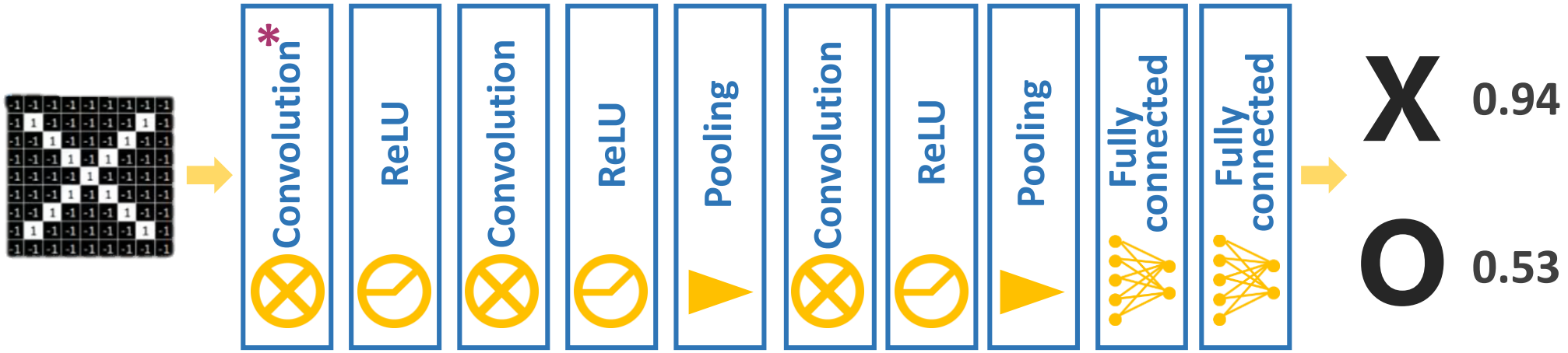
AKT1	*CDK12*	*FGFR1*	*PPP2R2A*
ATM	*CHEK1*	*FGFR2*	*RAD51B*
BARD1	*CHEK2*	*FGFR3*	*RAD51C*
BRCA1	*ESR1*	*MRE11*	*RAD51D*
BRCA2	*FANCA*	*NBN*	*RAD54L*
BRIP1	*FANCD2*	*PALB2*	*TP53*
CCNE1	*FANCL*	*PIK3CA*	*PTEN*



SOFIVA GENOMICS

Convolutional Neural Networks (CNNs)

A set of pixels become a set of votes

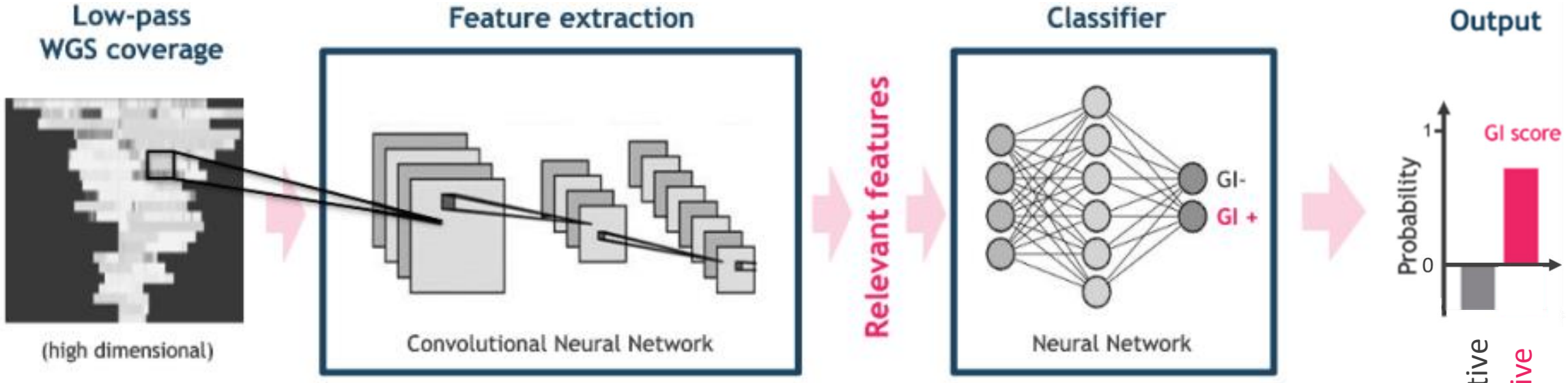


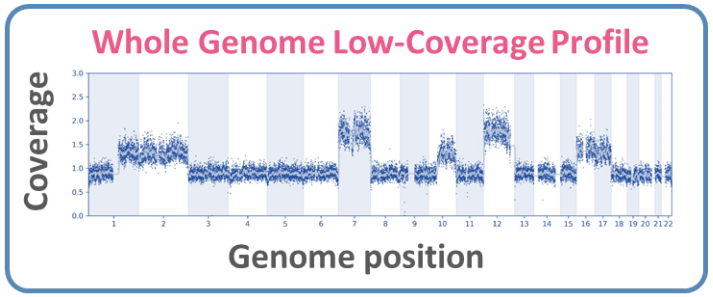
* Filtering: the math behind the match

SOFIVA GENOMICS

CNNs – Genome Integrity Index

- Transform low-pass WGS (~1x) coverage profile into an “image”
- Use CNNs to classify images as GI positive and GI negative

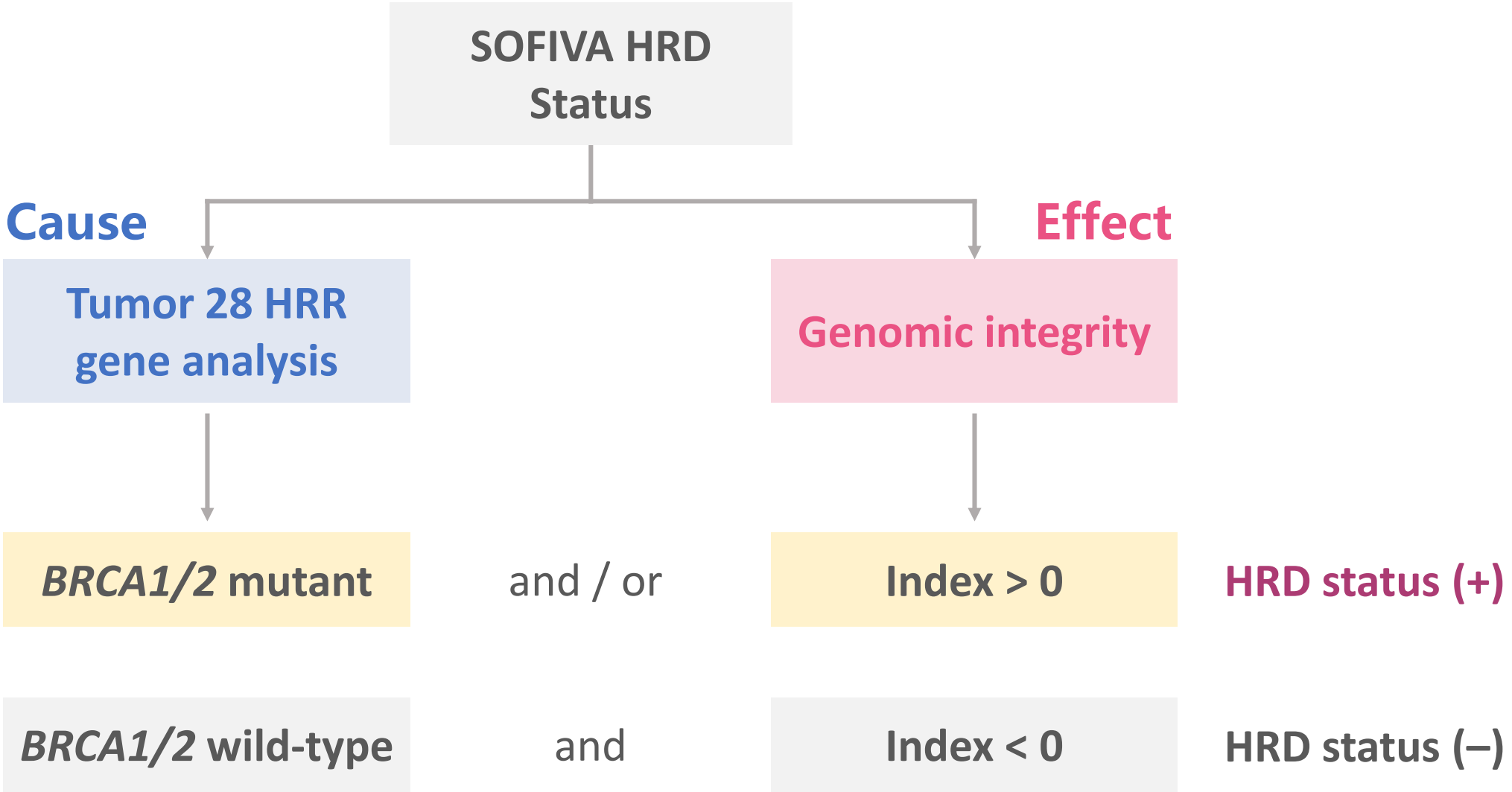




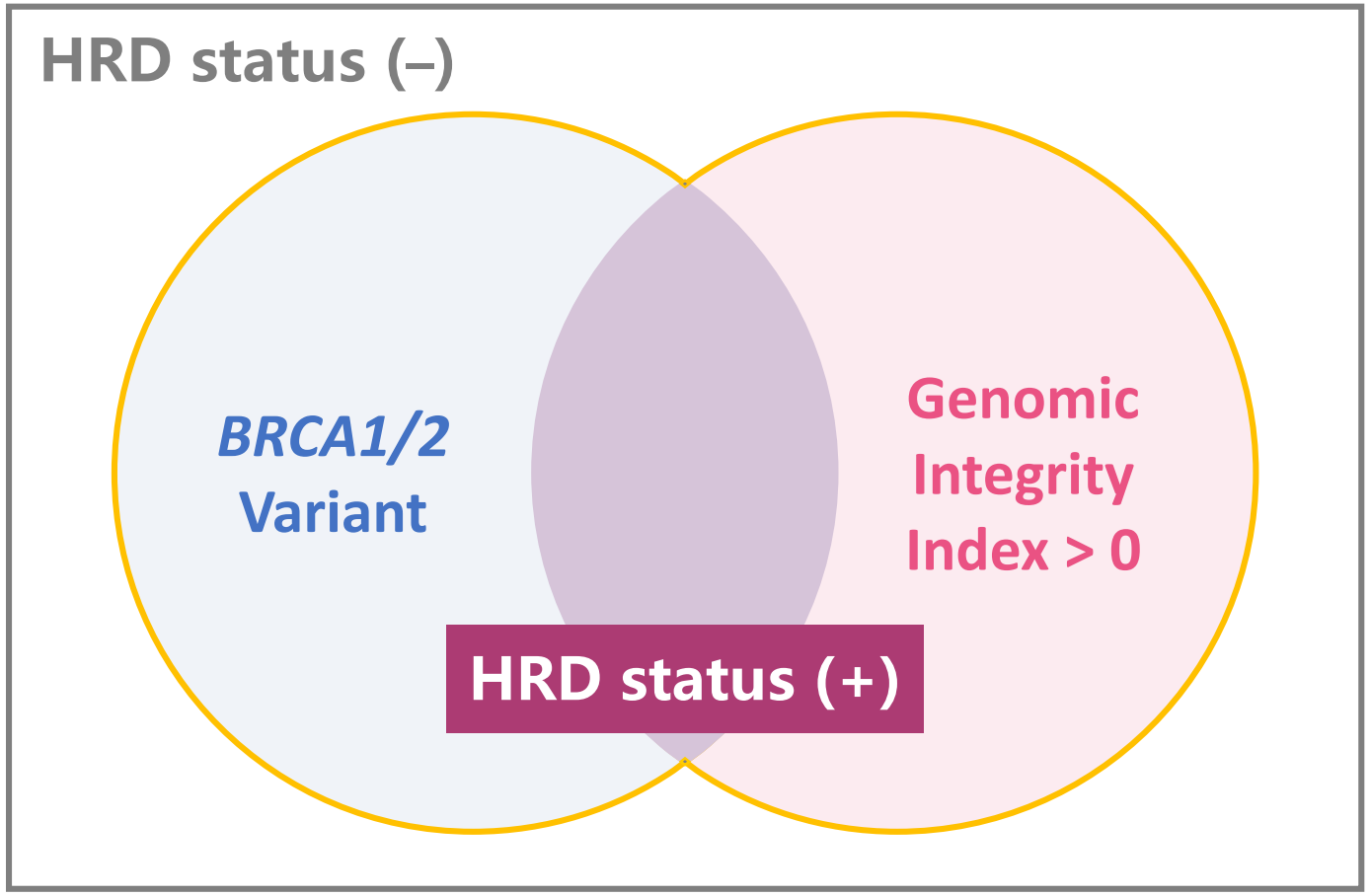
Genomic Integrity Index

SOFIVA GENOMICS

SOFIVA HRD Status – Interpretation of Results



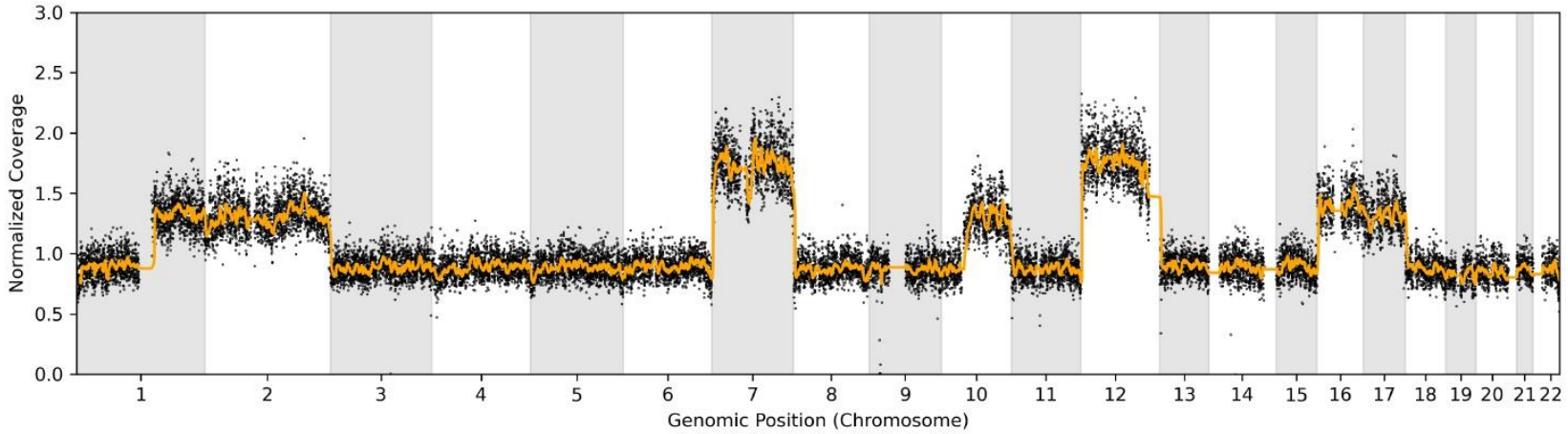
SOFIVA HRD Status – Interpretation of Results



SOFIVA
GENOMICS

SOFIVA HRD Status – Case Report

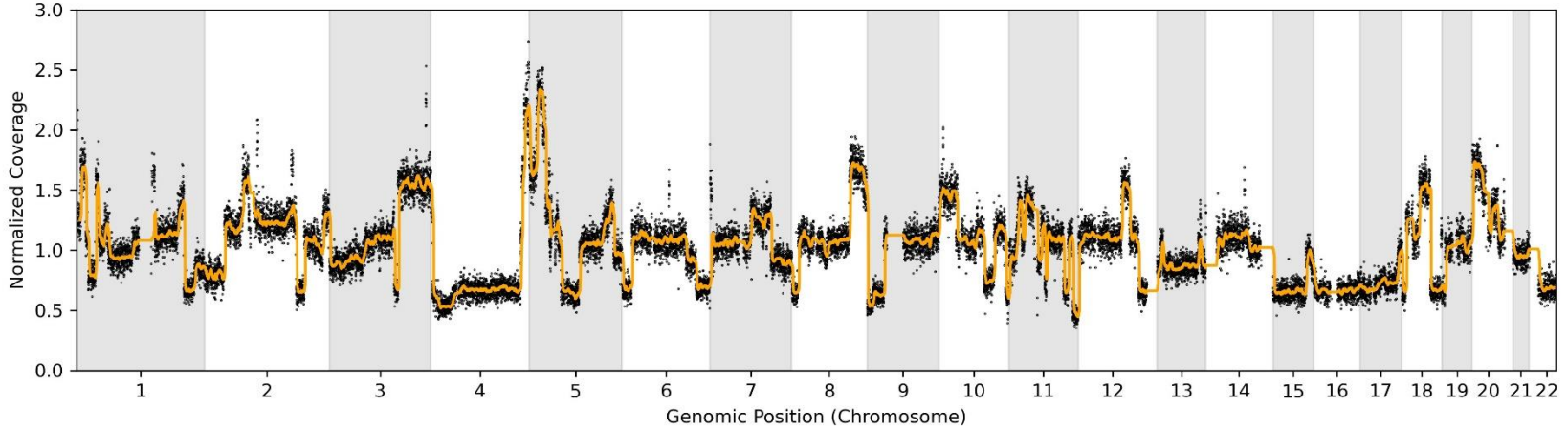
HRD: Negative



- Genome integrity index = **-13.8**
- 28 HRR gene: **wild-type**

→ HRD status: **Negative**

HRD: Positive



- Genome integrity index = **14.1**
- 28 HRR gene: **BRCA1 deletion**

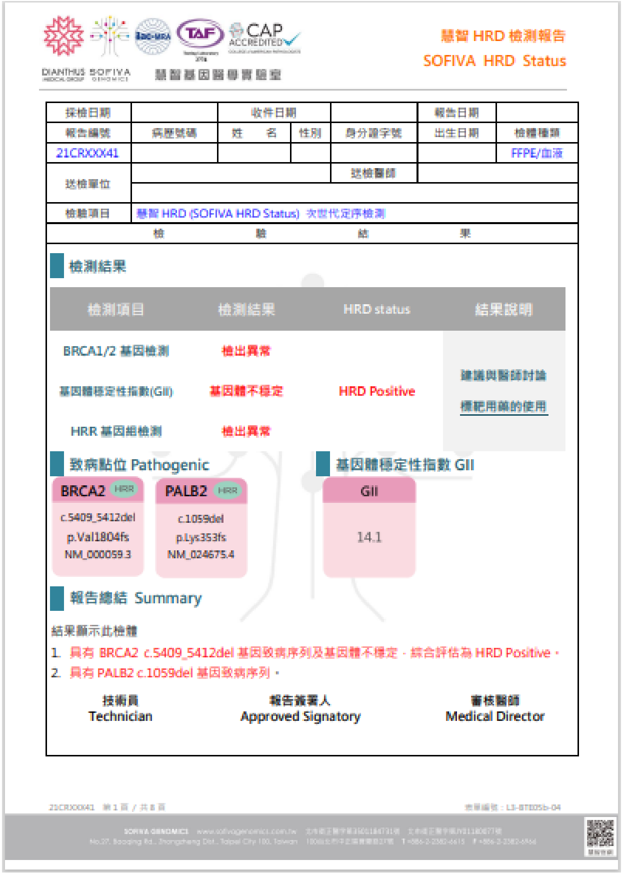
(BRCA1 c.3858_3861del 74.75%)

→ HRD status: **Positive**

→ Sanger: **Germline mutation**

SOFIVA GENOMICS

SOFIVA HRD Status – Report



慧智 HRD 檢測報告
SOFIVA HRD Status

慧智基因醫學實驗室

採檢日期		收件日期		報告日期	
報告編號	病歷號碼	姓名	性別	身分證字號	出生日期	檢體種類
21CRXXX41						FFPE/血液

送檢單位 / 送檢醫師

檢驗項目：慧智 HRD (SOFIVA HRD Status) 次世代定序檢測

檢驗結果

檢測結果

檢測項目	檢測結果	HRD status	結果說明
BRCA1/2 基因檢測	檢出異常		建議與醫師討論
基因體穩定性指數(GII)	基因體不穩定	HRD Positive	標靶用藥的使用
HRR 基因組檢測	檢出異常		

致病點位 Pathogenic

BRCA2 HRR: c.5409_5412del p.Val1804fs NM_000059.3

PALB2 HRR: c.1059del p.Lys353fs NM_024675.4

基因體穩定性指數 GII

GII: 14.1

報告總結 Summary

結果顯示此檢體

1. 具有 BRCA2 c.5409_5412del 基因致病序列及基因體不穩定，綜合評估為 HRD Positive。
2. 具有 PALB2 c.1059del 基因致病序列。

技術員 Technician　報告簽署人 Approved Signatory　審核醫師 Medical Director

檢測結果

檢測項目	檢測結果	HRD status	結果說明
BRCA1/2 基因檢測	檢出異常		建議與醫師討論
基因體穩定性指數(GII)	基因體不穩定	HRD Positive	標靶用藥的使用
HRR 基因組檢測	檢出異常		

致病點位 Pathogenic

BRCA2 HRR	PALB2 HRR
c.5409_5412del	c.1059del
p.Val1804fs	p.Lys353fs
NM_000059.3	NM_024675.4

基因體穩定性指數 GII

GII
14.1

報告總結 Summary

結果顯示此檢體

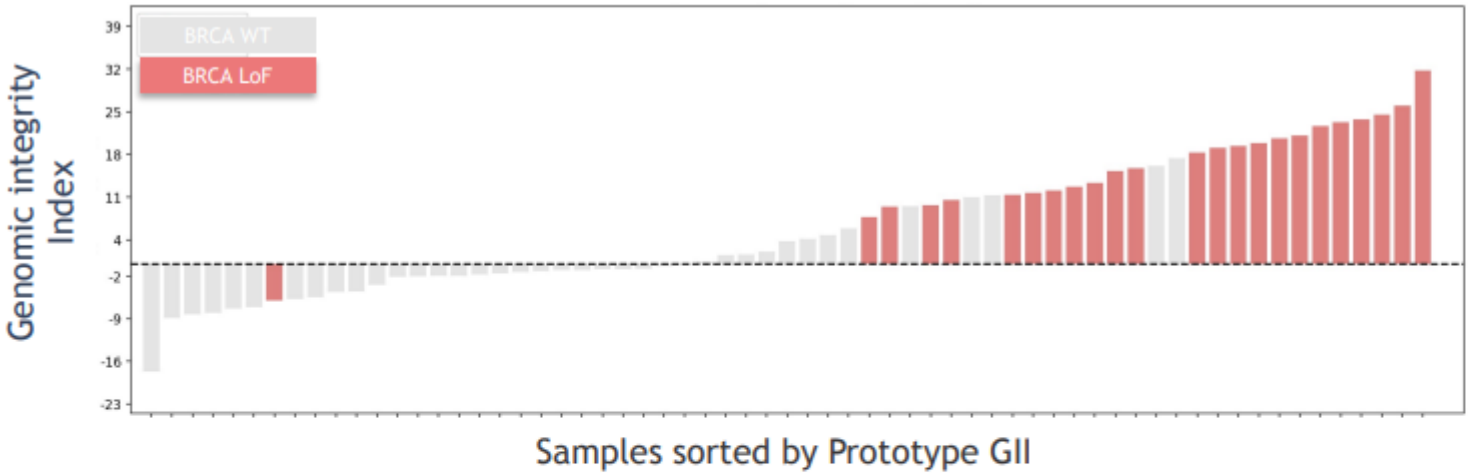
1. 具有 BRCA2 c.5409_5412del 基因致病序列及基因體不穩定，綜合評估為 HRD Positive。
2. 具有 PALB2 c.1059del 基因致病序列。

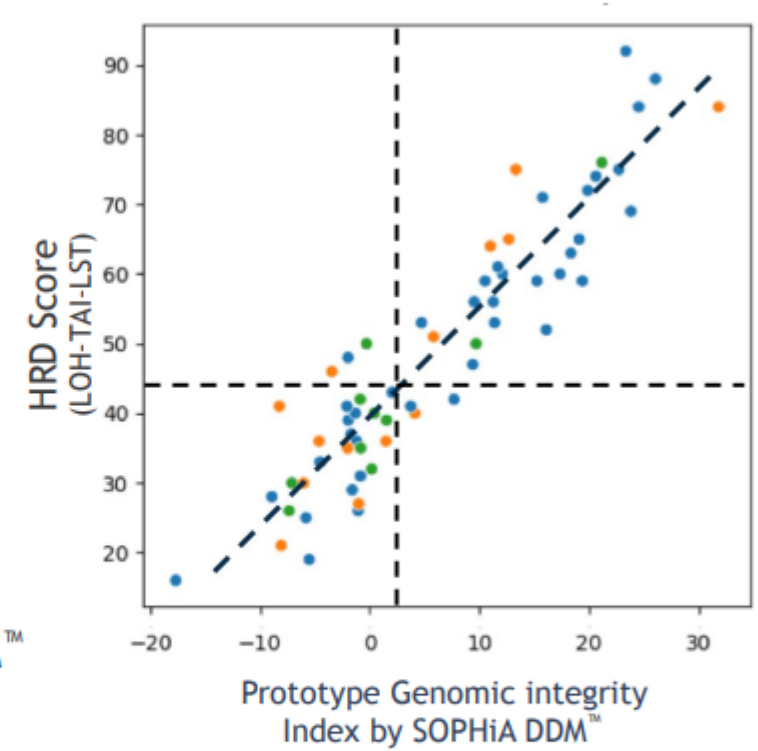
SOFIVA GENOMICS

Concordance Data – Internal Study

SOPHiA GENETICS

- The SOPHiA solution was assessed using 62 high-grade serous Ovarian Cancer samples (public data)





Conclusion: *BRCA* mutated samples are correctly classified as HRD positive via Prototype Genomic Integrity Index analysis by SOPHiA DDM™

Conclusion: Prototype Genomic Integrity Index by SOPHiA DDM™ strongly correlates to HRD Score (LOH + TAI + LST)

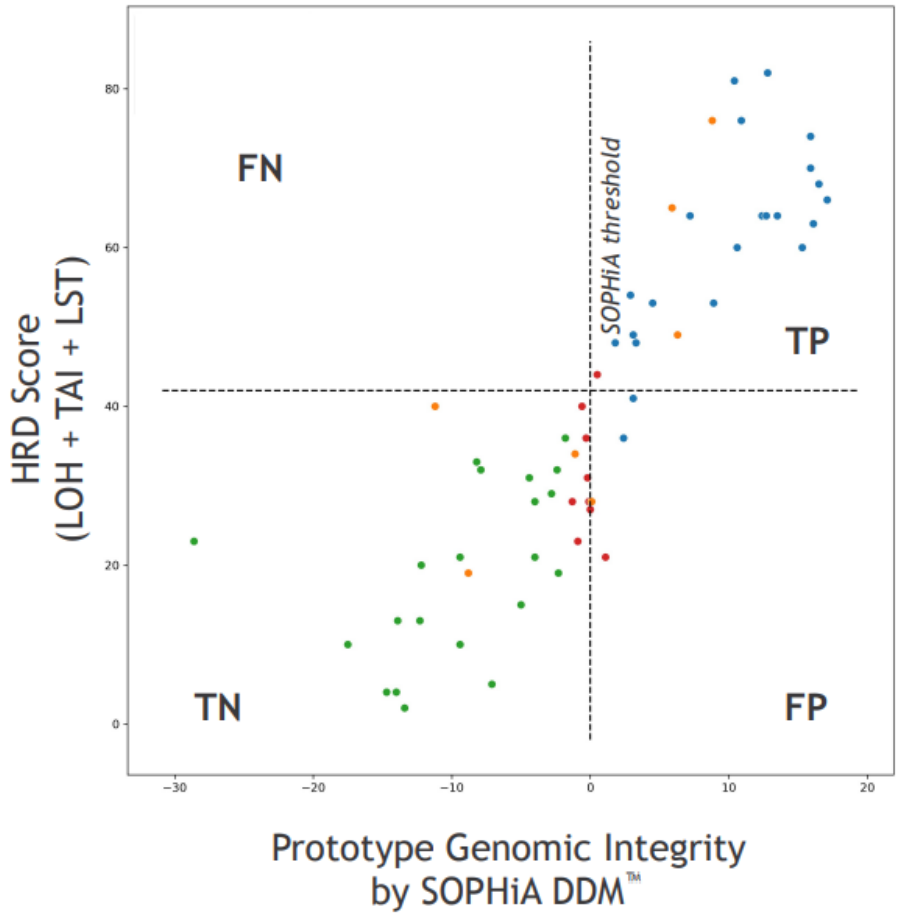
Patch et al., Nature 2015

Product in development - Not for use in diagnostic procedures

Data on file

Concordance Data – External Study

SOPHiA GENETICS



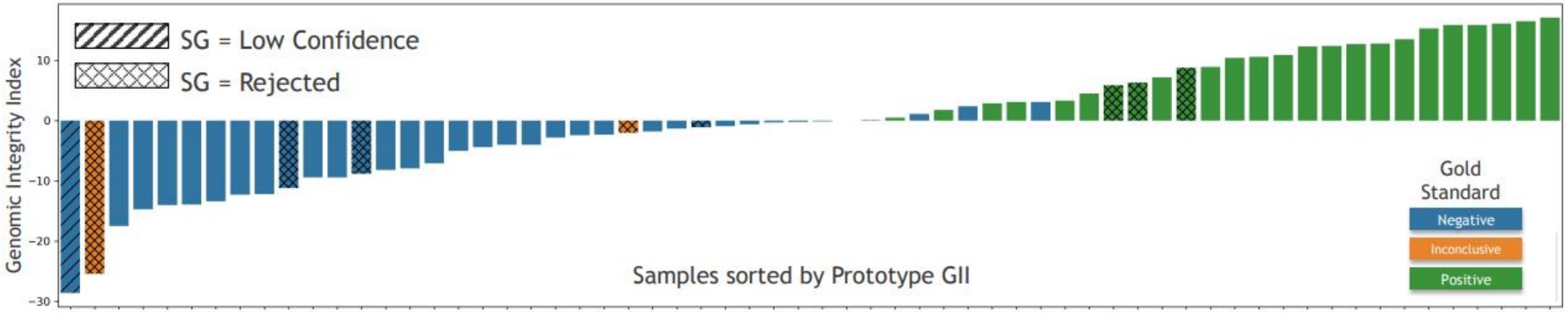
- 53 samples passed SOPHiA DDM™ sample QA
- Observed concordance to HRD Score (LOH + TAI + LST) : **94%**

Product in development - Not for use in diagnostic procedures

Concordance Data – External Study (will have peer to peer review publish)

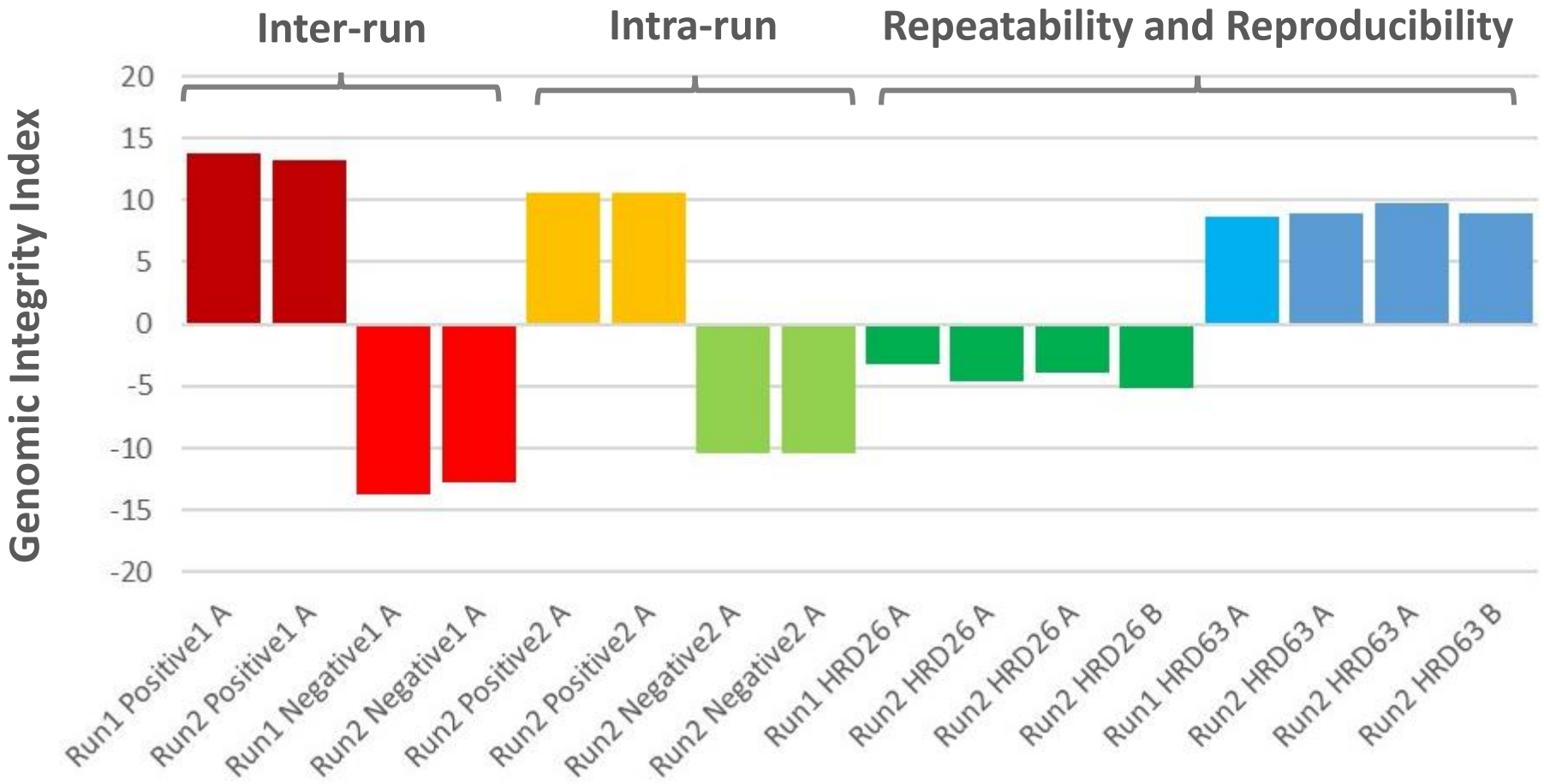
SOPHiA GENETICS

- Overall excellent concordance with the published method using HRD Score (LOH + TAI + LST)



Product in development - Not for use in diagnostic procedures

SOFIVA HRD Status – Repeatability and Reproducibility



SOFIVA GENOMICS

SOFIVA HRD Status – Overview

檢體需求	石蠟包埋切片 + 全血
檢測內容	• HRD status • *BRCA1/2*基因 (含gBRCA1/2 LGR) • 28個HRR基因突變偵測 • 基因組完整性指數GII
檢測平台	• NGS：HRR基因定序 + Low-pass WGS • MLPA：針對g*BRCA1/2* LGR偵測 • Sanger定序：確認基因突變來源為遺傳性或自發性
解析範圍	相關基因全外顯子 / 全基因組
偵測類型	SNV / InDel / CNV (LGR)* / GII
檢測時間	10個工作天**

*針對*BRCA1/2* **以認證實驗室收到合格檢體後開始計算

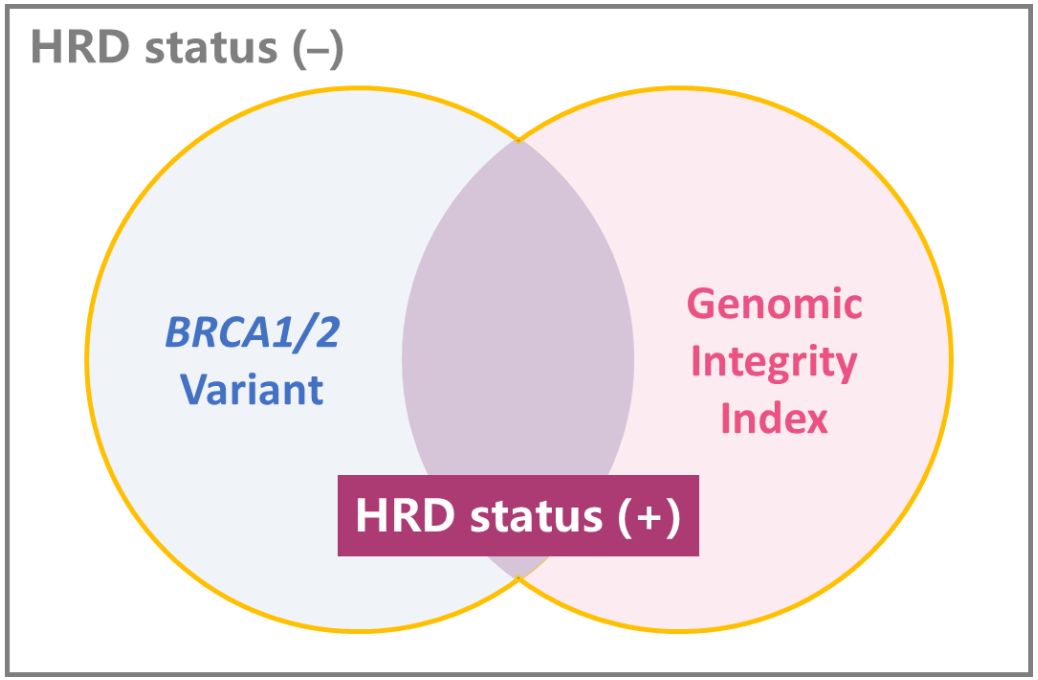
■ 最終HRD結果判讀

HRD(+)：*BRCA1/2* mutant 及/或 GII > 0; HRD(–)：*BRCA1/2* wild-type 及 GII < 0

SOFIVA GENOMICS

SOFIVA HRD Status – Features and Advantages

- 28 HRR genes (including *BRCA1/2*)
- Genomic Integrity Index
- Low-pass WGS
- Sanger sequencing
- Cost-effective



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GENOMICS

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慧智基因股份有限公司

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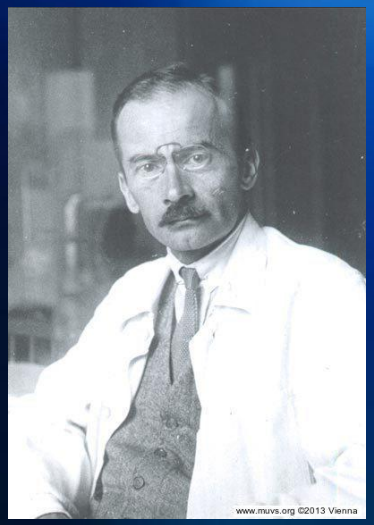
台北市100中正區寶慶路27號

口服避孕藥之演進

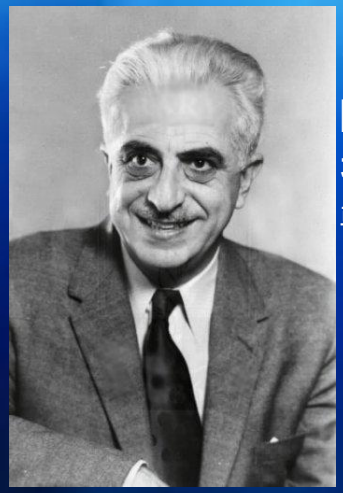
蔡啟智 醫師

花蓮門諾醫院婦產科

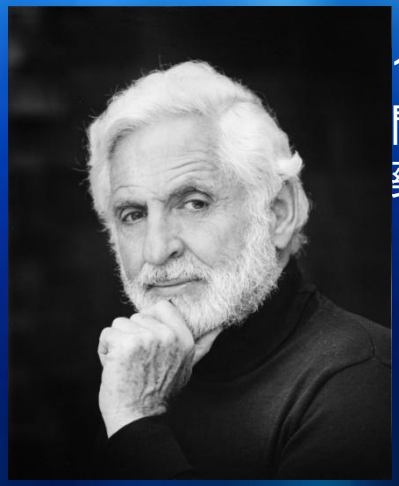
避孕藥發展



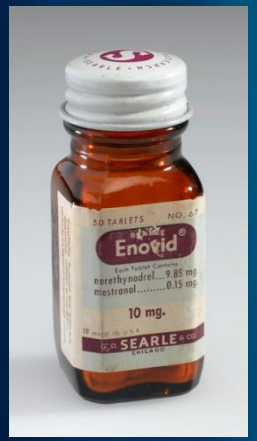
生理學家Ludwig Haberlandt首次揭示了大腦和卵巢分泌的荷爾蒙可調節女性月經，並從動物實驗中揭示避孕的原理。



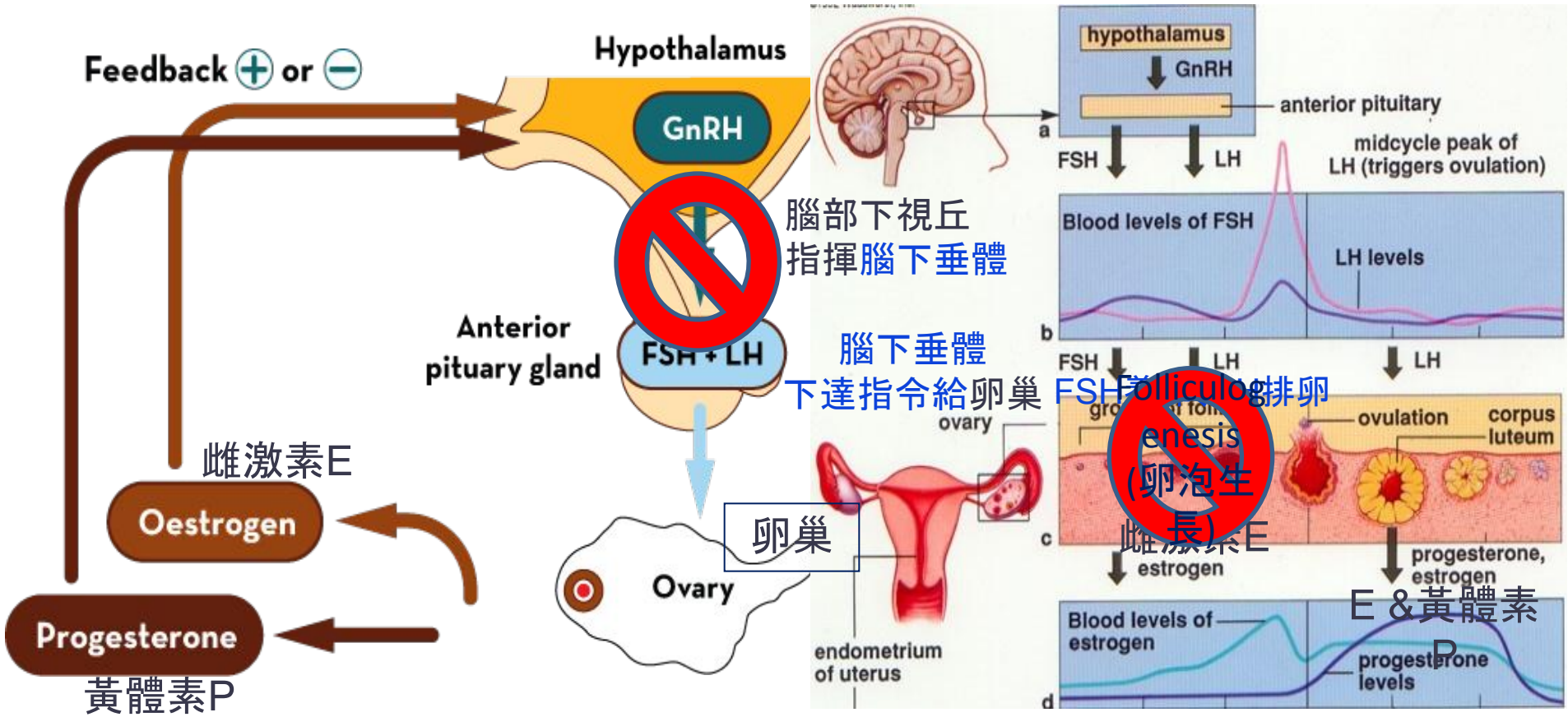
1953年生物學家Pincus確定動物施打黃體素之後就會暫停排卵。



1960年化學家Djerassi開發出第一個口服避孕藥Enovid。



排卵、賀爾蒙分泌與回饋

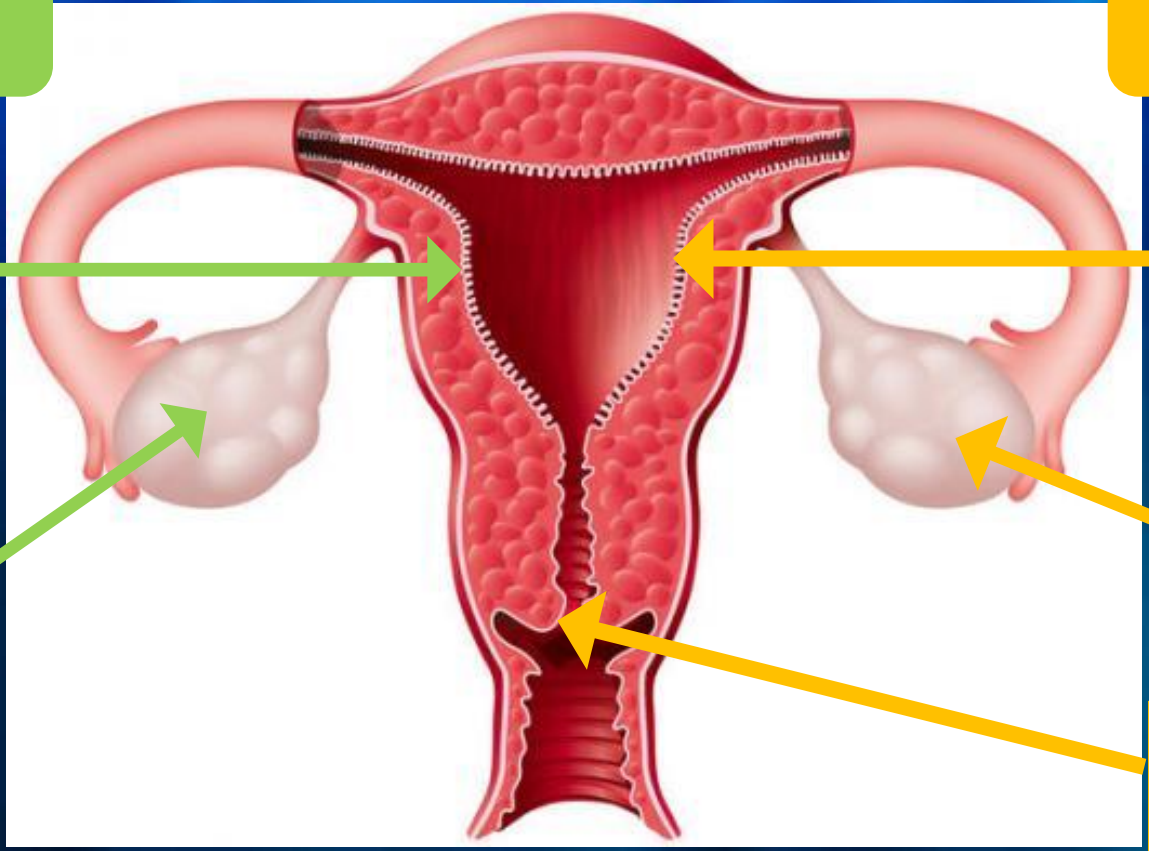

Feedback ⊕ or ⊖
Hypothalamus
GnRH
Anterior pituary gland
FSH + LH
雌激素E
Oestrogen
Progesterone
黃體素P
Ovary
卵巢
endometrium of uterus
腦部下視丘
指揮腦下垂體
腦下垂體
下達指令給卵巢 FSH follicular排卵
enesis
(卵泡生長)E
hypothalamus
GnRH
anterior pituitary
FSH
LH
midcycle peak of LH (triggers ovulation)
Blood levels of FSH
LH levels
ovulation
corpus luteum
progesterone, estrogen
Blood levels of estrogen
progesterone levels
E &黃體素P

避孕藥中荷爾蒙的角色

Role of Estrogen

Enhances cycle control through stabilizing the endometrium

Inhibits follicular development



Role of Progestagen

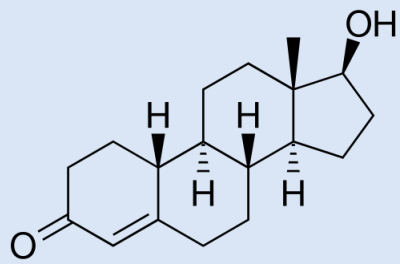
Change endometrium making implantation less likely

Inhibits LH surge: prevents ovulation

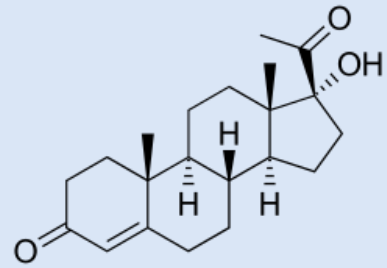
Thickens cervical mucus impedes sperm

合成黃體素來源

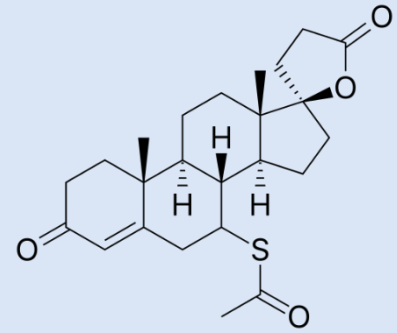
19-Nortestosterone

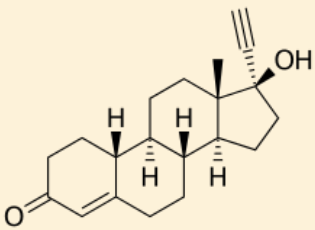


17α-Hydroxyprogesterone

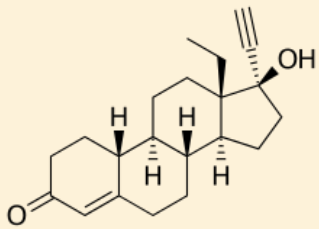


17α-Spironolactone

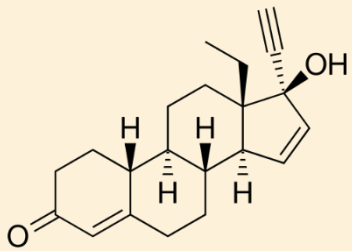




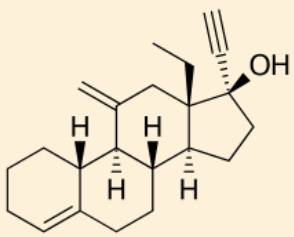
Norethisterone (1st)



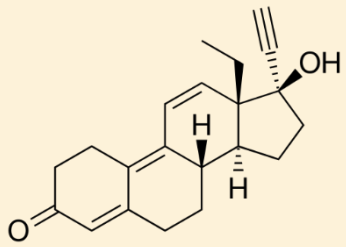
Levonorgestrel (2nd)



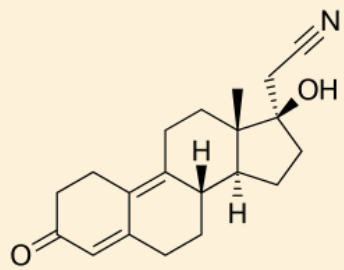
Gestodene (3rd)



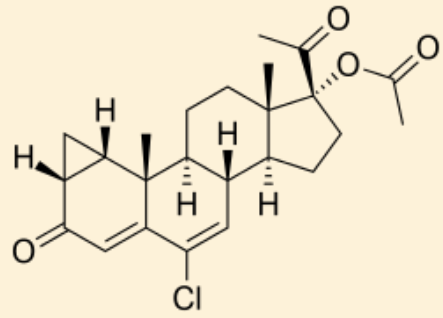
Desogestrel (3rd)



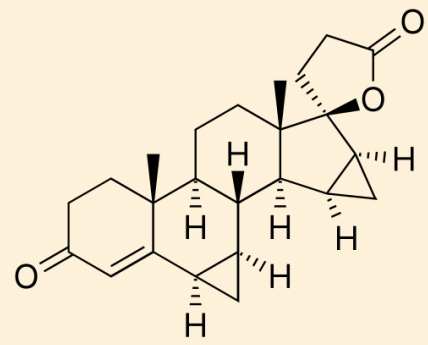
Gestrinone (3rd)



Dienogest (4th)



Cyproterone acetate (4th)



Drospirenone (4th)

避孕藥發展

Yuzpe method

Danazol
Mifepristone

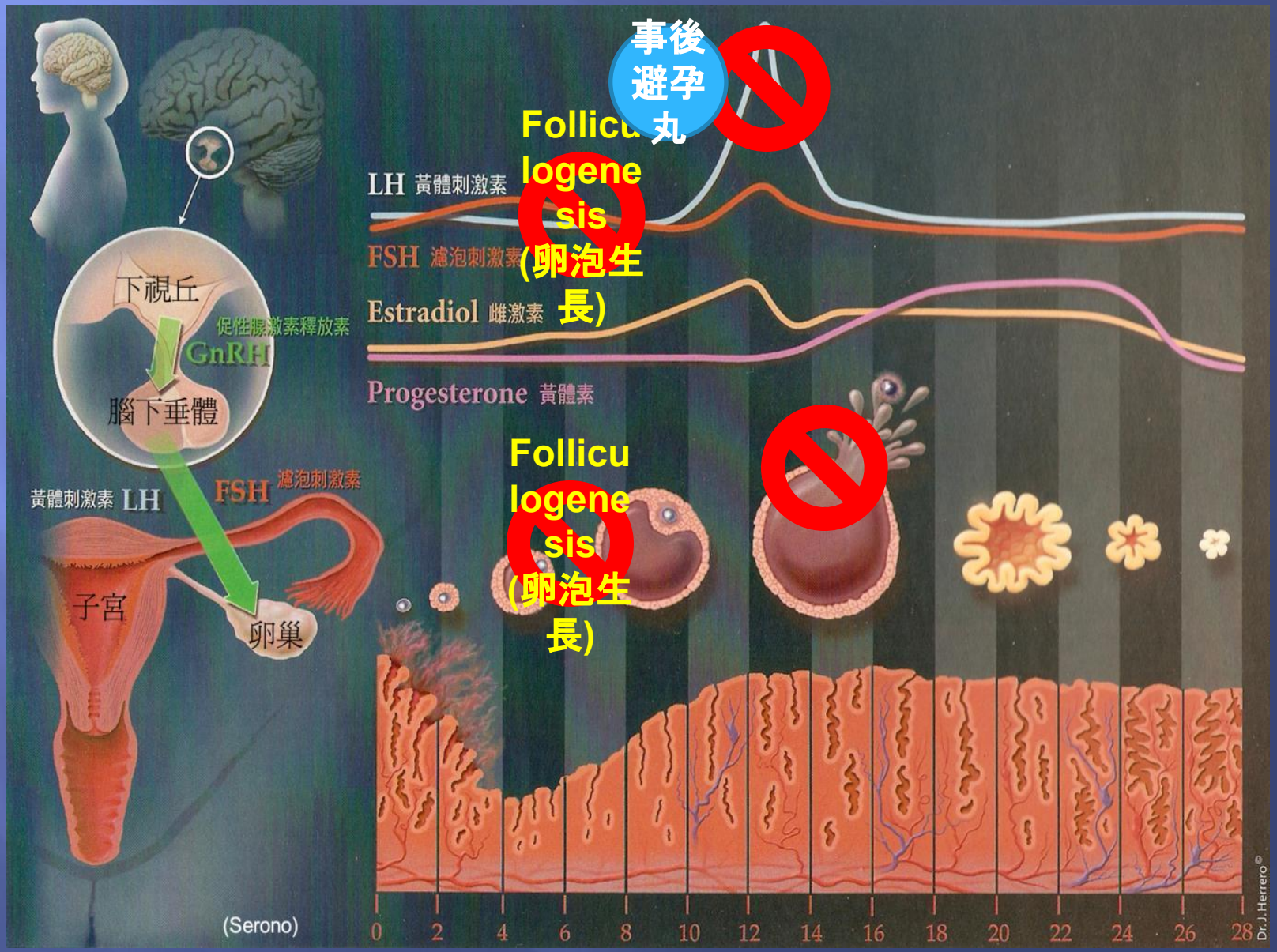
Levonorgestrel + EE
(Preven)

Levonorgestrel
(Plan B, 愉婷錠)

Ulipristal acetate
(Ella One)

常規避孕藥
事後避孕藥

荷爾蒙避孕法:抑制排卵/卵泡生長



作用機轉


HORMONE LEVEL
LH
FSH
ESTROGEN
PROGESTERONE
STOP
FOLLICULAR DEVELOPMENT
事後避孕藥
使濾泡暫時停止發育
延後排卵
1. 12.13.14.15. 16.17.18.19.20.21.2223.2425.26.2728.
FOLLICULAR PHASE
OVULATORY PHASE
LUTEAL PHASE

Yuzpe Method

- **唯一含雌激素的事後避孕藥**
- PREVEN™ Emergency Contraceptive Kit
- 0.25mg levonorgestrel + 0.05mg ethinyl estradiol
- 事後72小時內服用2顆，12小時候再服用2顆
- 頭痛、噁心、嘔吐、乳房脹痛等副作用發生率較高
- 成功率75%
- 考量有效性及副作用，現今多以單方黃體素為主流

Ulipristal Acetate

- **最新的事後避孕藥**
- Ulipristal acetate 30 mg
- 作用機轉與mifepristone同為SPRM
- 事後120小時內服用一顆
- 常見副作用：噁心、腹痛、嗜睡、頭痛、暈眩
- 成功率：依服藥時間而不同 (24小時內>95%)

Credit: Courtesy of Watson Pharmaceuticals

Lancet 2010; 375: 555–62

Levonorgestrel

- **臨床經驗最多的事後避孕藥**
- 單顆藥錠含Levonorgestrel 1.5mg[1]
- 事後72小時內服用1顆[1]
- 常見副作用：噁心、腹痛、嗜睡、頭痛
- 成功率：依服藥時間而不同(24小時內>95%)
- 無與Levonorgestrel 相關的致死案例
- 不會增加子宮外孕的風險[3]

1. Safe Plan PI
2. Lancet 2010; 375: 555–62
3. Obstet Gynecol 115(6):1263-6. Jun, 2010

事後避孕藥禁忌症

- Yuzpe method：[1]
  - 與一般常規避孕藥禁忌症相同
    心血管疾病患者
    血栓類病史
    嚴重的**肥胖**或高膽固醇血症
    35歲以上
    抽菸
- Levonorgestrel與Ulipristal acetate：[2,3]
  - 已知對LNG / UPA 或附型劑過敏者

1. Preven PI
2. Plan B PI
3. Ella One PI

影響事後避孕藥效果的因素

- **事發當天排卵**

  黃體素事後避孕藥的作用機制是阻止濾泡排卵，若無保護性生活當天已排卵，則無法有效阻止受孕。

- **太晚服藥**

  無論是Yuzpe、LNG或UPA，均須在事後72小時內，最久120小時內服藥，若超過120小時，建議使用IUD。

- **BMI值≧30**

  研究顯示BMI≧30的婦女使用事後避孕藥的懷孕機率是BMI<25的3.6倍。

- **同一月經週期內再次發生無保護性生活**

  研究顯示用藥後，在同一月經週期內再次發生無保護性行為，比有避孕的婦女多3.3倍的意外懷孕機率。

*Contraception. 2011;**84**:363-7.*

避孕藥中黃體素種類

Generation	Progestagen	Product
1st	Norethisterone	Zoesyn 洛依欣
2nd	Levonorgestrel	Microgynon 欣無妊 Winstop T/28 溫不妊(三相型)
3rd	Desogestrel	Mercilon 美適儂
	Gestodene	Gynera 祈麗安/Meliane玫麗安
4st	Cyproterone acetate	Diane-35 黛麗安
	Drospirenone	**Gveza 愛己/愛薇** Yasmin悅己 / Yaz悅姿

避孕藥種類

現今使用的都是低劑量雌激素0.02-0.035mg，主要差異在黃體素的不同。

第一代
黃體素

1960

第二代黃體素

1980s

第三代黃體素

容易長痘痘及水腫

1990s

治療為主，避孕為輔，血栓風險較高。

可治療痘痘，但容易水腫

第四代黃體素
DRSP

2000s

較不易長痘及水腫

新一代黃體素
DRSP

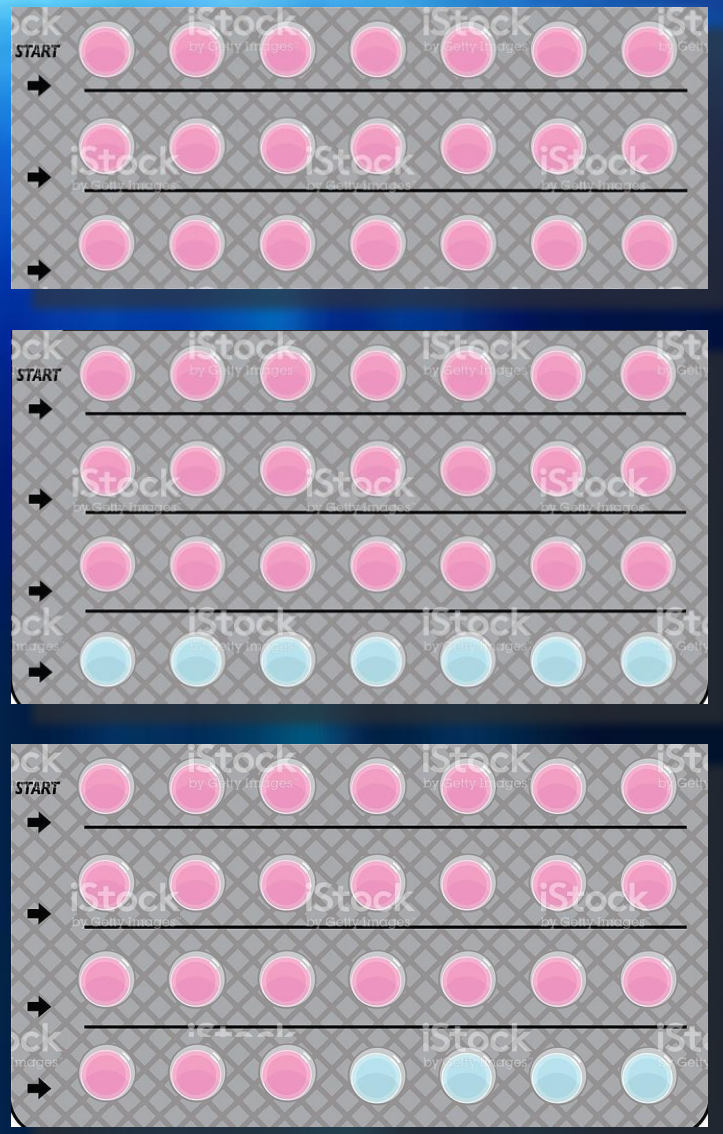
2017

加強抗痘、消水腫，效果提升。

服藥方式

- ✔ 月經來第五天開始吃
- ✔ 21顆裝-連續吃21天，停藥7天
- ✔ 28顆裝-連續吃不停藥
- ✔ 停藥期間或服用空白錠期間

  會有消退性出血



有效錠

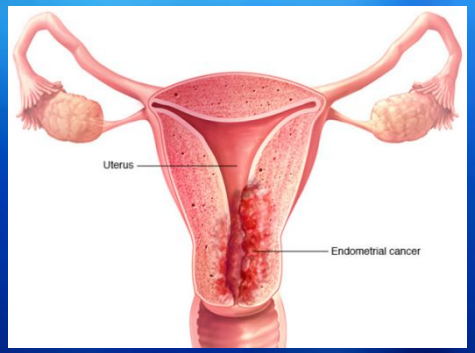
空白錠

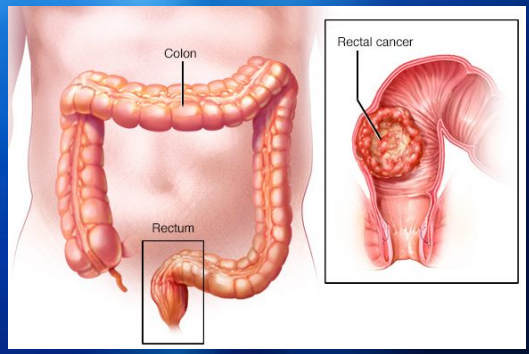
臨床應用

- **Primary Use**
  - Prevent pregnancy
- **Secondary Uses**
  - Heavy or irregular menstruation，月經紊亂，經血多
  - Endometriosis，子宮内膜異位症
  - Polycystic ovary syndrome，多嚢性卵巣
  - Dysfunctional uterine bleeding，功能性出血，亂經

常規避孕藥的「附」作用

- **Decrease 12% in overall cancer risk**





  - 乳癌及子宮頸癌雖有增加風險，但會在停用OC後5年內消失。
  - 子宮內膜癌、卵巢癌及大腸直腸癌的降低風險好處會至少持續30年。

- **Improve acne**
  - Cyproterone, Drospirenone

- **Reduce edema**
  - Drospirenone

Ther Adv Drug Saf 2014, Vol. 5(5) 201–213

荷爾蒙活性與相關副作用

Estrogenic	Progestogenic	Androgenic
		 

口服避孕藥中黃體素比較

市售避孕藥雌激素均為低劑量0.02-0.035mg

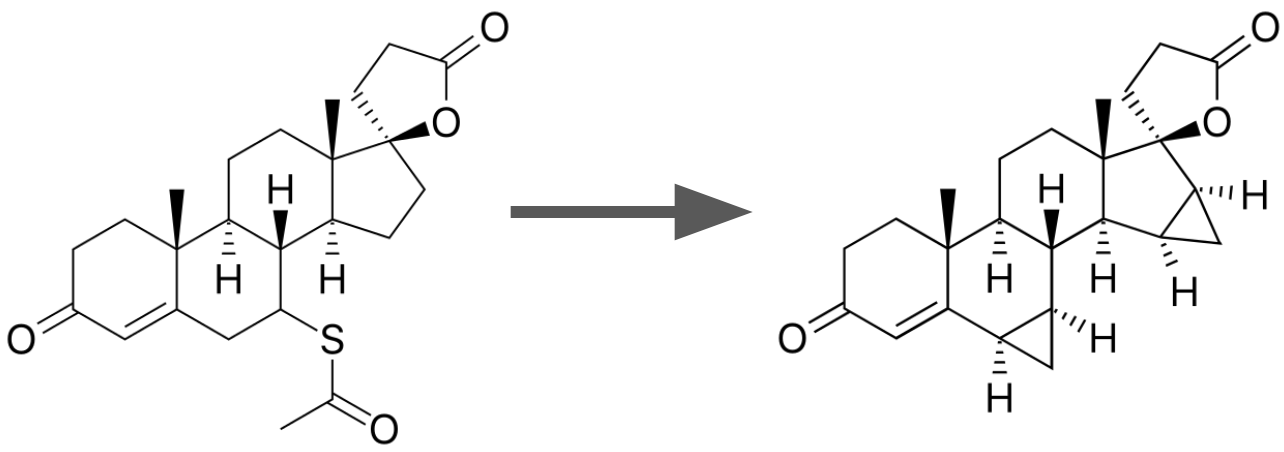
Generation 黃體素新舊	Type of Progestogen 黃體素種類	Androgenic 雄性化活性 （出油、痘痘、掉髮）	Anti-androgenic 抗雄性化活性 （皮膚細緻）	Anti-mineralocorticoid 抗礦物皮質類固醇 （消除水腫）
New	Drospirenone Plus 3mg	–	++	++
4th	Drospirenone 3mg	–	+	+
未分類	Cyproterone 2mg	–	+++	–
3rd	Gestodene 0.075mg	+	–	(+)
3rd	Desogestrel 0.15mg	+	–	–
2nd	Levonorgestrel 0.15-0.25mg	++	–	–
1st	Norethisterone 1mg	+	–	–

+ 作用明顯 ； (+) 作用輕微 ； – 沒有作用

Contraception 1996;54:243-51. Climacteric 2003;6 Suppl 3:49-54. Ann N Y Acad Sci 1995;761:311-35.
Contraception 2000;62:29-38. Gynecol Endocrinol 1999; 13:316-26.

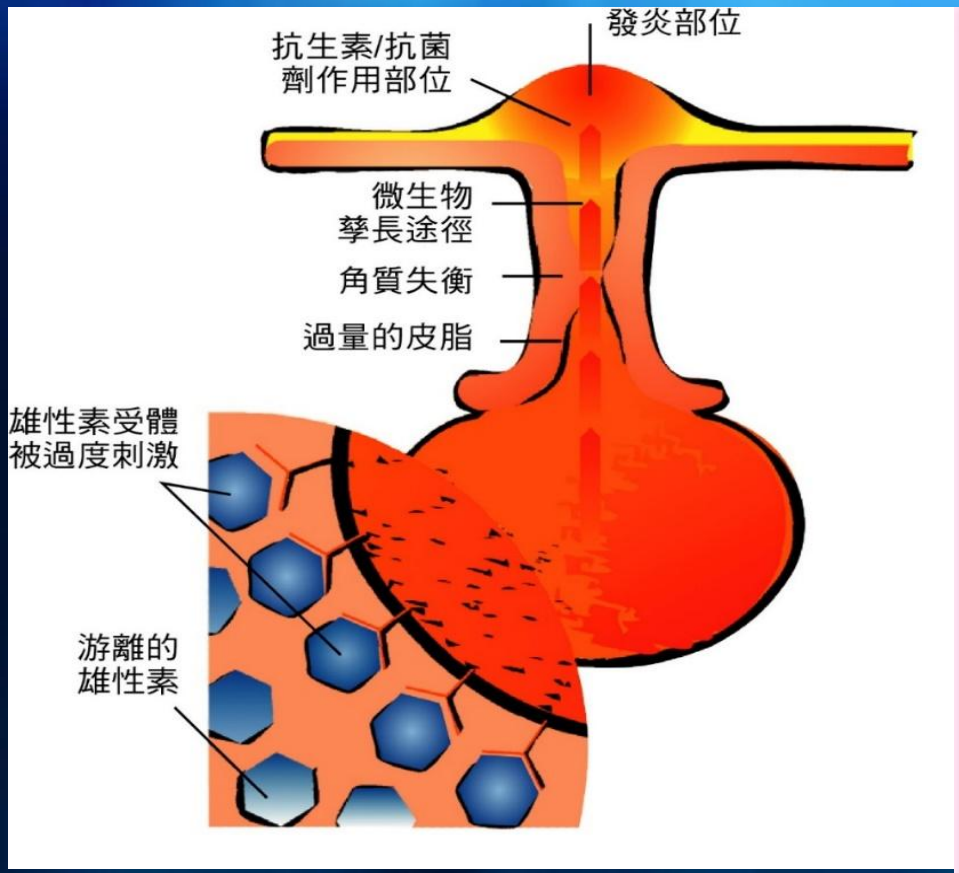
第四代天然黃體素Drospirenone

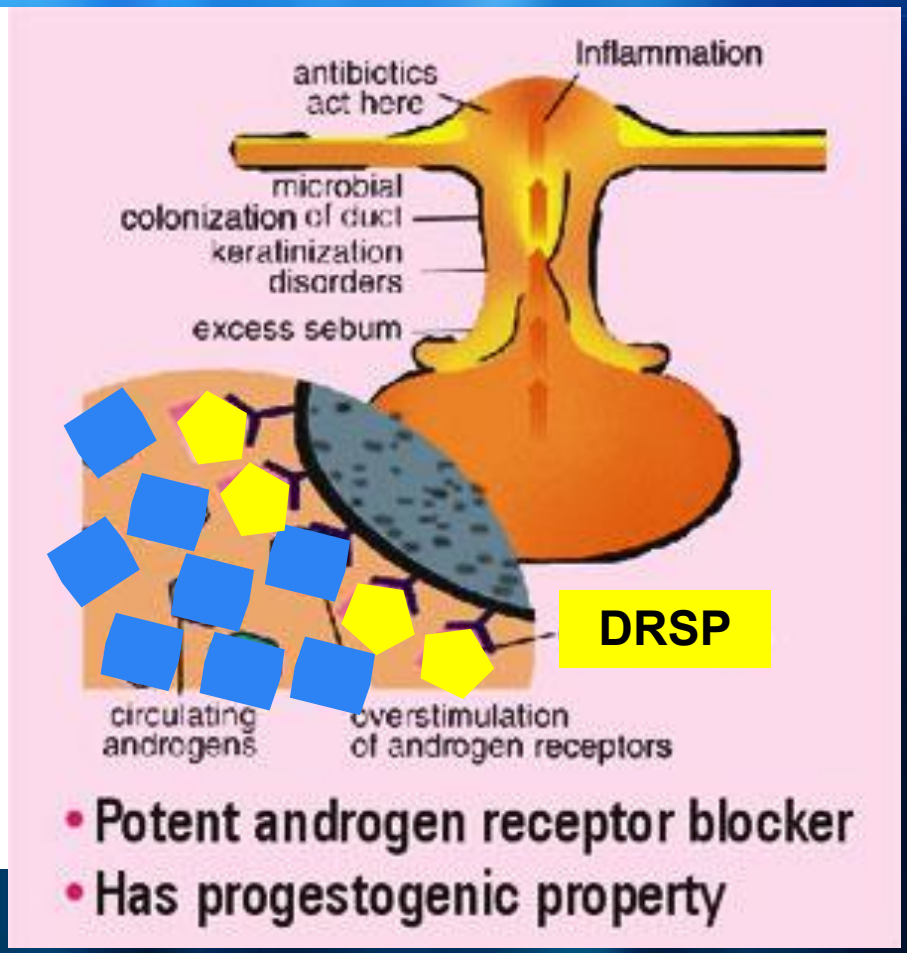
- 與人體內天然黃體素藥理作用最相似的黃體素。
- 17α-spironolactone衍生物，具有抗雄性化(anti-androgenic)及抗礦物皮質類固醇(anti-mineralocorticoid)的特性。



17α-spironolactone　　Drospirenone

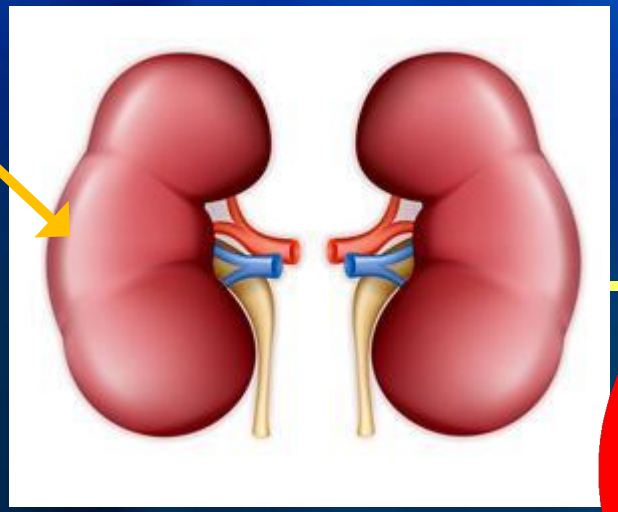
DRSP改善痘痘肌


發炎部位
抗生素/抗菌
劑作用部位
微生物
孳長途徑
角質失衡
過量的皮脂
雄性素受體
被過度刺激
游離的
雄性素


Inflammation
antibictics
act here
microbial
colonization of duct
keratinization
disorders
excess sebum
DRSP
circulating
androgens
overstimulation
of androgen receptors
• Potent androgen receptor blocker
• Has progestogenic property

DRSP抑制水分蓄積

DRS
P



Angiotensinogen血壓素
原

Adrenal gland腎上腺

Aldosterone醛固酮

Aldosterone
eceptor

水　腫

體重　加

血壓升

乳脹及觸痛

其他水分蓄積相關症狀

口服避孕藥禁忌症

- 現有或曾有靜脈或動脈血栓/血栓性栓塞症病史或腦血管意外
- 現有或曾有血栓症的前兆
- 具靜脈或動脈血栓症的高風險
- 曾有局部神經症狀之偏頭痛
- 併有血管問題的糖尿病
- 現有或曾患嚴重的肝臟疾病且肝功能指數仍未回復正常時
- 嚴重腎功能不足或急性腎衰竭
- 現有或曾有肝臟腫瘤(良性或惡性)
- 患有或疑似有受性類固醇影響(例：在生殖器官或乳房處)的惡性腫瘤
- 不明原因的陰道出血
- 已知懷孕或疑似懷孕

那些人血栓風險較高？

- 體重過重BMI > 30 kg/m^2
- 年齡超過35 歲，抽菸
- 曾有近親在50 歲以下發生過血栓
- 最近幾週剛生產完
- 最近進行手術
- 下肢長期靜止不動
- 長途旅程(例如長程飛機)
- 患有心血疾病

血栓風險

Table 3. Risk of developing venous thromboembolism in a year according to the European Medicines Agency [European Medicines Agency, 2013].

Women **not using** a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a combined hormonal contraceptive (CHC) containing **levonorgestrel, norethisterone or norgestimate**	About 5–7 out of 10,000 women
Women using a CHC containing **etonogestrel or norelgestromin**	About 6–12 out of 10,000 women
Women using a CHC containing **drospirenone, gestodene or desogestrel**	About 9–12 out of 10,000 women
Women using a CHC containing **chlormadinone, dienogest or nomegestrol**	Not yet known

[1]Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products.

1st, 2nd

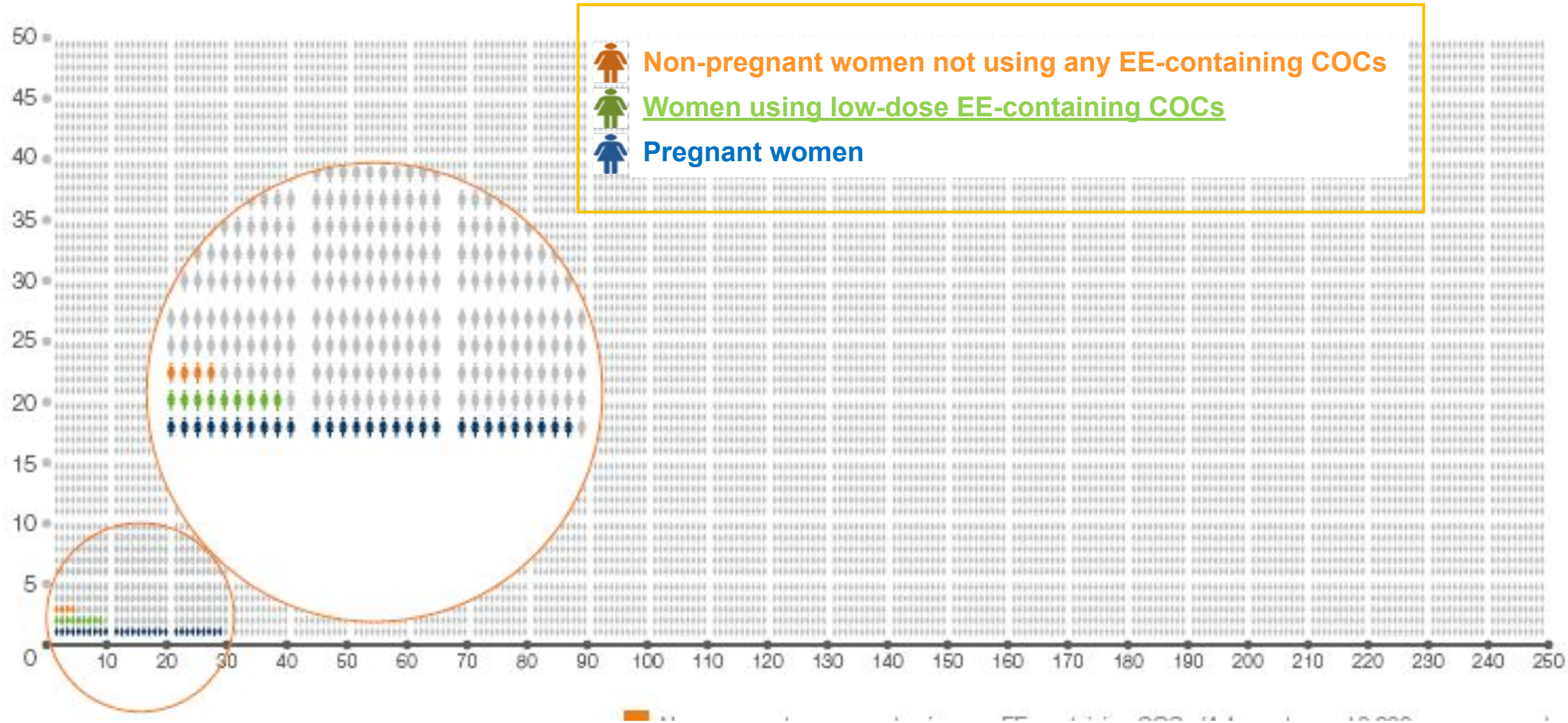
VS

3rd, 4th

↑0.04%

Pregnant women : About 29 out of 10,000

VTE incidence*



*Per 10,000 women-years
EE: Ethinylestradiol
Dinger et al. Contraception 2007;75(5):344–54

Journal of Thrombosis and Haemostasis, **10**: 992–997 DOI: 10.1111/j.1538-7836.2012.04720.x

ORIGINAL ARTICLE

Sex hormone-binding globulin as a marker for the thrombotic risk of hormonal contraceptives

M. RAPS,* F. HELMERHORST,*† K. FLEISCHER,‡ S. THOMASSEN,§ F. ROSENDAAL,* J. ROSING,§

- SHBG及APC resistance作為OC血栓風險評估指標。

SHBG

- 雌激素高，血栓風險高。
- 雌激素會促進SHBG合成，黃體素會降低SHBG濃度。
- 避孕藥=雌激素+黃體素

因此以SHBG來評估避孕藥血栓風險。

APC resistance

- 活化蛋白C可抑制血栓形成。
- 活化蛋白C阻抗越高，蛋白C越不容易活化，越容易產生凝血。

因此以APC resistance來評估避孕藥血栓風險。

Journal of Thrombosis and Haemostasis, **10**: 992–997 DOI: 10.1111/j.1538-7836.2012.04720.x

含Cyproterone成分之OC，SHBG濃度最高，蛋白C活化的阻抗最大。

ORIGINAL ARTICLE

Sex hormone-binding globulin as a marker for the thrombotic risk of hormonal contraceptives

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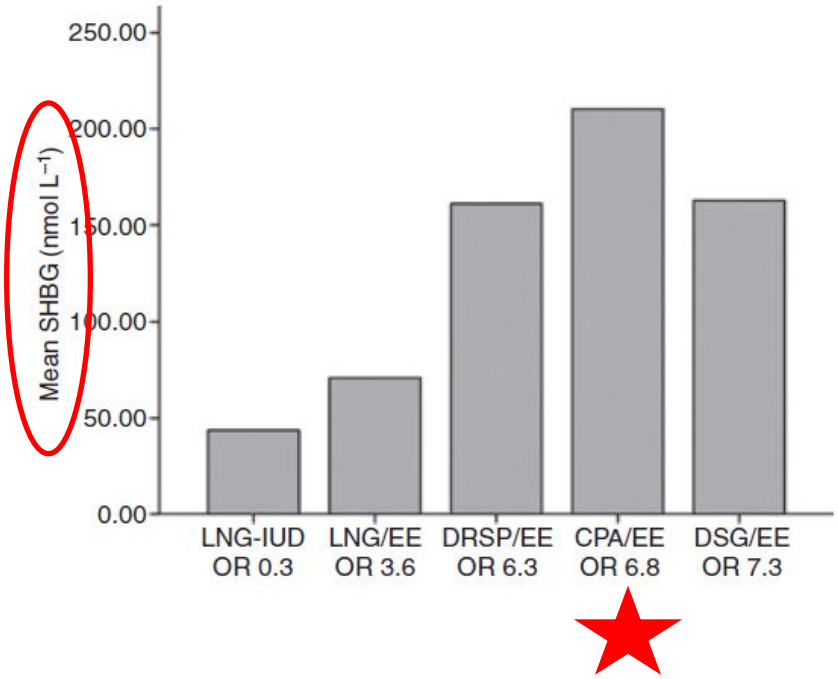

		APC resistance (ratio)		
		Compared with non-use		
Contraceptive	*N*	Mean	MD	95% CI
None	13	1.54	Ref.	
LNG-IUD	60	0.85	− 0.69	− 1.03 to − 0.36
Cu-IUD	17	1.03	− 0.51	−0.93 to − 0.09
LNG/EE	72	2.66	1.12	0.69 to 1.54
DSG/EE	18	3.94	2.40	1.93 to 2.86
DRSP/EE	47	3.53	1.98	1.49 to 2.48
CPA/EE	22	4.00	2.46	2.07 to 2.84
ENG/EE (ring)	6	3.02	1.47	0.94 to 2.02
NGM/EE (patch)	7	3.12	1.57	0.87 to 2.28

activated protein C (APC) resistance levels

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REVIEW ARTICLE

Gynecology

WILEY International Journal of Gynecology Obstetrics FIGO

A systematic review and meta-analysis of venous thrombosis risk among users of combined oral contraception

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Meta分析顯示，與LNG相比，含Cyproterone成分之避孕藥，VET風險最高。

TABLE 2 Pooled estimates (95% confidence intervals) of unadjusted risk ratios for venous thromboembolism among users of combined oral contraceptives by progestogen type compared with levonorgestrel in published meta-analyses.[a]

Meta-analysis	Cyproterone	Desogestrel	Dienogest	Drospirenone	Gestodene	Norgestimate
Present analysis	2.04 (1.55–2.49)	1.83 (1.55–2.13)	1.46 (0.57–5.41)	1.58 (1.12–2.14)	1.67 (1.32–2.10)	1.14 (0.94–1.32)
Bateson, 2016[49]						
Prospective cohort studies	–	–	–	0.94 (0.75–1.18)	–	–
Retrospective cohort studies	–	–	–	1.82 (1.60–2.06)	–	–
Stegeman, 2013[9]	1.6 (1.1–2.2)	1.8 (1.4–2.2)	–	1.6 (1.2–2.1)	1.5 (1.2–2.0)	1.0 (0.7–1.3)
Martinez, 2012[7]			–			
Risk ratio	–	1.93 (1.31–2.85)	–	1.67 (1.10–2.55)	1.33 (1.08–1.63)	–
Odds ratio	1.65 (1.30–2.11)	1.62 (1.33–1.97)	–	–	1.49 (1.13–1.96)	1.11 (0.84–1.46)
Kemmeren, 2001[6]	–	1.7 (1.2–2.6)	–	–	1.5 (1.2–2.4)	–

[a]Estimates are given as risk ratios.

使用OC在VTE 風險的時間模式

- 在使用的第一個月風險最高，然後會下降到較穩定的程度[1,2]
- 在COC間的轉換(不中斷)，轉換一開始並不會有特別高的現象 [2]
- 但是,當女性停了4周以上再重新開始使用OC或轉換到其他品牌OC，VTE的風險則會增加[2]

[1]Dinger et al. Contraception 2007;75(5):344–54;
[2]Dinger et al. Pharmacoepidemiol Drug Saf 2010;19(S1):S214–5

DRSP

Background of the Invention

Drospirenone has the chemical formula (2'S, 6R, 7 R, 8R, 9S,10ft, 13S, 14S, 15S, 16S)-1 ,3', 4', 6, 7, 8, 9, 10, 11 , 12, 13, 14, 15, 16, 20, 21-hexadecahydro-10, 13-dimethylspiro[17H-dicyclopropa[6,7: 15, 16]cyclopenta[α]phenanthrene-17,2'(5'H)- furan]-3,5'(2H)-dione. Drospirenone is a synthetic progestational compound having a molecular weight of 366.49 and a molecular formula of $C_{24}H_{30}O_3$. Ethinyl estradiol has the chemical formula (17α)-19-norpregna-1 , 3,5(10)-trien-20-yne-3,17-diol. Ethinyl estradiol is a synthetic estrogenic compound having a molecular weight of 296.4 and a molecular formula of $C_{20}H_{24}O_2$.

YASMIN® 28 Tablets is an oral contraceptive regimen consisting of 21 active film coated tablets each containing 3.0 mg of drospirenone and 0.030 mg of ethinyl estradiol and 7 inert film coated tablets. The inactive ingredients are lactose monohydrate NF, corn starch NF, modified starch NF, povidone 25000 USP, magnesium stearate NF, hydroxypropyl methyl cellulose USP, macrogol 6000 NF, talc USP, titanium dioxide USP, ferric oxide pigment, yellow NF. The inert film coated tablets contain lactose monohydrate NF, corn starch NF, povidone 25000 USP, magnesium stearate NF, hydroxypropylmethyl cellulose USP, talc USP and titanium dioxide USP.

U.S. Patent No. 5,976,570 describes a process for making a pharmaceutical composition comprising the steps of: (i) preparing an aqueous medium comprising one or more pharmaceutically acceptable surfactants, wherein the quantity of said surfactant or surfactants is sufficient to support a medicinal agent in solution; and (ii) granulating said one or more low dosage medicinal agents in said aqueous medium to form a qranulation.

U.S. Patent No. 6,787,531 describes a pharmaceutical composition comprising from about 2 mg to about 4 mg of micronized drospirenone particles, about 0.01 mg to about 0.05 mg of 17α-ethinyl estradiol, and one or more pharmaceutically acceptable carriers. Micronized is defined as a surface area of greater than 10,000 cm^2/g, and the following particle size distribution as determined under a

Summary of the Invention

The invention provides a rapidly-dissolving oral dosage pharmaceutical composition for inhibiting ovulation in a mammal, said composition comprising drospirenone or a pharmaceutically acceptable salt or ester thereof, optionally ethinyl estradiol or a pharmaceutically acceptable salt, ester or ether thereof, a surfactant and at least one pharmaceutically acceptable excipient, wherein the drospirenone has a surface area of less than 10,000 cm^2/g.

According to another aspect, the invention provides a method of inhibiting ovulation in a mammal, in particular, a human female, comprising administering to said mammal, a rapidly-dissolving oral dosage pharmaceutical composition comprising drospirenone or a pharmaceutically acceptable salt or ester thereof, optionally ethinyl estradiol or a pharmaceutically acceptable salt, ester or ether thereof, a surfactant and at least one pharmaceutically acceptable excipient, wherein the drospirenone has a surface area of less than 10,000 cm^2/g.

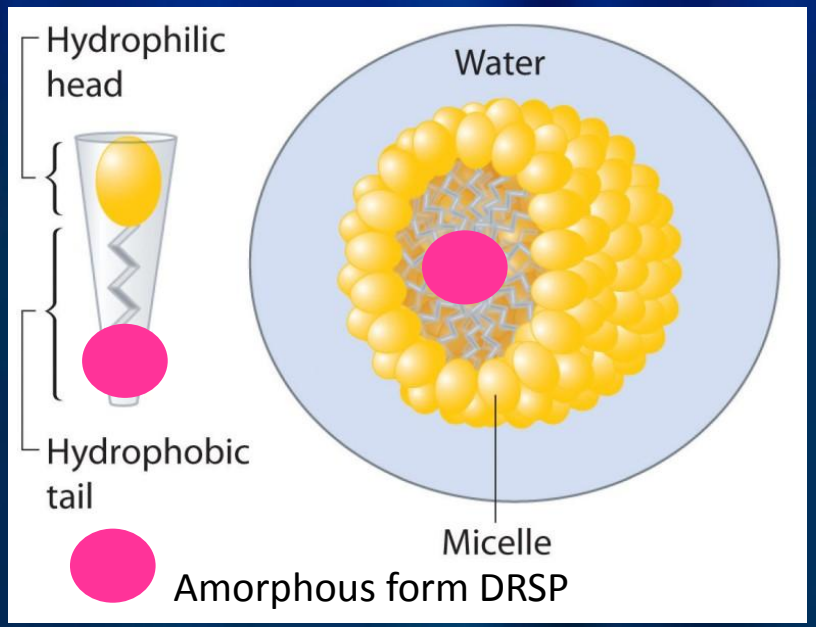
The pharmaceutical compositions of the invention do not require micronization of the drospirenone in order to achieve rapid dissolution of the drospirenone from the composition.

Gveza

新一代DRSP

特殊載體 + Amorphous form DRSP

- 不需微粒化即可溶解於水
- 非微粒化，降低肝臟首度效應的影響
- 提高生體可用率，增加抗雄性化、抗礦物皮質類固醇效果
- 延長半衰期，血中濃度更穩定，提高耐受性



示意圖

DRSP比較

產品	Gveza 愛己 plus	Yasmin悅己	Yaz 悅姿
製造廠	CHEMO	Bayer	Bayer
產地	西班牙	德國	德國
成分	DRSP 3mg + EE 0.03mg	DRSP 3mg + EE 0.03mg	DRSP 3mg + EE 0.02mg
包裝(tab/box)	21	21	28
使用技術	**非結晶型DRSP+特殊載體**	結晶型DRSP+微粒化處理	結晶型DRSP+微粒化處理+籠晶包覆
肝臟首度效應的影響	**非微粒化，活性不易受影響**	微粒化，活性較易被破壞	籠晶包覆，保護藥物活性
臨床特性	1.生體可用率提高，抗痘、抗水腫效果較好。 2.半衰期延長，血中濃度較穩定。 3.噁心嘔吐機率降低。(臨床醫師經驗) 4.頭痛機率極低(臨床醫師經驗)。	1.避孕同時抗痘、抗水腫。	1.無須停藥。 2.週期控制不易，較易點狀出血。 3.生體可用率高，抗痘、抗水腫效果好。 4. EE濃度極低，減少EE副作用，但須注意骨鬆問題。

謝謝收看！

卵巢癌減積手術後熱化療

陳盈希

摘要

卵巢癌是婦科惡性腫瘤中的第一死因，由於大部份的卵巢癌在早期沒有明顯的症狀，或是症狀沒有特異性，所以大部份被發現是卵巢癌的時候，通常都已經擴散至腹腔，成為晚期的癌症，約75%的患者已達到第三或第四期而且復發率高。治療方案多為最佳的減積手術(Optimal debulking)及化學治療，目標是延長這些患者的生存率。在過去的幾年中，全球不同腫瘤中心採用的最引人注目的方法之一是腹腔溫熱化學治療(Hyperthermic intraperitoneal chemotherapy，HIPEC)。腹腔溫熱化學治療」是在對腫瘤進行最佳的減積手術之後，將化療藥物加溫至40～43℃在腹腔內循環灌洗，以高溫的物理傷害及化療藥劑的毒性殺死腹腔內、臟器表面、腹膜表面肉眼看不見但可能殘存或游離的腫瘤細胞。這種熱療與化療協同作用的原理是利用腫瘤細胞的低耐熱特性，高溫可破壞腫瘤細胞膜及增加其通透性，再讓化療藥劑殺死腫瘤細胞。

HIPEC治療適用於胃癌、結直腸癌和原發性腹膜癌等不同類型的癌症。對於卵巢癌的治療，這項技術長期以來一直存在爭議，但在 van Driel 等人的隨機試驗結果之後，HIPEC 被納入 NCCN 指南。本次報告將討論在2020年針對HIPEC的系統性回顧及統合性分析，並針對實際使用HIPEC治療的臨床案例進行討論。

參考資料:
1. Hyperthermic intraperitoneal chemotherapy (HIPEC) for ovarian cancer recurrence: systematic review and meta-analysis. Stefano Cianci, Gaetano Riemma, Carlo Ronsini, Pasquale De Franciscis, Marco Torella, Antonio Schiattarella, Marco La Verde,Nicola Colacurci. Gland Surg. 2020 Aug; 9(4): 1140–1148. [PMCID: PMC7475376]

重現**Okadayashi radical hysterectomy**步驟演示

陳姵辰

Title: Radical hysterectomy in cervical cancer performed with Okabayashi method: a video demo

Abstract

- Background: Present a video with Okabayashi method in the early stage of cervical cancer.
- Patient and Methods: A 68-year-old female had chief complaint of postmenopausal vaginal bleeding for over one year. Pelvic examination showed easy contact bleeding of the cervix and pap smear showed a cervical squamous cell carcinoma. The tumor marker showed CEA 1.3 ng/mL; SCC 3.3 ng/mL; CA-125 15.4 U/mL; CA 19-9 8.6 U/mL. MRI revealed a uterine cervical lesion with a diffusion restricted pattern, favoring cT1b1N0M0.
- Results: Okabayashi method was performed. The patient was under ETGA and put in supine position. The abdomen and vagina were draped as usual. First, the high midline vertical incision over lower abdomen was made. Bilateral round ligament was ligated and cut. Identified the paravesical space and isolated the uterine artery, ligated and cut. Then isolated the ureter. Divided the cardinal ligament and separated the urinary bladder. Created the entrance of the ureter tunnel, separated the anterior and posterior leaf of vesicouterine ligament. Cut the rectovaginal ligament. Lastly, extirpated the uterus. Bilateral salpingo-oophorectomy and pelvic lymph node dissection were done.
- Conclusions: The operative time was 264 minutes, blood loss was 1300 mL and leukocyte poor RBC was transfused. No severe complication was noted during the operation. Pathologic report showed squamous cell carcinoma of cervix, grade 2, pT1b2, FIGO stage IB2 with tumor size 3.5cm without regional lymph node invasion.