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Identifying the best diagnostic test for ovarian cancer

Change from RMI –
Why? And what to?

Presented by : Dr Vivian Do
(on behalf of Professor Sudha
Sundar)



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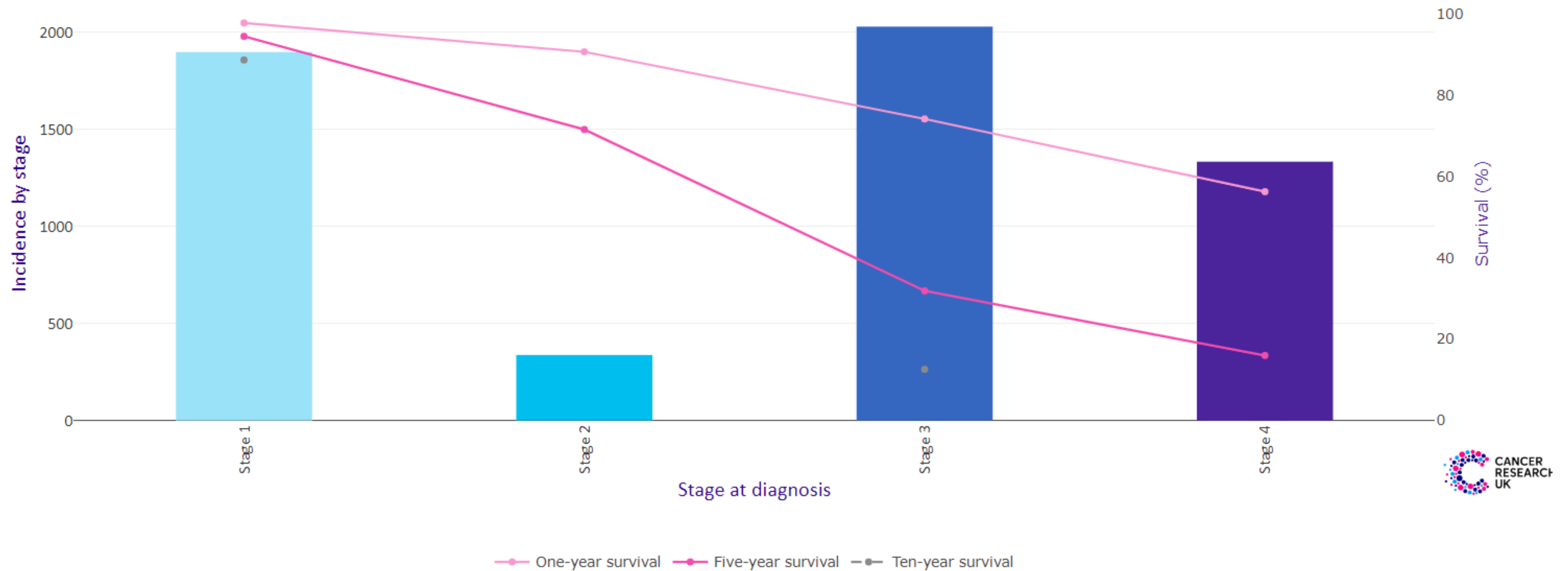
Financial Disclosure for: Professor Sudha Sundar

I have the following financial relationships with ACCME defined ineligible companies to report over the past 24 months:

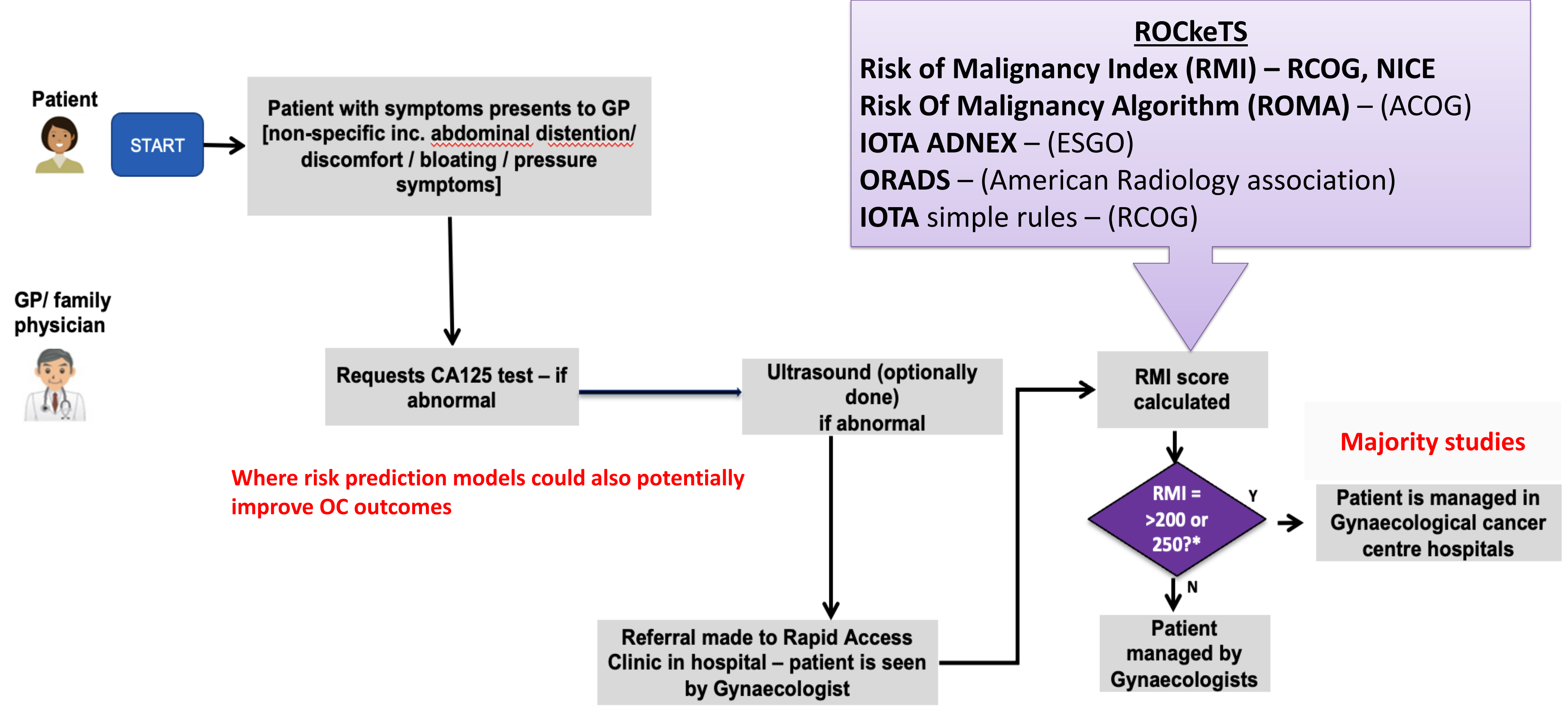
Honoraria from Astra Zeneca, GSK, MSD, Immunogen.

Research grant with AoA diagnostic to use samples and data from ROCkeTS for work not included in this presentation

Incidence (2018) and Survival of Cancer Cases by Known Stage at Diagnosis, Ovarian cancer, England



UK SoC Diagnostic Pathway for Ovarian Cancer



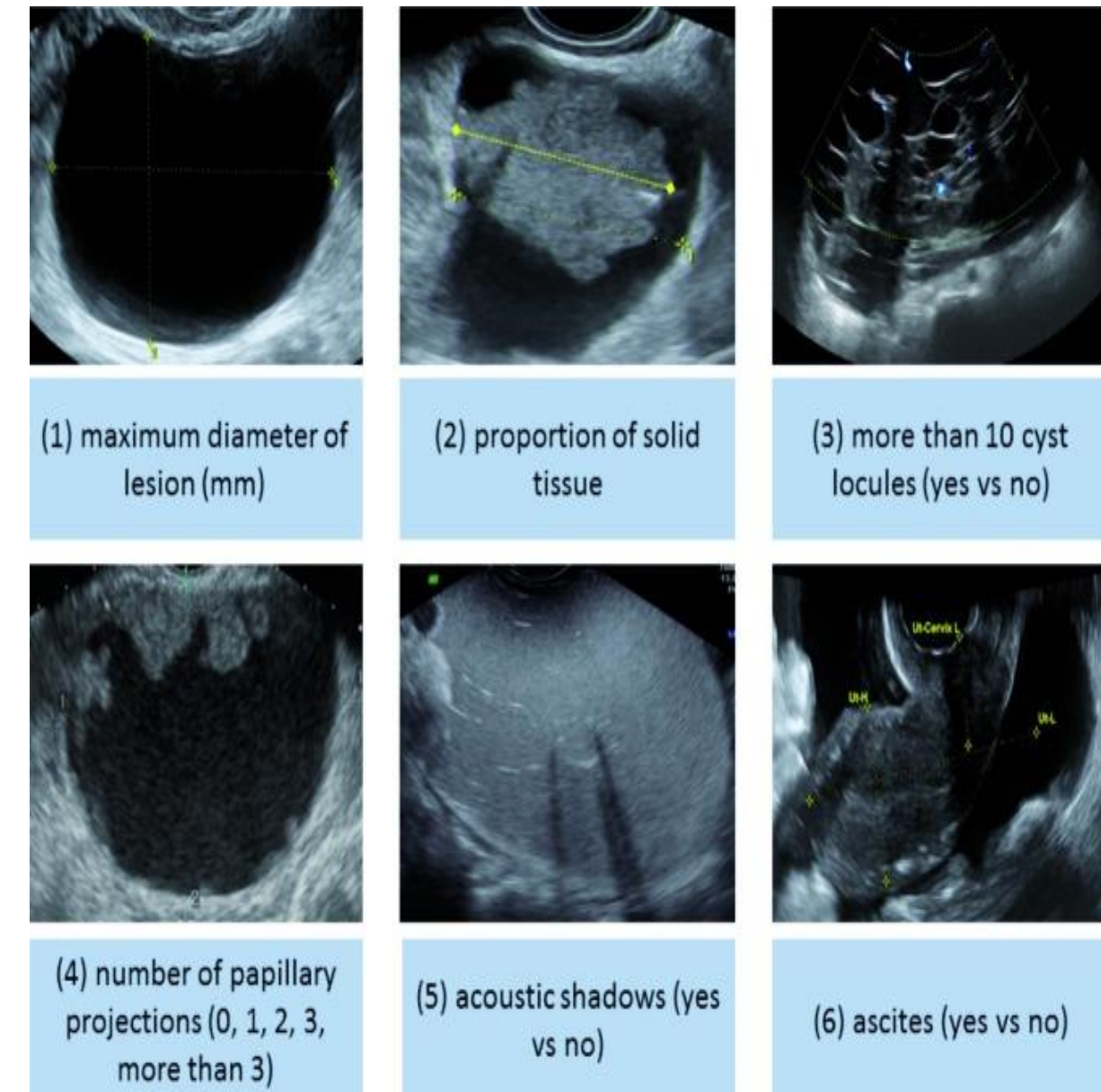
International Ovarian Tumour Analysis Group (IOTA)

Terms, definitions and measurements to describe the sonographic features of adnexal tumors: a consensus opinion from the International Ovarian Tumor Analysis (IOTA) group

D. TIMMERMAN, L. VALENTIN*, T. H. BOURNE†, W. P. COLLINS‡, H. VERRELST§ and I. VERGOTE

Department of Obstetrics and Gynaecology, University Hospitals KU Leuven, Leuven, Belgium, *Department of Obstetrics and Gynaecology, University Hospital, Malmö, Sweden, †Department of Obstetrics and Gynaecology, St. George's Hospital Medical School, University of London, London, UK, ‡King's College, University of London, UK and §Department of Electrical Engineering, ESAT-SISTA, Katholieke Universiteit Leuven, Belgium

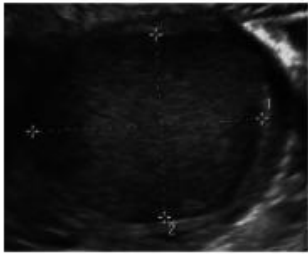
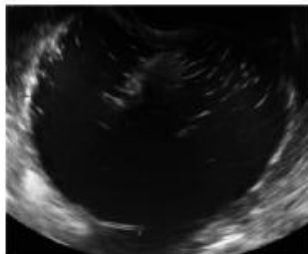
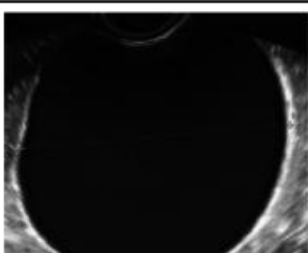
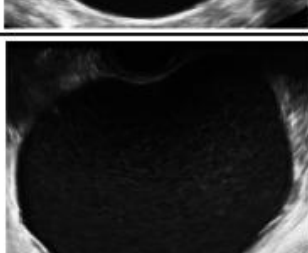
- IOTA Simple Rules ('M' rules and 'B' rules)
- IOTA ADNEX
 - Multiclass prediction model
 - 6 ultrasound descriptors
 - 3 clinical descriptors



Van Calster B et al Practical guidance for applying the ADNEX model from the IOTA group to discriminate between different subtypes of adnexal tumors. Facts Views Vis Obgyn. 2015;7(1):32-41. PMID: 25897370; PMCID: PMC4402441.

IOTA ADNEX 2-step strategy

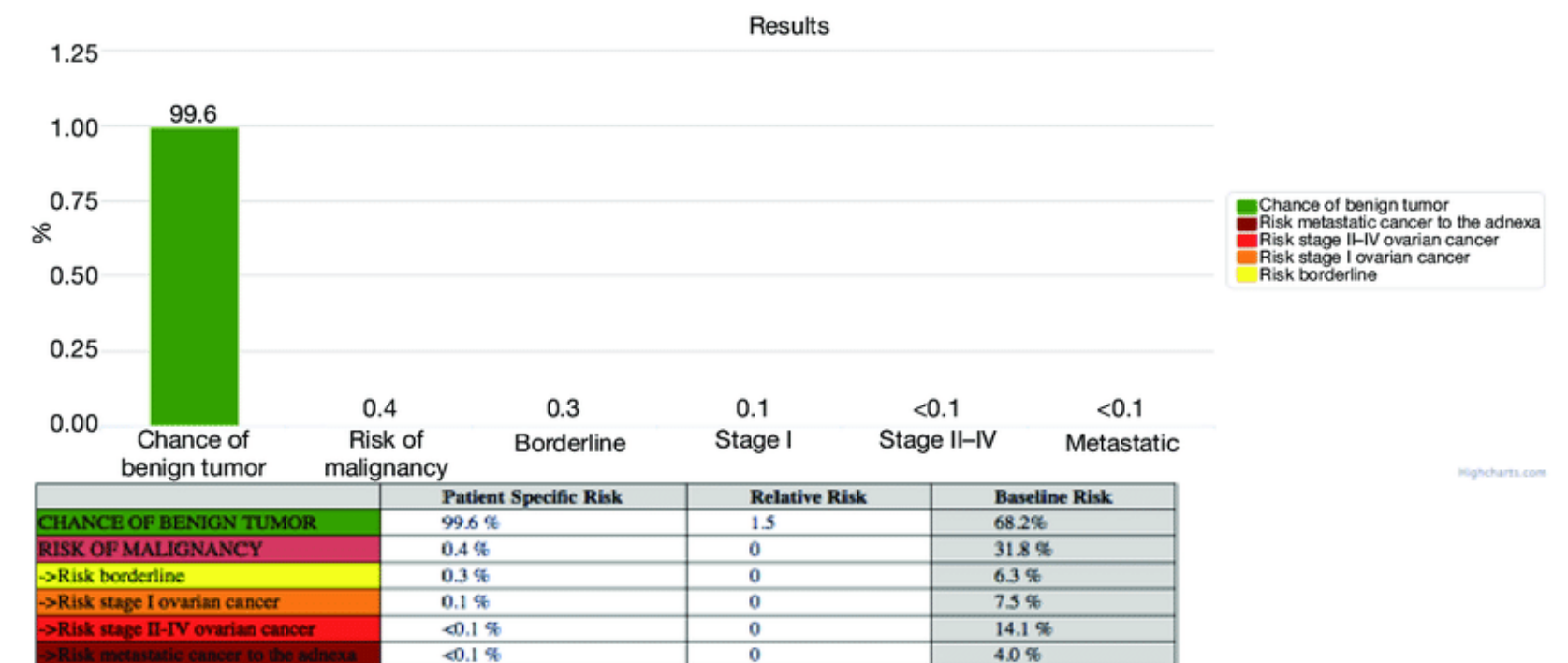
Step 1: Modified Benign Descriptor

	Descriptor 1: Unilocular cyst with ground-glass echogenicity and largest diameter < 10 cm, in a premenopausal woman (suggestive of endometrioma)
	Descriptor 2: Unilocular cyst with mixed echogenicity, acoustic shadows and largest diameter < 10 cm, in a premenopausal woman (suggestive of benign cystic teratoma)
	Descriptor 3: Unilocular cyst with anechoic cyst fluid, smooth internal walls and largest diameter < 10 cm, in a pre- or postmenopausal woman (suggestive of simple cyst or cystadenoma)
	Descriptor 4: All other unilocular cysts with smooth internal walls and largest diameter < 10 cm, in a pre- or postmenopausal woman


If not applicable

Step 2: Calculate ADNEX score

1. Age of the patient at examination (years) 53
2. Oncology center (referral center for gyn-oncol)? no
3. Maximal diameter of the lesion (mm) 55
4. Maximal diameter of the largest solid part (mm) 3
5. More than 10 locules? no
6. Number of papillations (papillary projections) one
7. Acoustic shadows present? yes
8. Ascites (fluid outside pelvis) present? no
9. Serum CA-125 (U/ml) 7.8



Applicable in 37% of masses
Associated risk of malignancy <1%

Aims of ROCkeTS

Identify best diagnostic test for ovarian cancer in pre and post menopausal women

- Prospective multicentre cohort study with all women undergoing all diagnostic tests against same reference standard - Histology or 12 month follow-up
- Recruit mainly from rapid access clinics (first presentation to hospital) to establish best test in low prevalence settings
- **USS in non-expert hands (non-medical sonographers)**



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Eligibility Criteria: Inclusion and Exclusion

Inclusion: Women referred with symptoms of suspected OC

- A raised Ca125 test result OR
- Abnormal imaging result showing a lesion OR
- Both a raised CA125 test and an abnormal imaging result showing a lesion
- Patients able to provide informed consent.

Exclusion:

- Active ovarian malignancy or non ovarian malignancy
- USS simple cyst < 5 cm



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Primary and Secondary Outcomes

Primary Outcome:

- Primary invasive ovarian malignant neoplasm (ovarian / fallopian tube / primary peritoneal) versus benign / normal

Secondary Outcomes:

- Primary invasive , secondary malignancy, borderline neoplasms and neoplasms of uncertain or unknown behaviour versus benign/ normal
- Analysis with borderline tumours grouped with benign
- Analysis in patients scanned by IOTA QA passed practitioners
- Analysis in high volume recruiting sites (>50 patients/site)
- Sensitivity analysis with multiple imputation for missing data



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Index tests, comparator and reference standard

Index tests

- IOTA ADNEX model and IOTA sRRisk model at 3% and 10% thresholds
- RMI1 at 200 threshold
- ROMA at thresholds
- IOTA simple rules
- CA125 at 35 IU/ml.
- Posthoc - ORADS at 10% (ORADS 1-3 versus 4-5)

Comparator test – Risk of malignancy, RMI1 at 250 threshold.



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Sonographer training and QA in ROCKETS

- Level 2 sonographers
- Sonographers at participating sites received 1 day in person and online US training
- Assessed by written examination
- Participation in ROCKETS study requires IOTA certification
- Quality assessment
 - Sample of ultrasound images and reports were centrally reviewed by IOTA team (US experts)
 - Pass if 1st 3 scans were accurately annotated

Diagnostic performance by secondary outcome definition of ovarian cancer - Postmenopausal

Index test combination	Threshold	Diagnosis based on reference standard, n=1,214		Number of Participants, n (%)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	C-index (AUC) (95% CI)	Positive predictive value (PPV) (%) (95% CI)	Negative predictive value (NPV) (%) (95% CI)	Pairwise comparison with RMI 1 ^a (250) (95% CI), p-value, number of participants
		Present n=353	Absent n=861							
RMI 1, n (%)	Missing	44 (12.5)	68 (7.9)							
	≥200	231 (65.4)	124 (14.4)	1,102 (90.8)	74.8 (69.5, 79.5)	84.4 (81.6, 86.8)	0.86 (0.84, 0.89)	65.1 (59.9, 70.0)	89.6 (87.1, 91.7)	Se: -3.6 (-5.9, -1.2), p=0.0010 Sp: 3.0 (1.7, 4.3), p<0.001, n=1,102
	<200	78 (22.1)	669 (77.7)							
	≥250	220 (62.3)	100 (11.6)							
	<250	89 (25.2)	693 (80.5)		71.2 (65.8, 76.2)	87.4 (84.9, 89.6)		68.8 (63.4, 73.8)	88.6 (86.2, 90.8)	*
ROMA, n (%)	Missing	51 (14.4)	95 (11.0)							
	≥14.4%	280 (79.3)	441 (51.2)	1,068 (88.0)	92.7 (89.2, 95.4)	42.4 (38.9, 46.0)	0.87 (0.85, 0.90)	38.8 (35.3, 42.5)	93.7 (90.6, 96.0)	Se: -19.5 (-24.8, -14.3), p<0.001 Sp: 43.1 (39.3, 46.9), p<0.001, n=974
	<14.4%	22 (6.2)	325 (37.7)							
	≥25.3%	251 (71.1)	207 (24.0)							
	<25.3%	51 (14.4)	559 (64.9)							
	≥27.7%	242 (68.6)	181 (21.0)							
	<27.7%	60 (17.0)	585 (67.9)							
	≥29.9%	238 (67.4)	154 (17.9)							
	<29.9%	64 (18.1)	612 (71.1)							
ADNEX, n (%)	Missing	59 (16.7)	151 (17.5)							
	≥3.0%	290 (82.2)	491 (57.0)	1,004 (82.7)	98.6 (96.6, 99.6)	30.8 (27.5, 34.4)	0.89 (0.86, 0.91)	37.1 (33.7, 40.6)	98.2 (95.5, 99.5)	Se: -27.9 (-33.4, -22.4), p<0.001 Sp: 56.1 (52.2, 60.1), p<0.001, n=1,003
	<3.0% (Secondary)	4 (1.1)	219 (25.4)							
	≥10.0%	270 (76.5)	295 (34.3)							
	<10.0% (Primary)	24 (6.8)	415 (48.2)		91.8 (88.1, 94.7)	58.5 (54.7, 62.1)		47.8 (43.6, 52.0)	94.5 (92.0, 96.5)	Se: -21.1 (-26.4, -15.8), p<0.001 Sp: 28.5 (24.7, 32.3), p<0.001, n=1,003



ROCKeTS – Conclusion – Postmenopausal

- Consistently across all analyses, three tests improved on sensitivity of RMI (>90%) - IOTA ADNEX at 10% , 3% and ROMA 14.4. Of these, IOTA ADNEX at 10% had least drop of specificity.
- Valuing sensitivity over specificity - IOTA ADNEX at 10% in real-world practice has highest sensitivity and should be considered the new standard of care diagnostic test in ovarian cancer for postmenopausal women.

Risk-prediction models in postmenopausal patients with symptoms of suspected ovarian cancer in the UK (ROCKeTS): a multicentre, prospective diagnostic accuracy study

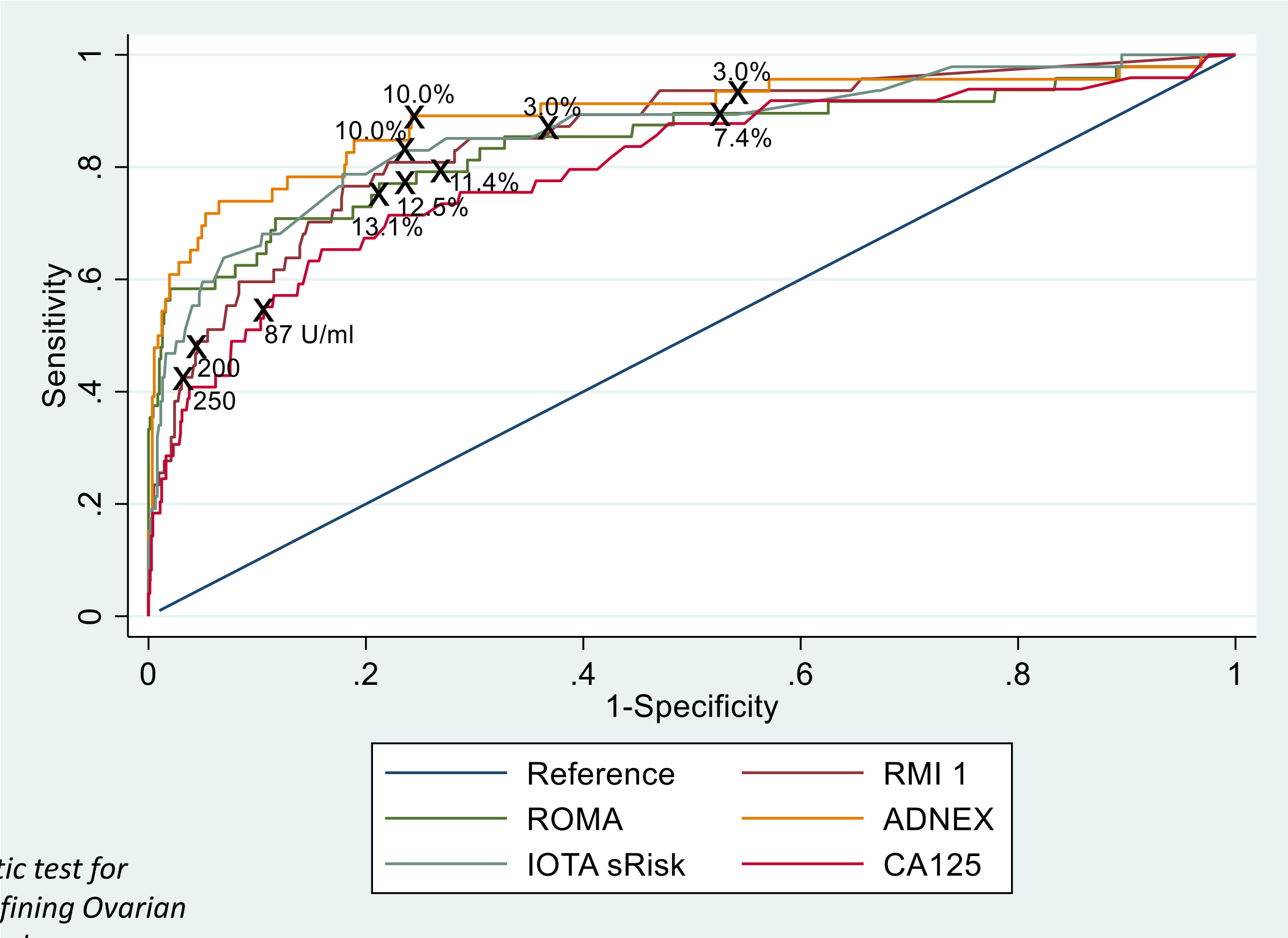
*Sudha Sundar, Ridhi Agarwal, Clare Davenport, Katie Scandrett, Susanne Johnson, Partha Sengupta, Radhika Selvi-Vikram, Fong Lien Kwong, Sue Mallett, Caroline Rick, Sean Kehoe, Dirk Timmerman, Tom Bourne, Ben Van Calster, Hilary Stobart, Richard D Neal, Usha Menon, Alex Gentry-Maharaj, Lauren Sturdy, Ryan Ottridge, Jon Deeks, for the ROCKeTS collaborators**



Results for premenopausal women

- Plenary at IGCS
- Presentation at RCOG, Oman
- Under review, BMJ

ROC curve for premenopausal women – primary outcome



Sundar Set al. Identifying the best diagnostic test for Ovarian Cancer - results from ROcKeTS (Refining Ovarian Cancer Test accuracy Scores). BMJ submitted.

Diagnostic performance statistics of index test combinations by primary outcome definition of ovarian cancer in the pre protocol change cohort.

Index test combination	Threshold	Diagnosis based on reference standard, n=799		Number of Participants, n (%)	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	C-index (AUC) (95% CI)	Positive predictive value (PPV) (%) (95% CI)	Negative predictive value (NPV) (%) (95% CI)	Pairwise comparison with RMI 1 ^a (250) (95% CI), p-value, number of participants
		OC n=49	No OC n=750							
RMI 1, n (%)	Missing	2 (4.1)	125 (16.7)							
	≥200	23 (46.9)	29 (3.9)	672 (84.1)	48.9 (34.1, 63.9)	95.4 (93.4, 96.9)	0.853 (0.792, 0.914)	44.2 (30.5, 58.7)	96.1 (94.3, 97.5)	Se: -6.4 (-15.5, 2.7), p=0.2500 Sp: 1.1 (0.1, 2.1), p=0.0156, n=672
	<200	24 (49.0)	596 (79.5)							
	≥250	20 (40.8)	22 (2.9)							
	<250	27 (55.1)	603 (80.4)							
ROMA, n (%)	Missing	1 (2.0)	48 (6.4)							
	≥7.4%	43 (87.8)	372 (49.6)	750 (93.9)	89.6 (77.3, 96.5)	47.0 (43.3, 50.8)	0.844 (0.769, 0.918)	10.4 (7.6, 13.7)	98.5 (96.6, 99.5)	Se: -47.8 (-64.4, -31.2), p<0.0001 Sp: 49.3 (45.0, 53.7), p<0.0001, n=636
	<7.4%	5 (10.2)	330 (44.0)							
	≥11.4%	38 (77.6)	189 (25.2)							
	<11.4%	10 (20.4)	513 (68.4)							
	≥12.5%	37 (75.5)	164 (21.9)							
	<12.5%	11 (22.4)	358 (47.7)							
	≥13.1%	36 (73.5)	149 (19.9)							
	<13.1%	12 (24.5)	553 (73.7)							
ADNEX, n (%)	Missing	3 (6.1)	179 (23.9)							
	≥3.0%	43 (87.8)	311 (41.5)	617 (77.2)	93.5 (82.1, 98.6)	45.5 (41.4, 49.7)	0.891 (0.827, 0.955)	12.1 (8.9, 16.0)	98.9 (96.7, 99.8)	Se: -52.2 (-68.8, -35.6), <0.0001 Sp: 50.8 (46.5, 55.1), p<0.0001, n=617
	<3.0% (Secondary)	3 (6.1)	260 (34.7)							
	≥10.0%	41 (83.7)	142 (18.3)							
	<10.0% (Primary)	5 (10.2)	429 (57.2)							
	<10.0% (Primary)	8 (16.3)	472 (62.9)							

Conclusion

- IOTA ADNEX at 10% delivered by non-expert sonographers receiving appropriate training, certification and Quality assurance has high sensitivity and acceptable specificity.
- IOTA ADNEX at 10% should be considered new standard of OC diagnostic in premenopausal and postmenopausal women.



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Cost Consequence Analysis for Ovarian Cancer

- **RMI 200** was cheapest but highest cancer deaths
- **ADNEX 3%** had the least cancer deaths and greatest diagnostic yield
- **ADNEX model alone based strategies** were characterised by **high sensitivity but lower specificity**, resulting in potentially **unnecessary costs** associated with the management of false positive results.

ADNEX 2 step strategy offers the best-balanced model

Implementation considerations

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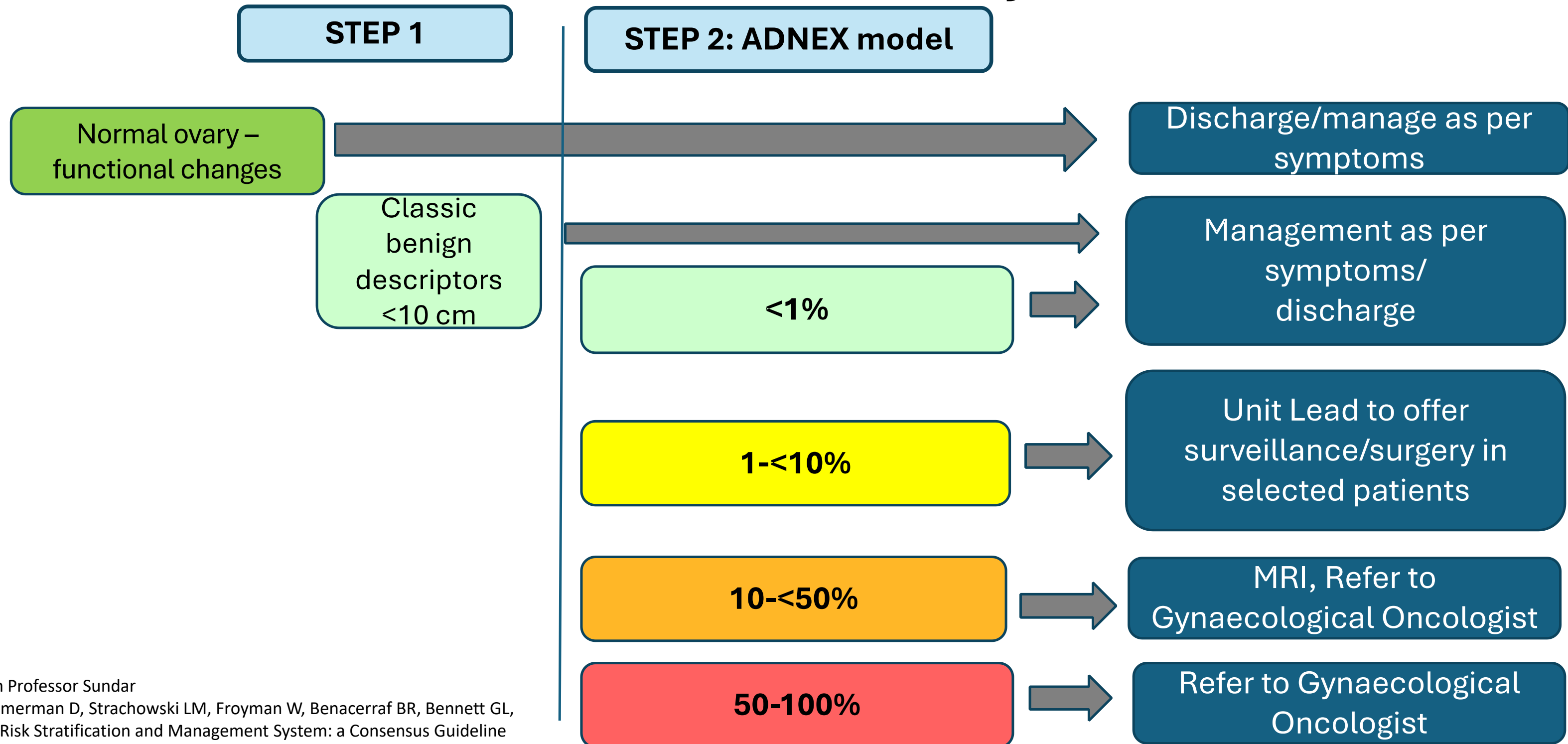
Risk-prediction models and clinical challenges in the ROCkeTS study – Authors' reply

[Sudha Sundar](#)^a  · [Clare Davenport](#)^b · [Katie Scandrett](#)^b · [Dirk Timmerman](#)^c · [Tom Bourne](#)^d · [Jon Deeks](#)^b

[Affiliations & Notes](#) ∨ [Article Info](#) ∨ [Linked Articles \(1\)](#) ∨

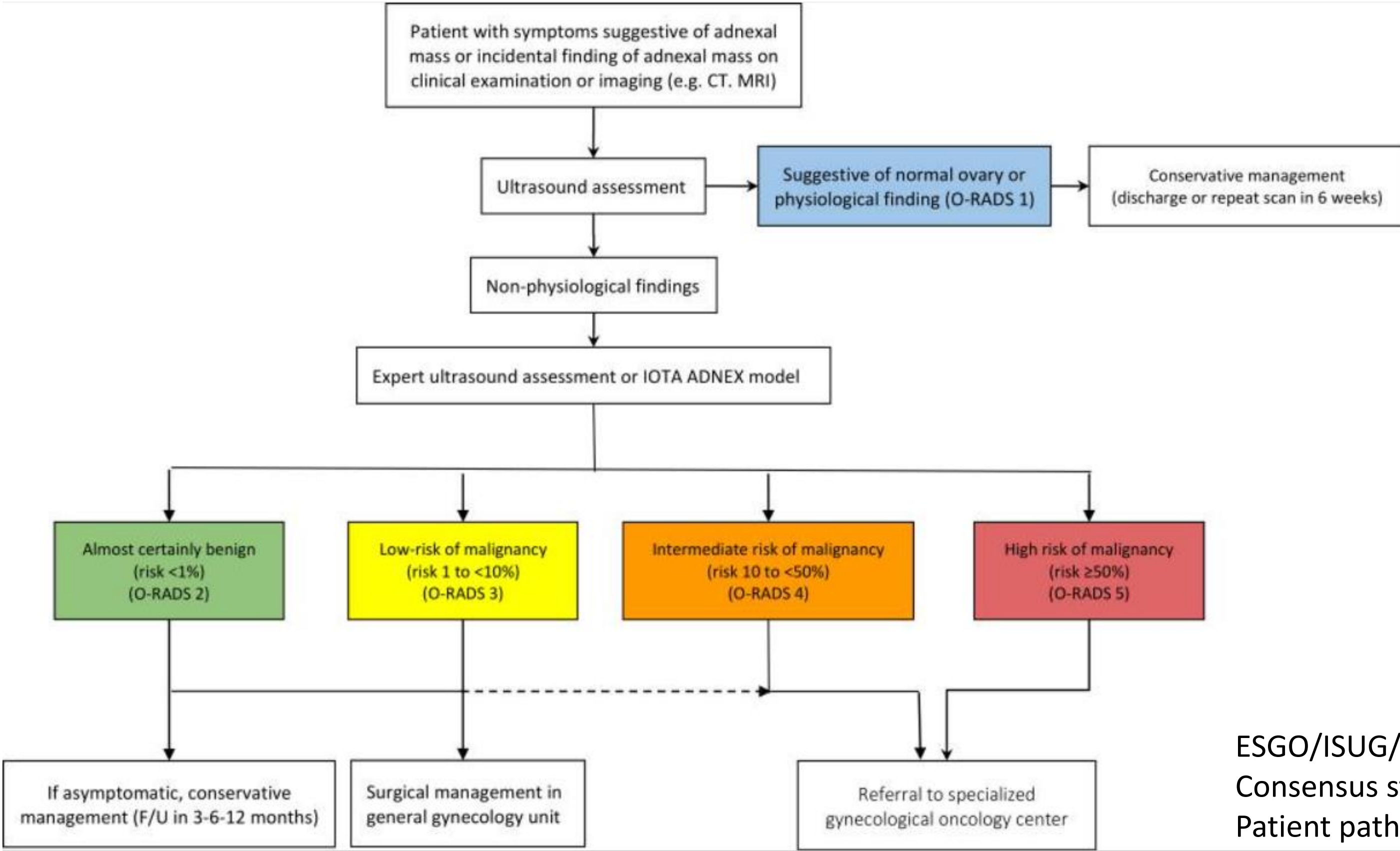
**FOR CLINICAL IMPLEMENTATION, A TWO-STEP STRATEGY WITH IOTA ADNEX
OFFERS BEST TRADE-OFF FOR SENSITIVITY AND SPECIFICITY**

Implementation of two-step strategy IOTA ADNEX-ORADS in secondary care



Personal file from Professor Sundar
Andreotti RF, Timmerman D, Strachowski LM, Froyman W, Benacerraf BR, Bennett GL,
et al. O-RADS US Risk Stratification and Management System: a Consensus Guideline
from the ACR ovarian-adnexal reporting and Data System Committee. Radiology.
2020;294:168–85

ESGO/ISUG/IOTA/ESGE Consensus statement 2021

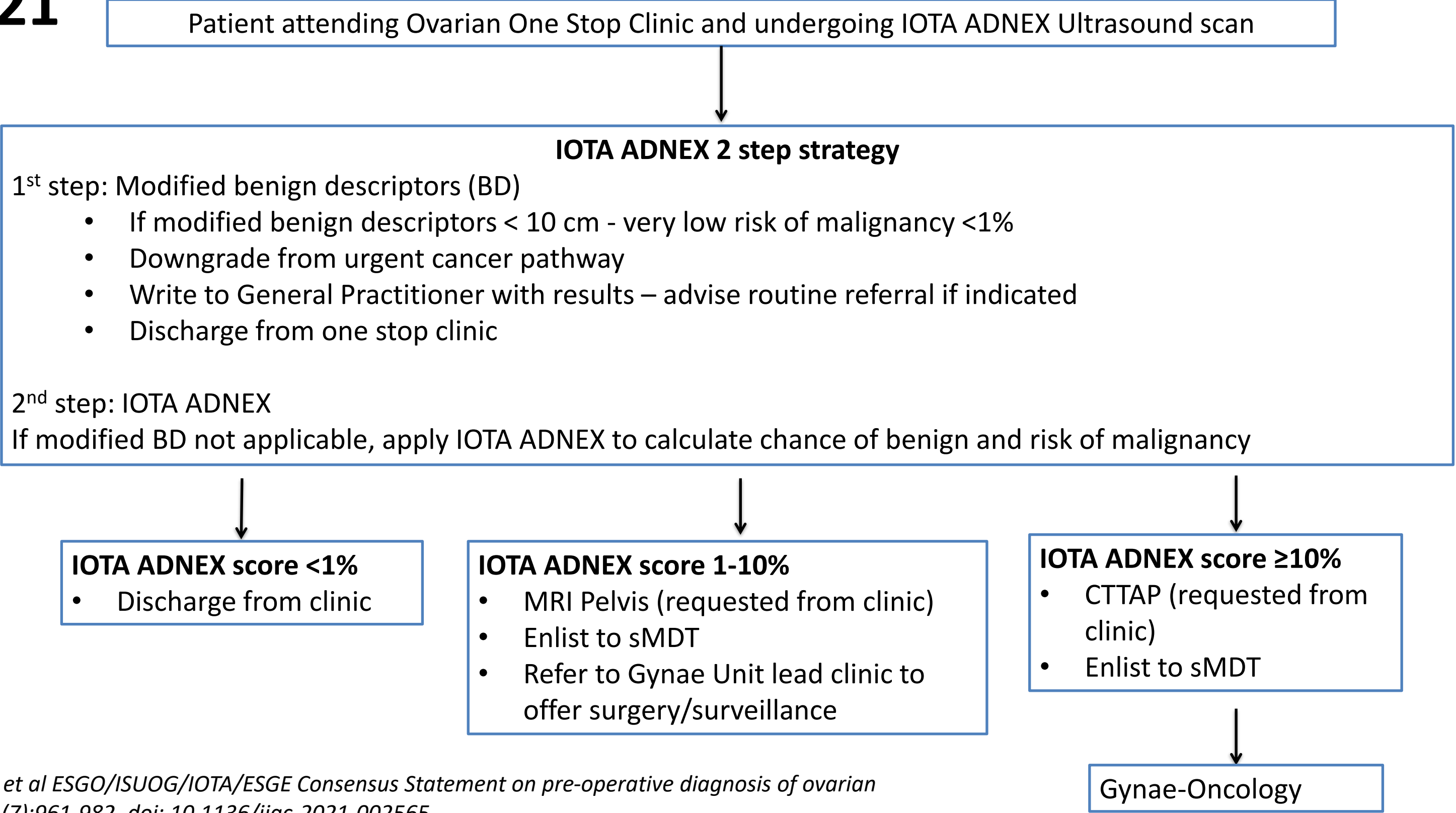


ESGO/ISUG/IOTA/ESGE
Consensus statement:
Patient pathway

IOTA ADNEX Implementation in a one stop clinic setting across 2 NHS hospitals

- Quality improvement project
- Multi-centre observational cohort study across 2 NHS hospitals
 - Sandwell and West Birmingham NHS Trust (SWBH): June 2023 – Jan 2025
 - Walsall Healthcare NHS Trust: October 2023 – Jan 2025
- Once weekly clinic (3-5 patients per clinic session)
 - Patients referred from primary/secondary care with suspected ovarian cancer on an urgent suspected cancer referral pathway
 - Clinical consultation alongside IOTA ADNEX pelvic ultrasound used to triage adnexal mass and guide further management
 - SWBH: Sonographer delivered ultrasound service
 - Walsall Hospital: Gynaecologist delivered ultrasound service

Proposed diagnostic pathway based off ESGO/ISUOG/IOTA/ESGE consensus 2021



1.Timmerman D, Planchamp F, Bourne T, et al ESGO/ISUOG/IOTA/ESGE Consensus Statement on pre-operative diagnosis of ovarian tumors. *Int J Gynecol Cancer*. 2021 Jul;31(7):961-982. doi: 10.1136/ijgc-2021-002565.

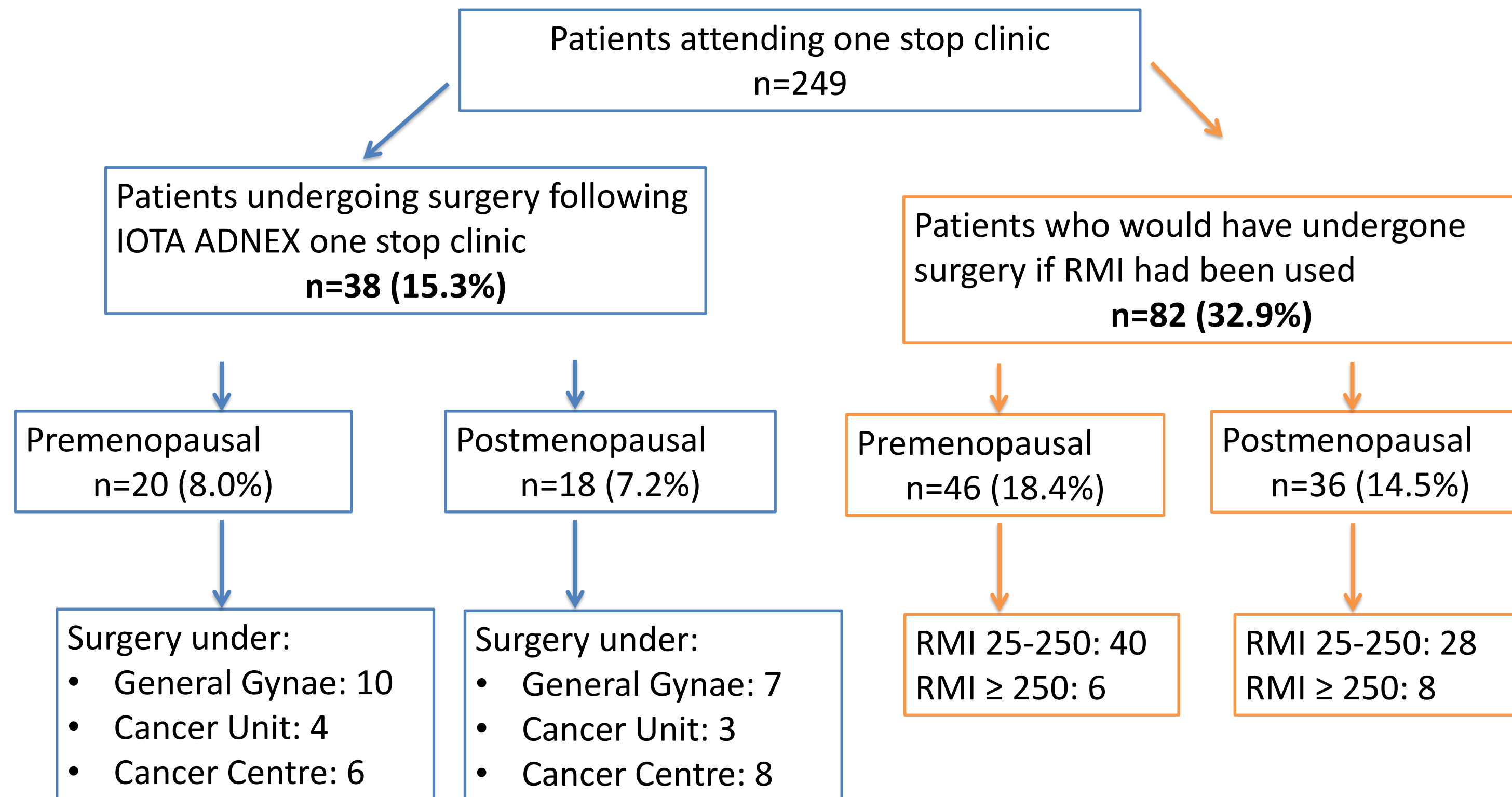
2.Landolfo C, Bourne T, Froyman W et al. Benign descriptors and ADNEX in two-step strategy to estimate risk of malignancy in ovarian tumours: retrospective validation in IOTA5 multicenter cohort. *Ultrasound Obstet Gynaecol*. 2023; 61(2):231-242

3. Dr Do V. Presentation: Outcomes following IOTA-ADNEX implementation in 2 NHS ‘One-Stop’ clinics: an observational cohort study. IOTA, Leuven Congress 2025. [Internet] [Cited 2025 June 09] Available at: [Vivian Do - IOTA Congress Abstract / IOTA Plus](#)

Results

- Until January 2025, a total of 249 patients were seen
- 9 confirmed ovarian cancer cases - histology
- No cancer cases were missed

Surgical outcomes following use of IOTA-ADNEX in a one stop clinic setting compared to RMI



Process metric outcomes from IOTA ADNEX triaging in a one stop clinic setting

Outcomes	Total number of patients (n=249)
Discharged within 3 months	153 (61.4%)
Same day discharge from clinic	100 (40.2%)
Follow up with surveillance	52 (23.3%)
Further imaging requested:	
CT	36 (14.4%)
MRI	47 (18.9%)

Summary


- ✓ Enabled early stage cancer to be picked up correctly and identified all cases of ovarian cancer
- ✓ Reduced unnecessary surgery by 17.7% in comparison to RMI triaging
- ✓ Enabled 40.2% same day discharges from clinic, supporting NHS Faster Diagnosis Standards



Gynaia

Basics


Introduction Module - Basics of transvaginal

 Lecture B01
Basics of transvaginal ultrasound


Ovarian Programme


Module 1 - Introduction to IOTA


 Lecture O01
Introduction, IOTA studies to date


 Lecture O02
IOTA terms and definitions


Module 2 - Benign Descriptors & the 2-Step Strategy

 Lecture O03
Pattern Recognition/Benign Descriptors


 Lecture O04
Case examples of 'recognisable' masses


 Lecture O05
IOTA Simple Rules

 Lecture O06
ADNEX model and 2 step strategy


 Lecture O07
Case examples of 2 step strategy

Module 3 - Clinical Applications

 Lecture O08
O-RADS

 Lecture O09
Difficult Masses

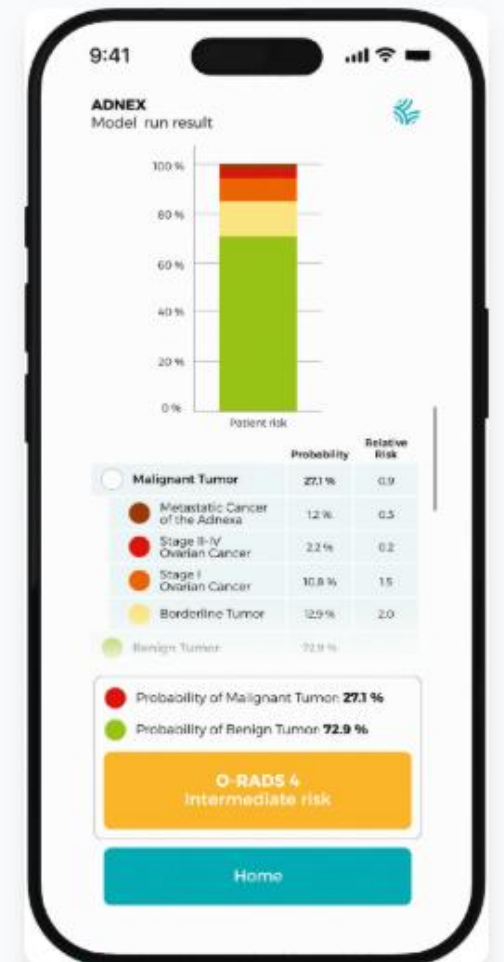
Module 4 - Concluding Remarks

 Lecture O10
Revision of key points

About the ADNEX App

The ADNEX app provides a user-friendly interface for applying the IOTA ADNEX risk model in clinical practice. It helps clinicians assess the risk of various types of adnexal masses, supporting better diagnostic accuracy and treatment planning.

With the latest ADNEX2 model update, the app now offers improved performance and broader applicability, including cases that are being managed conservatively. The interface is designed for efficient data entry and clear result presentation.



Change in practice

- BGCS guidance – available on <https://www.sciencedirect.com/science/article/pii/S0301211524003142>



European Journal of Obstetrics & Gynecology
and Reproductive Biology

Available online 21 June 2024

In Press, Journal Pre-proof ? What's this?



Expert Opinion

British Gynaecological Cancer Society
(BGCS) ovarian, tubal and primary
peritoneal cancer guidelines:
Recommendations for practice update
2024

Future research plans

- Investigation outcomes from implementation at scale at secondary care in UK hospitals – interrupted time series study
- Evaluation of IOTA ADNEX in primary care practice

Conclusion

- IOTA ADNEX at 10% delivered by non-expert sonographers receiving appropriate training, certification and quality assurance has high sensitivity and acceptable specificity.
- IOTA ADNEX at 10% should be considered new standard of OC diagnostic in premenopausal and postmenopausal women.
- Cost consequence analysis demonstrates that a two-step strategy offers the best balance between cost vs cancer death and is recommended for practice
- Implementation at scale will require careful consideration of facilitators and barriers.



References

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 2. Gentry-Maharaj A, Burnell M, Dilley J, Ryan A, Karpinskyj C, Gunu R, et al. Serum HE4 and diagnosis of ovarian cancer in postmenopausal women with adnexal masses. *Am J Obstet Gynecol*. 2020 Jan;222(1):56.e1-56.e17.
 3. Davenport CF, Rai N, Sharma P, Deeks J, Berhane S, Mallett S, et al. Diagnostic Models Combining Clinical Information, Ultrasound and Biochemical Markers for Ovarian Cancer: Cochrane Systematic Review and Meta-Analysis. *Cancers*. 2022 Jul 26;14(15):3621.
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 6. Kwong FL, Kristunas C, Davenport C, Aggarwal R, Deeks J, Mallett S, et al. Investigating harms of testing for ovarian cancer - psychological outcomes and cancer conversion rates in women with symptoms of ovarian cancer: A cohort study embedded in the multicentre ROCKeTS prospective diagnostic study. *BJOG Int J Obstet Gynaecol*. 2024 Sep;131(10):1400–10.
 7. Kwong FLA, Kristunas C, Davenport C, Deeks J, Mallett S, Agarwal R, et al. Symptom-triggered testing detects early stage and low volume resectable advanced stage ovarian cancer. *Int J Gynecol Cancer Off J Int Gynecol Cancer Soc*. 2024 Sep 25;ijgc–2024–005371.
 8. Sundar S, Agarwal R, Davenport C, Scandrett K, Johnson S, Sengupta P, et al. Risk-prediction models in postmenopausal patients with symptoms of suspected ovarian cancer in the UK (ROCKeTS): a multicentre, prospective diagnostic accuracy study. *Lancet Oncol*. 2024 Oct;25(10):1371–86.
 9. Sundar S, Davenport C, Scandrett K, Timmerman D, Bourne T, Deeks J. Risk-prediction models and clinical challenges in the ROCKeTS study - Authors' reply. *Lancet Oncol*. 2025 Jan;26(1):e4–5.
- Submitted, under review.
10. Identifying the best diagnostic test for Ovarian cancer in premenopausal women with non-specific symptoms – results from the ROCKeTS prospective, multicentre, cohort study. Sudha Sundar et al. *BMJ*
 11. A cost consequence analysis of six diagnostic strategies for ovarian cancer- a model based economic evaluation, Samuel Perry et al. *BJOG*.

Acknowledgments

- Funded by National Institute of Health Research, UK. HTA 13/13/01
- This study/project is funded by the NIHR Health Technology assessment programme. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care
- We thank our Project advisory group, our Cancer charity patient advocates from Target Ovarian cancer, patients and sites for support.
- Questions!

