Institution: Imperial College London

Unit of Assessment: 01 Clinical Medicine

Title of case study: Improved Diagnosis of Ovarian Cancer

Period when the underpinning research was undertaken: 2010-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Tom Bourne	Clinical Professor in Gynaecology	2008 to present
Ahmad Sayasneh	Clinical Research Fellow	2013-2015
Maya Al-Memar	Clinical Research Fellow	2013-2017
Chiara Landolfo	Clinical Research Fellow	2018-2020

Period when the claimed impact occurred: 2014 - 2020

Is this case study continued from a case study submitted in 2014? No

1. Summary of the impact (indicative maximum 100 words)

Distinguishing between ovarian cancer, which requires urgent surgery, and benign ovarian cysts that can be safely observed is a significant diagnostic challenge. The International Ovarian Tumor Analysis (IOTA) study, co-designed and co-chaired by Professor Bourne at Imperial College, developed ultrasound algorithms that represent the best available tests to diagnose ovarian cancer (sensitivity: 96%; specificity: 73%), reducing the number of misclassifications by over 50%.

These data have changed national guidelines in the UK, the US, France, Poland, Switzerland and Austria. The rules and models have been incorporated into the most commonly used ultrasound machines worldwide. An easy-to-use app has been developed, and a training programme has certificated over 10,000 doctors.

2. Underpinning research (indicative maximum 500 words)

Ovarian cysts are extremely common and ultrasound scanning is one of the key investigations to assess them. However, distinguishing cysts that are benign, and thus may be safely observed if they do not cause symptoms, from cysts that are malignant, which require rapid referral and surgery, is a major diagnostic challenge. In the UK, approximately 40,000 women undergo surgery for ovarian cysts annually. Surgery is frequently performed because malignancy cannot be confidently excluded - this means, in many cases, that surgery will have been unnecessary. Even for non-malignant cysts, identifying those that are likely to undergo torsion, an extremely painful and potentially fertility-threatening complication, is vital.

Any test designed to categorise ovarian cysts must be validated both for masses selected for surgery and for those deemed suitable for conservative, non-surgical management. Until the IOTA study, no such validated test existed.

The study recruited patients in seven phases, the first 5 of which have taken place during the REF assessment window. Phases 1 to 4 recruited >6,000 women in 24 centres from 10 countries. Phase 4 took place solely at Imperial College Healthcare NHS Trust, whilst phase 5 has recruited over 12,000 patients in 36 centres in 14 countries. Professor Bourne at Imperial College co-chaired the project and was involved in all aspects of study design, administration, interpretation of data and writing manuscripts. Ultrasound examiners recruiting participants collected clinical information

and performed transvaginal ultrasonography following a standardised protocol. Greyscale and colour Doppler ultrasound were used to characterise the morphology and vascularity of an ovarian or tubal mass if present. Information on a number of pre-defined ultrasound variables was also collected, and examiners described the ultrasound results using IOTA terminology.

In phases 1-4, histology of removed masses was used as the primary reference endpoint. The IOTA Simple Rules were developed (1), as well as a multiclass prediction model (ADNEX) that performed better (Area under the Curve [AUC] ADNEX: 0.94) than any existing test including the Risk of Malignancy Index (RMI). Furthermore, the ADNEX model can also sub-classify malignant masses as borderline (low malignant potential), invasive malignant, or metastatic. This is important as this facilitates fertility-sparing surgery in a borderline mass or the search for a primary site with metastasis (2).

The ADNEX model was subsequently validated for use by trainees and sonographers (3). The Simple Rules were then revisited to develop Simple Rules Risks, which gives a percentage likelihood of cancer rather than just a binary result, and a subgroup analysis allowed the researchers to quantify the risk of metastasis, providing evidence to support different surgical approaches (4).

IOTA phase 5 included all women with an ovarian mass. For masses selected for conservative management, the risk of malignancy or torsion/rupture over two years follow up, the primary endpoint, was minimal (0.4% and 0.3% respectively) (5). This study has shown that masses classified as benign are safe to manage using a watch-and-wait approach, avoiding the need for surgery.

IOTA phase 5 data were also used to validate further the performance of the Simple Rules and ADNEX model on all masses (6). Diagnostic performance was retained, demonstrating their use to select women for conservative management and characterise ovarian pathology prior to surgery.

3. References to the research (indicative maximum of six references)

(1) Timmerman, D., Ameye, L., Fischerova, D., Epstein, E., Melis, G.B., Guerriero, S., Van Holsbeke, C., Savelli, L., Fruscio, R., Lissoni, A.A., Testa, A.C., Veldman, J., Vergote, I., Van Huffel, S., Bourne, T., Valentin, L. (2010). Simple ultrasound rules to distinguish between benign and malignant adnexal masses before surgery: prospective validation by the IOTA group. *BMJ*; 341: c6839. DOI.

(2) Van Calster, B., Van Hoorde, K., Valentin, L., Testa, A.C., Fischerova, D., Van Holsbeke, C., Savelli, L., Franchi, D., Epstein, E., Kaijser, J., Van Belle, V., Czekierdowski, A., Guerriero, S., Fruscio, R., Lanzani, C., Scala, F., Bourne, T., Timmerman, D.; International Ovarian Tumour Analysis Group. (2014). Evaluating the risk of ovarian cancer before surgery using the ADNEX model to differentiate between benign, borderline, early and advanced stage invasive, and secondary metastatic tumours: prospective multicentre diagnostic study. *BMJ*; 349: g5920. DOI.

(3) Sayasneh, A., Ferrara, L., De Cock, B., Saso, S., Al-Memar, M., Johnson, S., Kaijser, J., Carvalho, J., Husicka, R., Smith, A., Stalder, C., Blanco, M.C., Ettore, G., Van Calster, B., Timmerman, D., Bourne, T. (2016). Evaluating the risk of ovarian cancer before surgery using the ADNEX model: a multicentre external validation study. *Br J Cancer*; 115(5):542-8. DOI.

(4) Froyman, W., Landolfo, C., Amant, F., Van den Bosch, T., Vergote, I., Coosemans, A., Testa, A., Valentin, L., Bourne, T., Van Calster, B., Timmerman, D. (2016). Morcellation and risk of malignancy in presumed ovarian fibromas/fibrothecomas. *Lancet Oncology*; 17(3):273-4. DOI.

(5) Froyman, W., Landolfo, C., De Cock, B., Wynants, L., Sladkevicius, P., Testa, A.C., Van Holsbeke, C., Domali, E., Fruscio, R., Epstein, E., Dos Santos Bernardo, M.J., Franchi, D., Kudla, M.J., Chiappa, V., Alcazar, J.L., Leone, F.P.G., Buonomo, F., Hochberg, L., Coccia, M.E.,

Guerriero, S., Deo, N., Jokubkiene, L., Kaijser, J., Coosemans, A., Vergote, I., Verbakel, J.Y., Bourne, T., Van Calster, B., Valentin, L., Timmerman, D. (2019). Risk of complications in patients with conservatively managed ovarian tumours (IOTA5): a 2-year interim analysis of a multicentre, prospective, cohort study. *Lancet Oncology*; 20(3): 448-458. DOI.

(6) Van Calster, B., Valentin, L., Froyman, W., Landolfo, C., Ceusters, J., Testa, A.C., Wynants, L., Sladkevicius, P., Van Holsbeke, C., Domali, E., Fruscio, R., Epstein, E., Franchi, D., Kudla, M.J., Chiappa, V., Alcazar, J.L., Leone, F.P.G., Buonomo, F., Coccia, M.E., Guerriero, S., Deo, N., Jokubkiene, L., Savelli, L., Fischerová, D., Czekierdowski, A., Kaijser, J., Coosemans, A., Scambia, G., Vergote, I., Bourne, T., Timmerman, D. (2020). Validation of models to diagnose ovarian cancer in patients managed surgically or conservatively: multicentre cohort study. *BMJ*; 370:m2614. DOI.

4. Details of the impact (indicative maximum 750 words)

Ovarian masses are extremely common, with an incidence of 5% – 15% in post-menopausal women. The large majority are benign. The underlying management strategy, therefore, is to distinguish between those that are benign and those that are potentially malignant, allowing conservative management where possible for those that are benign, and rapid referral to a gynaecological oncologist for those that are potentially malignant.

Ultrasound scanning is a critical test in the investigation of such ovarian masses. The IOTA Simple Rules is proven to result in a 2.6-fold reduction in the rate of surgery compared to use of the Risk of Malignancy Index (RMI) in the previous 2003 Royal College of Obstetricians and Gynaecologists (RCOG) guidelines, with, critically, no delay in cancer diagnosis at 12 months. The absolute 16% difference in rates of surgery means that, with 40,000 women being considered for ovarian cyst surgery in the UK each year, 6,500 fewer operations would take place after assessment by Simple Rules compared to assessment via RMI [**A**]. The IOTA Simple Rules algorithm can be used in routine clinical practice by junior doctors and ultra-sonographers to distinguish cancers from benign cysts, with significant impact upon patient care worldwide.

The IOTA Simple Rules were included in the revised UK Royal College of Obstetricians and Gynaecologists (RCOG) guidelines for management of ovarian cysts in premenopausal women in 2014 [**B**; pages 6-7]. IOTA Simple Rules have also been included in the RCOG guidance for diagnosis and management of cysts in postmenopausal women since 2016 [**C**; pages 17-18]. IOTA Simple Rules were included in the British Medical Ultrasound Society guidance in 2019 [**D**; page 66] and the British Gynaecological Cancer Society guidelines in 2017 [**E**; page 8].

In 2019, the IOTA Simple Rules formed the basis of the French national guidelines for the initial diagnosis of ovarian cancer, containing six citations to IOTA studies [**F**]. In 2020, the American College of Radiology and the Society of Radiologists in Ultrasound published the ultrasound risk stratification and management system. This lays out a guideline for the diagnosis and management of ovarian masses in the USA that is based on simple ultrasound descriptors and the IOTA ADNEX model [**G**; this guidance contains 15 citations to IOTA studies].

The IOTA ADNEX model has now been incorporated into the most commonly used high-end ultrasound machines for diagnostics internationally, including GE and Samsung [**H**].

To ensure the models are accessible, the Imperial team has developed two apps, available for Android and iOS [**I**]. The first app contains the logistic regression (LR)1 and LR2 models, as well as Simple Rules, and has been downloaded over 10,000 times. The second app features the ADNEX model and has been downloaded approximately 8,000 times. These apps are designed for use in routine clinical practice, as not all users will have access to high-end ultrasound machines, especially those working in low and middle-income countries.

The researchers at Imperial have implemented IOTA courses to teach IOTA ADNEX and Simple Rules, and IOTA exams to investigate the ability of clinicians to use the models. Over 10,300 people have passed the IOTA certification and are listed on the IOTA website [**J**].

5. Sources to corroborate the impact (indicative maximum of 10 references)

[**A**] Nunes, N., Ambler, G., Foo, X., Naftalin, J., Derdelis, G., Widschwendter, M., Jurkovic, D. (2017). Comparison of Two Protocols for the Management of Asymptomatic Postmenopausal Women with Adnexal Tumours - a Randomised Controlled Trial of Rmi/Rcog Vs Simple Rules. *Br J Cancer*; 116(2): 584-91 DOI.

[**B**] Royal College of Obstetricians and Gynaecologists Green Top Guideline number 62 Green–top Guideline No. 62 RCOG/BSGE Joint Guideline I November 2011. Reviewed and re-approved in 2014 see: https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg62/ (pages 6-7). Archived here.

[**C**] Royal College of Obstetricians and Gynaecologists Green Top Guideline number 34 for the management of Ovarian cysts in Postmenopausal women July 2016. Pages 6-7 https://www.rcog.org.uk/globalassets/documents/guidelines/green-top-guidelines/gtg_34.pdf (pages 17-18). Archived here.

[**D**] British Medical Ultrasound Society guidelines (page 66) https://www.bmus.org/static/uploads/resources/Guidelines_for_Professional_Ultrasound_Practice_v3_OHoz76r.pdf. Archived here.

[**E**] https://www.bgcs.org.uk/wp-content/uploads/2019/05/BGCS-Guidelines-Ovarian-Guidelines-2017.pdf (page 8). Archived here.

[**F**] Thomassin-Naggara I, Daraï E, Lécuru F, Fournier L [Diagnostic value of imaging (ultrasonography, Doppler, CT, MR, PET-CT) for the diagnosis of a suspicious ovarian mass and staging of ovarian, tubal or primary peritoneal cancer: Article drafted from the French Guidelines in oncology entitled "Initial management of patients with epithelial ovarian cancer" developed by FRANCOGYN, CNGOF, SFOG, GINECO-ARCAGY under the aegis of CNGOF and endorsed by INCa]. Gynecol Obstet Fertil Senol. 2019 Feb;47(2):123-133. DOI. Epub 2019 Jan 25.

[**G**] O-RADS US Risk Stratification and Management System: A Consensus Guideline from the ACR (American College of Radiologists). Ovarian-Adnexal Reporting and Data System Committee. Andreotti RF, Timmerman D, Strachowski LM, Froyman W, Benacerraf BR, Bennett GL, Bourne T, Brown DL, Coleman BG, Frates MC, Goldstein SR, Hamper UM, Horrow MM, Hernanz-Schulman M, Reinhold C, Rose SL, Whitcomb BP, Wolfman WL, Glanc P. **Radiology.** 2020 Jan;294(1):168-185. DOI.

[**H**] Examples of diagnostic integration in ultrasound machines:

- https://www.volusonclub.net/empowered-womens-health/a-guide-to-adnexal-mass-ultrasound-terminology/ (archived here).
- http://samsunghealthcare.com/resources/ccc/rwd/temp/06_pdf1.pdf (archived here).

[**I**] https://www.iotagroup.org/iota-models-software/adnex-risk-model (archived here).

[**J**] https://www.iotagroup.org/certified-members (archived here).