Gynaia

INSTRUCTIONS FOR USE ADNEX2

ADNEX model V1.1.3

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Label

Device Name	ADNEX2
UDI	(01) 05430004729037 (8012) v1.1.3
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Contents	Instructions for use of ADNEX2 release v1.1.3
	Hyperlink to the electronic instructions for use

Symbols



Explanation of symbols

UDI	Unique Device Identifier = UDI-DI +UDI PI
	UDI-PI = Software version
	Date of manufacture / release date
	Manufacturer
eIFU indicator	Consult instructions for use
MD	Medical Device

WARNING — Decision-support only, not stand-alone.
ADNEX2 provides probabilistic risk estimates intended to support clinical assessment. The device is intended to be used as one component within a multi-step clinical assessment pathway and is not intended to be used in isolation.

Device description

Intended Purpose	ADNEX2 is intended for use by IOTA-trained specialist healthcare professionals as an aid providing a probabilistic risk estimate that informs clinical decision-making in the assessment of women with adnexal masses. Based on selected clinical and ultrasound parameters, it provides probability estimates for outcome categories (benign, borderline, stage I invasive, stage II–IV invasive, and secondary metastatic). The outputs are intended to support, but not replace, established clinical management protocols and professional judgment. The device does not provide a diagnosis, does not prescribe or select a treatment, and does not recommend a management action. ADNEX2 is intended for being used in a two-step strategy, in those cases where the Benign Descriptors do not apply. ADNEX2 can be used with or without serum CA-125.
Intended user	Trained specialist healthcare professionals holding current Gynaia "IOTA ovarian classification training and certification" certificate
Patient target group	Non-pregnant women aged 18 years and older presenting with an adnexal mass for which the Benign Descriptors are not applicable (see precautions)
Contra indications	**ADNEX2 has not been validated in, and must not be used in, the following patient groups:** • Pregnant women. • Patients aged under 18 years (paediatric and adolescent). • Patients with a known prior ovarian malignancy or suspected recurrence; ADNEX2is not intended for use in recurrence settings.
Use in combination with other devices and software	N/A

Limitations of use	ADNEX2 is designed for clinical decision- support , is not intended for diagnostic purposes and must not be used as a stand-alone basis for clinical decisions. ADNEX2 can be used in all adnexal masses, but is intended for being used in a two-step strategy, in those cases where the Benign Descriptors do not apply

Operating instructions
Minimum System Requirements

Supported Browsers and System Requirements

Our medical device is accessed through a web application (the platform) that is compatible with a range of modern browsers on both desktop and mobile devices. This web application can also be installed on a personal device for a native-app-like experience. To ensure proper functionality, security, and the best user experience, it is essential to use a supported browser with the minimum required version. The platform will check to ensure it only works on supported devices.

Supported Browsers

The following browsers are supported for use with our medical device. Older versions of these browsers are not supported, and you must update to the specified version or higher.

- **Chrome (Desktop & Mobile)**: Version 82 or higher.
- **Edge (Desktop & Mobile)**: Version 82 or higher.
- **Firefox (Desktop & Mobile)**: Version 77 or higher.
- **Safari (Desktop & Mobile)**: Version 12 or higher.
- **Chromium-based browsers**: Any browser built on the Chromium engine (e.g., Brave, Opera) that is based on Chromium version 82 or higher should be supported, though official testing is limited to Chrome and Edge.

Browsers that have reached their "end-of-life" and are no longer receiving security updates, such as Internet Explorer, are not supported.

Hardware Requirements

The performance of the application is dependent on the hardware of your device. The following are general minimum system requirements to run the supported browsers and our application correctly on a desktop/laptop or a mobile phone.

Desktop/Laptop:

- **Processor:** A processor with support for SSE3 instructions (e.g., Intel Pentium 4 or newer) is a general requirement for modern browsers.
- **RAM:** 2GB for 64-bit browsers is the minimum, but 4GB or more is recommended for optimal performance.
- **Operating System:** An actively supported operating system such as Windows 10 or higher, macOS 12 (Monterey) or higher, or a recent version of a Linux distribution.
- **Screen Resolution:** A minimum resolution of 1024 x 768 is required.

Mobile Devices:

- **Operating System:** A modern mobile operating system that supports the latest versions of the browsers listed above (e.g., Android 10 or later, iOS 12 or later).
- **RAM:** 3GB RAM is recommended for optimal performance.

Installation

The application can be installed on a mobile device as a PWA (progressive web app) for quick access from the home screen, similar to a native app. The installation process varies slightly between operating systems.

On iPhone (iOS) using Safari:

1. Open the web application in the Safari browser.
2. Tap the **Share** button (a square with an arrow pointing upwards) at the bottom of the screen.
3. Scroll down and select **Add to Home Screen**.
4. You will be prompted to customize the name of the application. Tap **Add** in the top right corner to confirm.
5. The application icon will now appear on your home screen.

On Android using Chrome:

1. Open the web application in the Chrome browser.
2. An "Install app" prompt may appear automatically. If it does, follow the on-screen instructions.
3. If no prompt appears, tap the **three-dot menu** in the top-right corner of the browser.
4. Select **Add to Home screen** from the menu.
5. A pop-up will appear where you can customize the app's name. Tap **Add** to confirm.
6. The application icon will now be on your home screen and in your app drawer.

Performance characteristics

Clinical Benefits

ADNEX2 Clinical Benefit	Clinical Outcome Parameter
ADNEX2 provides clinical decision-support by informing IOTA-trained specialist healthcare professionals on the predicted risk of malignancy in adnexal masses. This clinical benefit is measured as Net Benefit (NB). NB assesses the quality of clinical decisions made based on the model and the risk threshold.	The NB of ADNEX2 ranges from 0.19 to 0.13 for thresholds from 1-40%, when used as part of the two-step strategy.

Clinical Performance

ADNEX2 Clinical Performance	Performance endpoint/measure
1. ADNEX2 is able to give probabilities to distinguish between benign and malignant adnexal masses. The risks predicted by ADNEX2 both with and without CA125 are well calibrated	When used in a two-step strategy, the AUC for discrimination between benign and malignant masses of ADNEX2 without CA125 is 0.94 (0.93-0.95) and with CA125 if available is 0.95 (0.93 to 0.96). The calibration plot of ADNEX2 is close to the diagonal line indicating perfect calibration in the whole population but calibration in individual centers varies.
2. ADNEX2 is able to give probabilities to distinguish different subclasses of malignant adnexal masses (borderline, stage 1 invasive, stage 2-4 invasive and secondary metastatic tumors)	Within the two-step strategy, AUCs for discrimination between malignant subtypes varied between 0.73 and 0.98 for ADNEX2 with CA125 if available. For ADNEX2 without CA125, AUCs between malignant subtypes varied between 0.65 and 0.98.

Algorithm Validation and Clinical Performance

The ADNEX2 algorithm is a recalibrated and refitted version of the originally published IOTA ADNEX model. The original ADNEX model was developed by the International Ovarian Tumor Analysis (IOTA) group at KU Leuven (Van Calster et al., BMJ, 2014; PMID: 25320247). The most comprehensive assessment of the ADNEX performance is a systematic review and meta-analysis including 47 validation studies, 17,007 tumours, 58 centres, and 28 countries (Barreñada et al., BMJ Medicine, 2024; doi: 10.1136/bmjmed-2023-000817).

ADNEX2 is the first model based on the real target population, both patients managed surgically and conservatively. It is also developed to fit into the two-step strategy. ADNEX2 was evaluated in an internal-external validation (also known as leave-center-out cross-validation) in the prospective multicentre IOTA5 cohort study. In this validation, ADNEX2 showed an AUC of 0.95 (0.93 to 0.96) to distinguish benign from malignant adnexal masses . Subtype prediction performance was also evaluated for borderline tumour, stage I primary invasive cancer, stage II–IV primary invasive cancer, and secondary metastatic tumour. The results showed that ADNEX2 performed comparably to the original ADNEX model. (Barreñada

et al., Ultrasound in Obstetrics & Gynecology, 2025; doi: 10.1002/uog.70055 - final manuscript currently being drafted)

Variable Influence – Understanding the Basis of the Result

ADNEX2 is based on the published IOTA ADNEX model developed by Van Calster et al. for estimating the probability that an adnexal mass is benign, borderline, stage I primary invasive, stage II–IV primary invasive, or secondary metastatic (Van Calster *et al.*, BMJ, 2014;doi: https://doi.org/10.1136/bmj.g5920).

The model uses a multinomial logistic regression approach that combines several clinical and ultrasound variables, including patient age, type of centre, serum CA-125 level (if available), lesion size, size of the solid component, number of locules, number of papillary projections, acoustic shadows and ascites. Each variable contributes to the final result through predefined model coefficients (weights).

Users should interpret the results together with the full clinical context.

Maintenance

No maintenance is required.

For both security and technical performance reasons (including speed, user experience, and accurate risk visualization) it is strongly recommended to use the latest available version of the operating system and browser on the device running the ADNEX2 application.

Warning and precautions

WARNING – Intended Use and Clinical Decision-Making	ADNEX2 provides probabilistic risk estimates intended to support clinical assessment of adnexal masses. The output is informative in nature and must be interpreted in the context of the full clinical picture, established guidelines, and clinician expertise. ADNEX2 does not recommend, determine, or automate clinical management actions, and does not replace clinical judgment. Clinical decisions remain the responsibility of the healthcare professional.
WARNING – Use Only Within Intended Population	Use outside the intended population (i.e. in patients under 18 years of age or pregnant patients) may result in outputs that are not clinically reliable within the intended use.
WARNING – Use by Trained Users Only	ADNEX2 is intended for use only by IOTA-trained specialist healthcare professionals who have completed appropriate training and hold a valid "IOTA ovarian classification training and certification" certificate. Access to the application is restricted by login and will not be granted to non-certified users. Incorrect interpretation by untrained or insufficiently trained users may result in misunderstanding of the model output and its clinical relevance
CAUTION – Correct Data Entry Required	Incorrect, incomplete, or inconsistent data entry may result in inaccurate risk estimates, which may affect how the output is interpreted within the broader clinical assessment

CAUTION – Input Validity and Applicability	Users must not bypass or ignore system checks or warnings. Doing so may reduce the reliability of the output and its appropriate use within the clinical assessment.
CAUTION – Use in Case of System Unavailability	If ADNEX2 is unavailable due to technical issues, patient management must not be delayed. An alternative clinically accepted assessment approach should be used such as IOTA Simple Rules with expert evaluation of adnexal masses when the rules cannot be applied. Information on IOTA Simple Rules and how to use them can be found on the Gynaia learning management system and in the open access publication by Timmerman *et al.* Ultrasound in Obstetrics & Gynecology, 2008, (https://doi.org/10.1002/uog.5365)..
CAUTION – Calibration and Generalizability	Predicted risks may not fully reflect local patient populations and should be interpreted in the context of local clinical experience and disease prevalence.
NOTICE – Instructions for Use Availability	Instructions for Use are provided electronically (eIFU). Paper copies are available upon request and are considered uncontrolled documents. Users are responsible for ensuring they consult the most current version before use.Failure to consult the Instructions for Use may increase the risk of incorrect interpretation or use.

Residual Risks - Information for Safety

Despite implementation of risk control measures in accordance with ISO 14971, residual risks remain due to the inherent statistical nature of predictive models. These residual risks cannot be eliminated without adversely affecting the benefit–risk profile of the device:

1.Overestimation of probabilities

ADNEX2 may overestimate the probability of malignancy in a benign adnexal mass.

Potential impact

If given disproportionate weight within the clinical assessment, this may contribute to unnecessary further diagnostic procedures, referral, or intervention.

Mitigation/Safe use:

- Interpret outputs within the full clinical context
- Consider alternative imaging strategies, tumour markers, and patient history

Apply specialist clinical judgment and follow applicable guidelines

2.Underestimation of probabilities

ADNEX2 may underestimate the probability of malignancy.

Potential impact

If given disproportionate weight, this may contribute to delayed further assessment or referral.

Mitigation / Safe use

- Do not rely on ADNEX2 as a stand-alone assessment
- Maintain appropriate follow-up and surveillance
- Follow clinical guidelines and MDT pathways

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3.Misinterpretation of probabilistic output

Probability outputs and subclassification results may be misunderstood.

Potential impact

Incorrect weighting within clinical decision-making

Mitigation/ Safe Use:

- Ensure appropriate training (IOTA certification)
- Interpret absolute vs relative risk correctly
- Use ADNEX2 outputs as one component of the overall clinical assessment and ensure that all input parameters are correctly understood and entered.

4.Population variability

Model performance may vary across clinical settings.

Potential impact

Predicted risks may not fully reflect local populations

Mitigation/ Safe Use:

- Interpret results in context of local prevalence
- Combine with clinical expertise

Data Security – User Responsibilities

Area	Physician Responsibility (Duty of Care)
Active Use & Logout	NEVER leave the application logged in and unattended. After every consultation or period of use, you must securely log out (or rely on the system's *immediate* automatic log-off feature).
Screen Privacy (Public View)	ENSURE Visual Privacy while using the application. Position your screen (PC, smartphone, tablet) so that it cannot be viewed by unauthorized persons**.**
Device Security	Your device must be secured with a strong PIN, password, or biometrics (fingerprint/face ID). Ensure the device's operating system and the application are updated **t**o the latest security versions.
Data Transmission	Only use the application over trusted, encrypted networks (e.g., your clinic's secured Wi-Fi or a trusted VPN).
Personal Data Export	Do not download or take screenshots of Protected Health Information (PHI) to your personal device's local storage unless absolutely necessary and immediately secure or delete the file after use**.**

DISCLAIMER

The manufacturer is not responsible for security breaches, data loss, or system compromise resulting from the user's failure to adhere to the security and data protection responsibilities outlined in this IFU, including but not limited to, the use of weak passwords, the use of unapproved operating environments, or failure to apply recommended software updates.

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Incidents and Support

For technical support or questions contact Gynaia support team via **support@gynaia.com**.

Serious incidents should be reported immediately to Gynaia and to the competent authority of the Member State in which the user/patient is established or the incident took place.

Document Version

Version	Issue date	Description of modification
1.0	27 October 2025	New document
1.1	28 November 2025	Updated version information because of new patch version to expose ADNEX base relative risk scores.
2.0	18 December 2025	Added clinical Benefits and NB number to CE label. Added Data security section and disclaimer
3.0	25 April 2026	Update Clinical Benefits and separated residual risks from the warnings – Information for Safety Table
4.0	30 June 2026	Update address UK-REP, Update Contraindications Added explanatory section on "*Variable Influence – How the Output is Generated*" and "*Performance Metrics and clinical validation*"
5.0	19 October 2026	Change of manufacturer address