

Ki-67 APP for IHC

Automated, Accurate and Objective

The Ki-67 APP from Visiopharm® is a part of the Oncotopix® Diagnostics product portfolio of CE-IVD labelled APPs. Correct assessment of the Ki-67 proliferative activity is crucial for proper patient management. Ki-67 evaluation in combination with HER2, ER and PR IHC results act as surrogate markers for gene expression subtypes and is used in place of the more expensive gene expression tests. Therefore high accuracy and alignment of IHC results are highly important (ref. 1-3).

The American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) and others have issued guidelines for Ki-67 counting, which are used worldwide. Despite efforts to standardize assay techniques and interpretation, scoring remains time-consuming and subjective with inherent inter- and intra-observer variability (ref. 4).

At Karolinska University Hospital the Ki-67 APP, in combination with the Visiopharm Image Analysis system, was evaluated in three cohorts on 436 breast



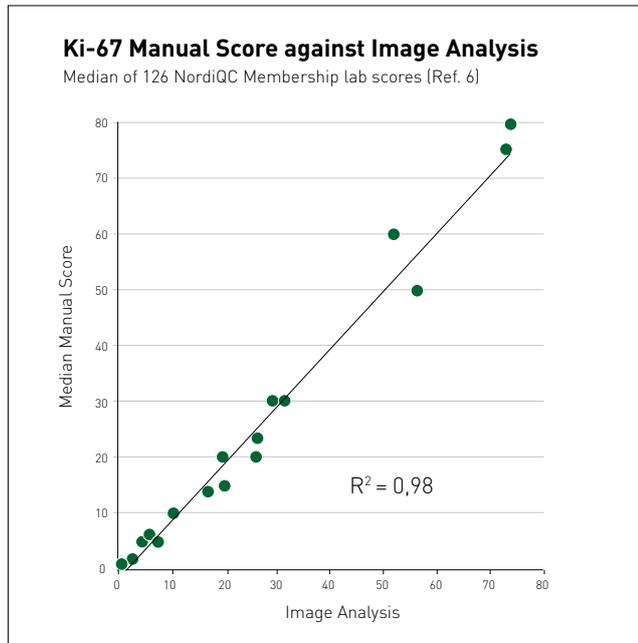
Apply Ki-67 APP, Breast Cancer to:

- **Save time** by eliminating manual counting
- **Reduce** inter- and intra-observer variability with computerized counting
- **Be more efficient** with a CE-IVD validated tool to simply review and sign-off
- **Feel certain** the analysis is performed according to the most used guidelines

cancer specimens with 28 years of follow up and their conclusion was that in most aspects the Ki-67 APP is a superior alternative to manual biomarker scoring (ref. 5). It also has the potential to reduce time consumption for pathologists, as many of the steps in the workflow are either automated or simple enough for a technician to manage without the presence of

a qualified pathologist. The pathologist only needs to review and sign off.

At NordiQC in Ålborg they compared the results of image analysis done by the Ki-67 APP on 20 samples already evaluated manually by 126 member laboratories and found a strong correlation between the APP and the median of the manual scores of $R^2 = 0.98$ (ref. 6).



Clinical Application and Performance Data

With the Ki-67 APP you get a solution that considerably cuts down manual time spent and produces a reliable result building on current guidelines.

Within the software the image analysis is performed with manually outlined regions of interest (ROI) defining the suitable areas for analysis, alternatively with the VirtualDoubleStaining™ feature enabled definition of ROIs can be automated and parallel analysis of a IHC tumor marker such as a Pancytokeratin can be applied to distinguish tumor cells from stromal and other non-tumor cells. Ki-67 is selectively measured within the ROI and results are expressed as a positive ratio.

References

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- Guiu S, Michiels S, Andre F et al. Molecular subclasses of breast cancer: how do we define them? The IMPAKT 2012 Working Group Statement. Ann Oncol 2012 23:2997-3006.
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- Dowsett M, et al. Assessment of Ki67 in Breast Cancer: Recommendations from the International Ki67 in Breast Cancer Working Group. JNCI Journal of the National Cancer Institute. 2011;103(22):1656-1664.
- Stålhammar G., Fuentes Martinez N., Lippert M et al. Digital image analysis outperforms manual biomarker assessment in breast cancer. Mod Pathol. 2016 Feb 26.
- Røge R, et al. 1st NordiQC Conference, June 2013
- Package Insert for Visiopharm Ki-67 APP, Breast Cancer, 4th Edition 2016

All automated image analysis of whole slide digital images is done on scanned sections stained with a Ki-67 IHC stain from any of the major staining providers.

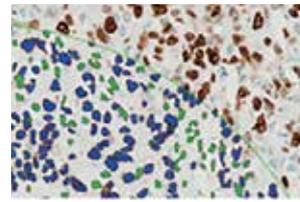


Figure 1.
Green dotted line marks part of a region of interest, scored for Ki-67 and CkMNF116. Green polygons constitute the Ki-67 proliferation index. Breast Cancer tissue.

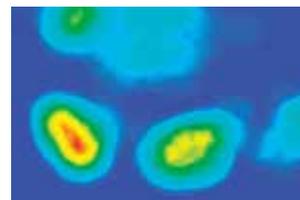


Figure 2.
Illustration of heat map function where the software has analyzed the digitized glass slide for tumor areas with highest concentration of cells stained by both the pancytokeratin (PCK) marker and Ki-67 (Ref. 5). Breast Cancer tissue.

Clinical Performance Data

Agreement [95% CI]	87.7% [83.1-91.5%] (ref. 7)
Slide Scanner	HAMAMATSU, GE/OMNYX, LECIA/APERIO
Stain Vendor	DAKO/Agilent, VENTANA/ ROCHE, LEICA



The Ki-67 APP for IHC provides an objective supplement to manual scoring without compromising the diagnostic sensitivity and specificity.

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