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APPENDIX S1.

Explanation to FotoFinder© ATBM master Moleanalyzer pro® system metrics.

Shape asymmetry: Calculation of the shape asymmetry index (SAI) is done by adding the halves of the mole mask together and dividing the area of the mole intersection by the area of the mole union mask (see Fig. S1.1.).

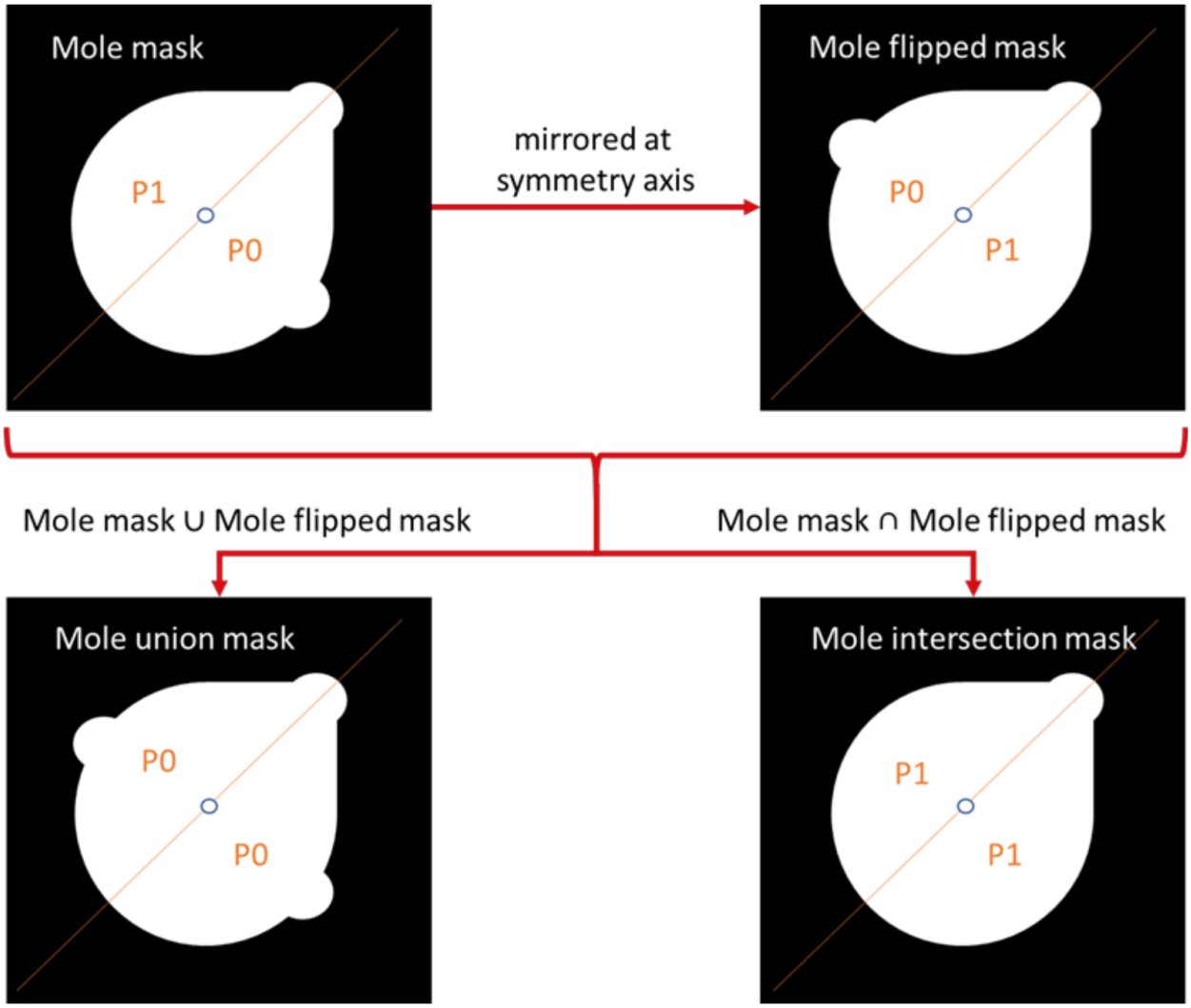

Fig. S2.1. Definition of mole union mask & mole intersection mask

Formula for calculating the SAI:

Shape asymmetry index = (Mole union mask area - mole intersecion mask area) / Mole union mask area

The SAI can range from 0 to 1. A score close to 1 means the mole is highly asymmetrical and the two halves differ considerably. A score of 0 means the mole is perfectly symmetrical.

Colour asymmetry: Calculation of the colour asymmetry index (CAI) is done by using the mole's mean grey value. For that the mole's grey value representation image is used.

In order to define the grey value representation the mean greyness for each of the two halves of the mole is calculated by the FotoFinder system (values range between 0 (black) and 255 (white)). Thereafter, the mean values are calculated for each mole half mask using the arithmetic mean of grey values for all pixels in the respective half:

mean greyness of mask half = sum of pixel grey values of mask half / number of pixels in respective mask half
The CAI is then calculated using the formula:
Colour asymmetry index = min (1, ((mean greyness P1 - mean greyness P0) / 10.5))
CAI values range between 0 and 1. A CAI close to 1 means the colour of the two mole halves strongly differ. A CAI of 0 means that the colour is completely identical all over the mole.

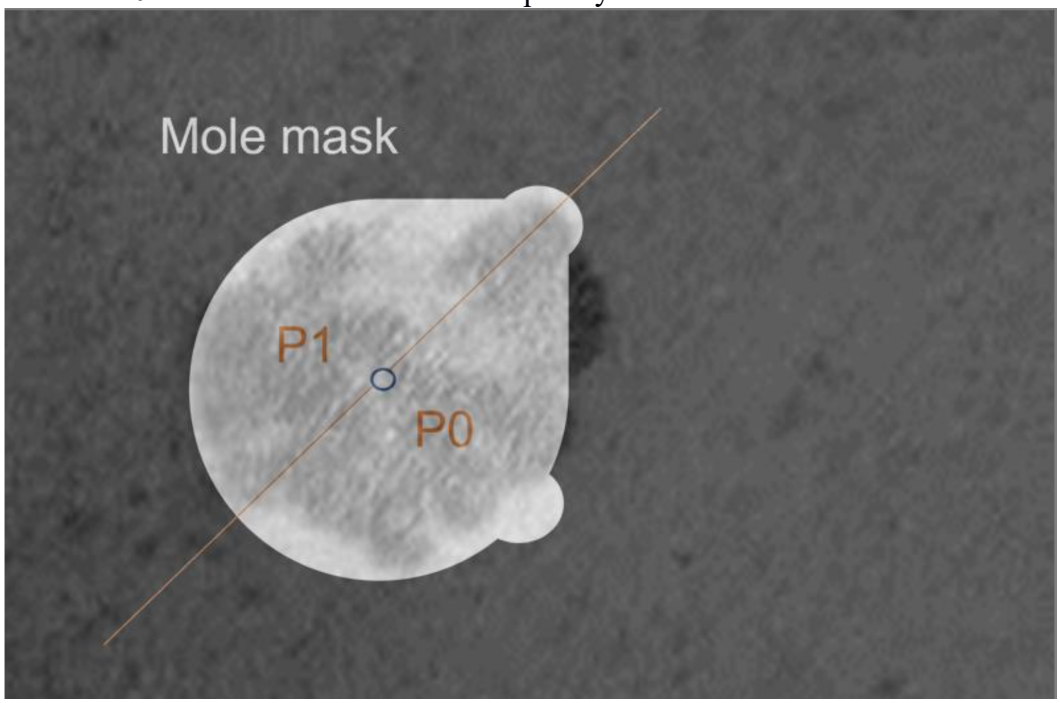

Fig. S2.2. Calculating the colour asymmetry

Ellipseness score: The ellipseness score is calculated by firstly calculating the minimum ellipse encompassing the whole mole mask. The ellipseness score is then calculated as the area of the mole divided by the area of the encompassing ellipse:
Ellipseness score = mole mask area / ellipse area
The ellipseness score ranges between 0 and 1.
The closer the score is to 1 the more regular the mole's borders are and the more elliptic the mole is. The closer the score is to 0 the more irregular the mole's borders are.

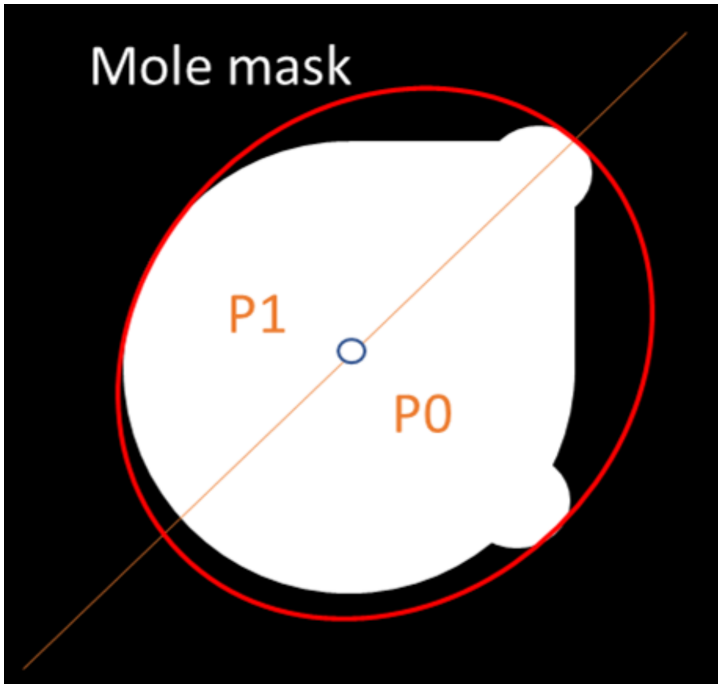

Fig. S2.3. Mole mask & encompassing ellipse

Border sharpness: The border sharpness metric describes how well a mole can be differentiated from the perilesional skin. It is determined using the mole's grey value representation as shown in Figure S1.4. Firstly, the mole mask is determined (red area). Secondly, the original mask is enlarged pixel by pixel until a change in grey values is detected or until a designated maximum distance to the original mask is reached. This new mole border marks the outer boundary (light grey). Mirroring the second step, the original red mole mask is decreased until either a sudden change in grey values is detected or until a designated maximum of negative distance to the original mask is reached. This new mole border marks the inner boundary (dark grey). Then the mean distance between the outer and inner mole boundary is calculated for each quarter of the mole. The mean distance (in mm) is defined as the border sharpness per ¼ of the mole border. Lastly, the four values per mole for each ¼ of the mole border are added and then divided by four in order to determine the mole's border sharpness value.

The border sharpness value gives an estimation of the area in which the mole transitions into the perilesional skin. The smaller the value, the more clearly distinguishable the mole is from the surrounding skin. The higher the value, the more difficult it is to determine where the mole starts or ends exactly.

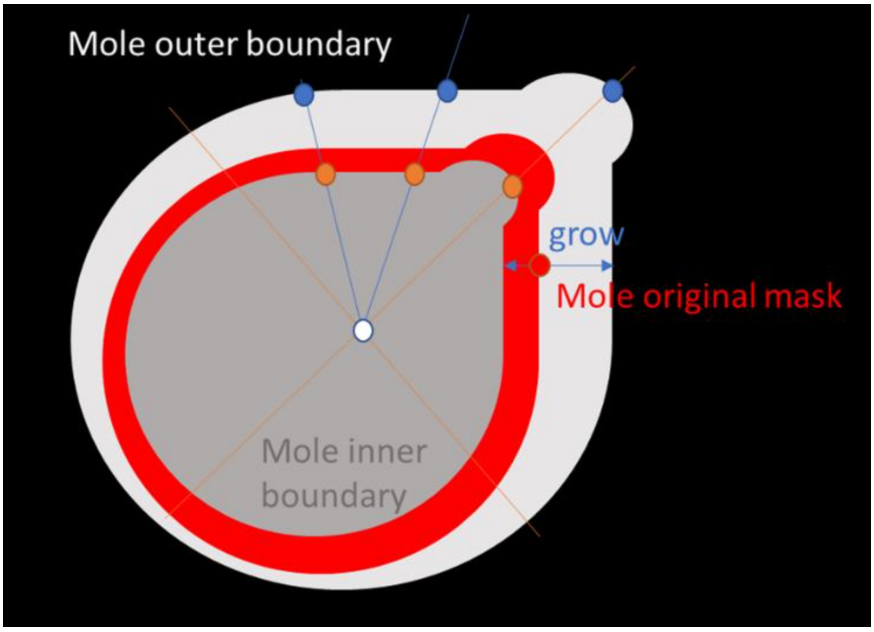

Fig. S2.4. Border sharpness evaluation

APPENDIX S2. Statistical analysis.
Analysed localizations and metrics
Localizations: abdomen, back, chest, head, lower extremity, upper extremity

Metrics:
- Area (in mm2) (sum of 4 sections; positive real number)
- Diameter (in mm): positive real number
- Number of colours; integer number
- Number of dots and globules; integer number
- Colour asymmetry (continuous real number from 0 to 1)
- Shape asymmetry (continuous real number from 0 to 1)
- Ellipseness (continuous real number from 0 to 1)
- Border sharpness (mean of 4 sections; positive real number)

Further specifications on analysis to the objectives
Pregnancy-related and postpartum modification in the aspect of MN
Analysis on MN changes in their aspect postpartum as compared to before and during pregnancy was performed by comparing mean MN aspect at all three time points: before, during and after pregnancy. Mean aspect per patient was used as the dependent variable, pregnancy status (before/during/after) as the explanatory factor and patient ID as a random variable (random intercepts). We further included an interaction between pregnancy phase ('before'/'during'/'after') and patient ID to estimate random coefficients. Age and BMI were included as covariates. To investigate whether the MN aspect during pregnancy and postpartum differ from the MN aspect before pregnancy, we used 'before pregnancy' as the reference level. To investigate whether MN aspect postpartum differs from MN aspect during pregnancy, we used 'postpartum' as the reference level.

Change in MN aspects between pregnant and non-pregnant women
We investigated whether melanocytic nevi change in their aspect in pregnant women as compared to non-pregnant women during the same time window using linear mixed-effect models assuming normal distribution of the error, with the mean aspect metrics (see list in Section 4.1.1) per patient at both time points as the dependent variable, pregnancy status, screening time and the interaction between pregnancy status and

screening time as the explanatory fixed factors, age and BMI as covariates and the patient ID as a random factor to account for the non-independence of the repeated measures over time within a given patient.
The following endpoints were log-transformed to comply with the modelling assumptions of normality: diameter, area, number of dots and globules, colour asymmetry and border sharpness.
To allow comparisons of the strength of the association between pregnancy and change in nevi aspect across all endpoints describing a nevus' aspect, we computed standardised effect sizes in the form of Cohen's d along with their 95% confidence intervals. Taking non-pregnant women as the reference group, we transformed the estimate for the pregnant women as estimated by the interaction between screening time and pregnancy status into Cohen's d.
By convention, and as suggested by Cohen, d 0.20 indicates very small effect size; 0.20 d 0.50 indicates small effect size; 0.50 d 0.8 indicates medium effect size; 0.80 d 1.2 indicates large effect size; 1.20 d 2 indicates very large effect size; d 2 indicates huge effect size.

Methods used to check assumptions of the main methods

Assumptions of linearity and normality of the error were validated via standard procedures based on visual inspection of the model residuals (residuals vs. predicted plots; normal QQ-plots).

Statement on p-values

P-values are a continuous measure of how surprising the results are if the null-hypothesis were true (e.g. pregnant and non-pregnant women do not differ in the alteration of MN). Results in this study are interpreted using p-values (the strength of the statistical evidence to reject the null hypothesis) together with effect sizes and 95% confidence intervals (the uncertainty around the point estimate).
Furthermore, since we explored whether nevus localization affects how nevi may change during pregnancy using separate models for each nevus localization, the risk of type I error (false positive) is greatly increased. Owing to the exploratory nature of the study, we did not correct for the multiplicity of tests. Nevertheless, no conclusion should be drawn based on any arbitrary threshold and p-values should be regarded very cautiously.