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A novel imaging technique as an adjunct to the *in vivo* diagnosis of nonmelanoma skin cancer

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Conflicts of interest
None declared.

Summary

Background Spectrophotometric intracutaneous analysis (SIAscopy) is a light-based imaging system capable of producing rapid images of melanin, blood and collagen of the skin. Although the SIAscope has been investigated for melanoma diagnosis, no formal study has been conducted to determine its use in the diagnosis of nonmelanoma skin cancer (NMSC).

Objectives A prospective study was conducted to investigate the potential for the SIAscope to diagnose NMSC.

Methods In total, 302 consecutive patients were recruited into the study, 363 lesions being scanned. Logistic regression analysis was used to construct a predictive model for NMSC diagnosis and receiver–operator characteristic curves were used to assess overall accuracy of the model.

Results A sensitivity of 98·0%, specificity of 95·7% and overall accuracy of 98·2% was found for NMSC diagnosis by the SIAscope model.

Conclusions Results suggest that the SIAscope may be a useful adjunct in the diagnosis of NMSC.

The development of spectrophotometric intracutaneous analysis (SIAscopy) in the past decade has led to the production of a portable system capable of rapid skin lesion imaging.[1,2] A small hand-held light-emitting unit, attached to a laptop computer, is gently apposed to a skin lesion; the light emitted from the unit encompasses the visible light and infrared spectrum (400–1000 nm) and is absorbed or reflected by the skin components, known as chromophores, up to the depth of the papillary dermis. Any remitted light is received by the unit to be processed by the computer software. Known models of light interaction with human skin allow the application of complex mathematical calculations, producing parametric maps of the skin lesion within a few seconds, illustrating the melanin, blood and collagen in the area of concern (Fig. 1), together with a dermatoscopic image.

The ability for the SIAscope to aid in the diagnosis of melanoma has been extensively researched in recent years, with notable advances being made by Moncrieff *et al.*[2] and Dolianitis and Kelly.[3] Sensitivities of 82·7–91% and specificities of 80–82% in the various studies are encouraging and imply a possible role for spectrophotometry in melanoma management. The use of the SIAscope in nonmelanoma skin cancer (NMSC) diagnosis has not been formally investigated, however, and a prospective study was therefore conducted to assess the sensitivity, specificity and diagnostic accuracy of the SIAscope for these lesions.

Materials and methods

Regional Ethics Committee approval was granted for this study (REC ref. 04/Q0101/101). Patients were recruited from the Departments of Plastic Surgery and Dermatology at the Norfolk and Norwich University Hospital, Norwich. The patients had been referred by their general practitioner (GP) to these departments for assessment of their skin lesions, on grounds of suspicion of tumour or of the lesion being physically or cosmetically irritating. All patients were examined by a specialist consultant and were either discharged, managed nonsurgically, or underwent excision or biopsy of the lesion under local anaesthesia. Only the latter group was considered eligible for this study, as a histopathological diagnosis made by an expert in pathology was to be used for this study as the 'gold standard' diagnosis with which to compare the SIAscope images.

Patients under 16 years of age were excluded from the study. The number of paediatric lesions excised at the units is few in comparison with those excised from adults, and they are rarely found to be tumours. Children are often extremely anxious of coming to hospital, and it was not felt appropriate

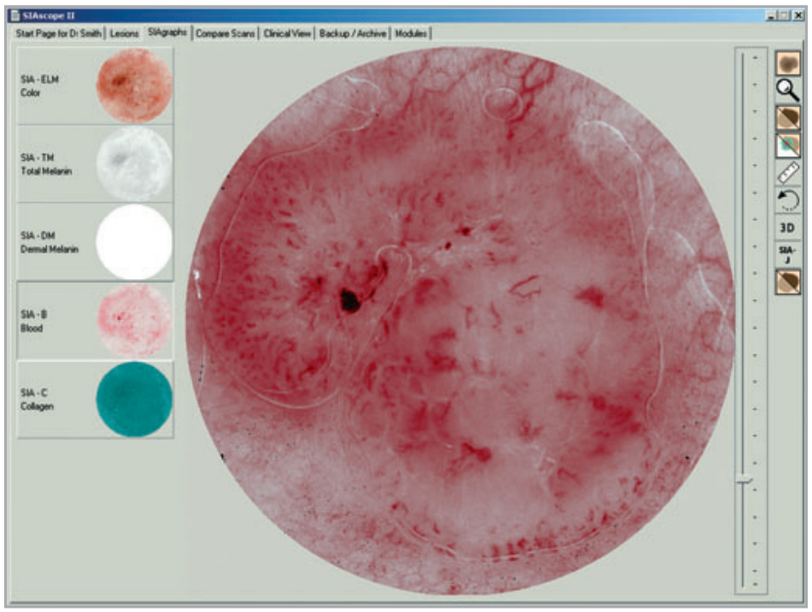

Fig 1. The SIAgraphs are displayed on a laptop computer. The images on the left of the screen show the dermatoscopic image, dermal melanin, total melanin, blood and collagen for the area of concern. Clicking on an image opens the image in the main window, in this case the blood image for a basal cell carcinoma.

to run the risk of increasing anxiety by the use of a 'skin scanner' for the purposes of gaining little extra information.

Following consent, patients had SIAgraphs taken of their lesion prior to surgery. Throughout the study, a single SIAscope II (AstronClinica, Cambridge, U.K.), operated by a single researcher (H.T.), was used to capture and view SIAgraph images of the skin lesions. Lesions located near to the eye, on the ear, or on the nasal bridge were excluded from the study as the 12-mm diameter flat-screened handset of the SIAscope poorly accommodates such curved surfaces, resulting in excess light leakage and unreadable SIAgraphs. Similarly, lesions with thick adherent crust were not scanned as light penetration through the crust is minimal and images therefore contain little useful information. A Canon G5 digital camera, fitted with a polarizing filter to reduce surface light-scattering artefacts, was used for clinical image capture.

In practice, the SIAscope will be used by clinicians with varying dermatological experience; in considering the recording of clinical data, therefore, it was not felt suitable to record the specialists' clinical examination of the lesion for model-building purposes. These features would most probably be subjective (for example, does the lesion feel firm to touch?) and may vary from clinician to clinician, the accuracy of diagnosis varying with specialist experience. The data recorded were therefore of the history of the patient and lesion, and objective clinical measures only (Table 1). Such data can be gathered regardless of the experience of the clinician and are therefore applicable across all grades of medical staff. It should be borne in mind, however, that even these clinical data can be subjective, although to a lesser degree. An example may of a patient referring to a symptom arising from a lesion as 'an itch' while another patient interprets similar stimuli as 'pain'. This information was transferred to an Excel (Microsoft Windows XP) spreadsheet, together with final histological diagnosis. The clinical data were categorized (Table 1) to allow for detailed data exploration. During the clinical data gathering and scanning, the investigator was kept blinded to any clinical diagnoses made of the lesion.

A pilot study of 20 lesions had been performed to hypothesize which SIA features may be indicative of NMSC. The presence of branched vessels within the lesion, flare or focal lesion paleness implied a possible diagnosis of NMSC. Collagen disruption had uncertain value in this small pilot study. A summary description of the four features is given in Table 2, with SIAgraph examples given in Figure 2. Following the collection of all data for the study, all SIAgraphs were examined for presence or absence of the four SIA features by the primary researcher (H.T.). To assess intra-rater reliability, a sample of 100 images was randomly drawn from the data and re-examined by the primary researcher 2 weeks after initial analysis. The time interval was felt necessary to avoid any possible bias due to memory of the image and associated features. A plastic surgery nurse practitioner with no experience of SIAscopy was then recruited to provide inter-rater reliability scores for scan analysis; a tutorial of 30 min was given to describe the methods of feature analysis before the nurse was shown the same 100 images. No external input was permitted during assessment of inter-rater or intra-rater reliability and both investigators were blinded to the histological diagnosis and previous SIAgraph analysis results. The results were used to produce kappa statistics to assess the inter-rater and intra-rater strengths of agreement.[4]

Table 1 The clinical data gathered, questions asked of the patient and categories used for logistic regression

Clinical feature	Question asked of patient	Subcategories tested for logistic regression
Age	How old are you?	< 20, > 20, > 30, > 40, > 50, > 60, > 75 years
Sex	Is the patient male or female?	Male: yes/no
Skin type (I–IV)	How easily do you tan or burn?	Skin type I: yes/no
Solar history	Have you ever spent a period of time living in a hot country, worked outdoors or often sunbathed or sunburned?	Sun exposure: yes/no
Previous NMSC history	Have you ever had a previous basal or squamous cell skin cancer?	Previous BCC: yes/no Previous SCC: yes/no
Diameter of lesion	Size of lesion measured in mm	< 5, ≥ 5, ≥ 7, ≥ 10, ≥ 15 mm
Recent growth	Has the lesion grown in size in the last 6 months?	Recent growth: yes/no
Symptoms	Does the lesion itch, bleed, crust or cause pain?	Itch: yes/no bleeding: yes/no crust: yes/no pain: yes/no

NMSC, nonmelanoma skin cancer; BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

Table 2 The four proposed SIA features and their descriptions

Histopathology	SIAscopy features	Feature name	SIAgraph
Microcirculatory changes: angiogenesis	Wide, branched vessels coursing towards/into the lesion	Branched vessels	Blood
Microcirculatory changes: ischaemia or tumour regression	Large focal area of absent blood within the lesion	Paleness	Blood
Microcirculatory changes: angiogenesis? inflammation?	Uniform dark red appearance throughout at least 2/3 of the lesion	Flare	Blood
Collagen disturbance, possible invasion through basement membrane	Paler or darker collagen areas where invasion is occurring	Collagen disturbance	Collagen

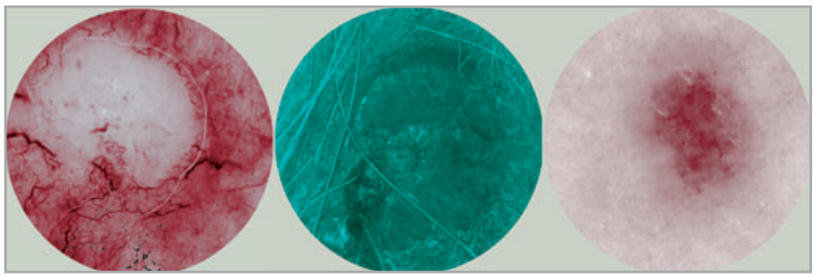

Fig 2. The appearances of the four proposed SIA features. The left image shows a blood image of a nodular basal cell carcinoma (BCC) with a large area of 'focal paleness' and numerous 'branched vessels' coursing into the lesion. The centre image shows 'collagen disturbance' in an infiltrative BCC image, and the right image shows vascular 'flare' (smudged red appearance) in a superficial BCC.

The clinical data and SIA features were separately analysed with logistic regression (SPSS version 11.5; SPSS Inc., Chicago, IL, U.S.A.) using forced entry techniques. The models produced were checked for consistency using both forwards and backwards stepwise techniques. The cut-off value for the predictor coefficients during model building was taken as $P < 0{\cdot}1$, and that for the final model was taken as $P < 0{\cdot}05$. Once the 'SIA' and 'clinical data' diagnostic models had been produced, receiver–operator characteristic (ROC) curves were constructed to compare the accuracy of the two models.[5] The clinical and SIA predictors were then grouped together to produce a combined model; the two separate SIA and clinical models could not simply be combined directly, however, as the models had been produced independently of each other. One model may have included or excluded predictors that would otherwise be significant or insignificant when interacting with predictors from the other model. All SIA and clinical predictors were therefore allowed to compete freely in a

forced entry analysis, again being checked for consistency with forwards and backwards stepwise techniques, the model-building cut-off being taken as $P < 0{\cdot}1$ and final cut-off being $P < 0{\cdot}05$ for predictor coefficients.

Results

From May 2004 to March 2005, SIAscope scans were taken of 412 lesions and corresponding clinical data collected. Of these, 10 had incomplete data forms and 14 had no histological diagnosis at the time of writing, and 25 scans were corrupted, mostly due to light leakage. In total, 49 (11·9%) of the scans were unsuitable for inclusion in the study. The incidence of corrupted images became less frequent in the latter stages of the study, perhaps indicating that experience may play a part in gaining readable scans, including the recognition of surfaces that are not readily amenable to scanning (e.g. the ear). The model-building dataset therefore comprised 363 consecutively gained images of lesions from 302 patients (212 women, 90 men; age range: 16–91 years), and included 152 NMSCs of which three were squamous cell carcinomas (SCCs). A more comprehensive list of histopathological diagnoses is given in Table 3.

The kappa scores for the SIAscope (Table 4) revealed encouraging inter-rater and intra-rater reliability for the features of branched vessels and focal paleness, implying that these features may be easily recognized, even after limited training. Although flare had good intra-rater reliability, the results were less satisfactory for inter-rater reliability. Collagen disturbance fared relatively poorly on both forms of reliability. The results for flare and collagen disturbance were unsurprising as the recognition of these features is more subjective than the other two SIA predictors, although further future research may help to refine the definition of these features and improve their kappa scores. Despite the poor reliability for collagen, it was decided not to exclude this predictor from the model building as it may have still proven to be a valuable contributor to the diagnostic model.

Univariate analysis was performed on the SIA and clinical predictors. No single predictor produced results accurate enough to be considered as clinically useful on its own. Logistic regression analysis of the four SIA features produced a diagnostic model consisting of the features 'branched vessels', 'paleness' and 'flare', with sensitivity of 98·0% (95% confidence interval, CI 94·3–99·2) and specificity of 95·7% (95% CI 92·1–97·1). The clinical data produced a diagnostic model which included the features 'age > 60 years', 'skin type I', 'previous history of basal cell carcinoma (BCC)', 'previous sun exposure', 'recent increase in lesion size' and 'history of the lesion bleeding' or 'crusting'. The other recorded clinical features, including the objective 'diameter of lesion', were found to have poor significance values in this study and therefore to be unsuitable for inclusion in the diagnostic model. The sensitivity for the 'clinical diagnosis' model was 77·6% (95% CI 70·2–84·0) and specificity 84·8% (95% CI 79·3–89·4).

The SPSS software calculates the probabilities for a diagnosis given the presence or absence of features, and then uses these results to construct ROC curves (Fig. 3) and to calculate the areas under the respective curves. From Table 5 it can be seen

Table 3 Histopathological composition of the dataset

Lesion	Number	Percentage
Basal cell carcinoma	149	41·0
Squamous cell carcinoma	3	0·8
Melanoma	6	1·7
Melanocytic naevus	62	17·1
Dermatofibroma	19	5·2
Actinic keratosis	11	3·0
Intradermal naevus	33	9·1
Seborrhoeic keratosis	39	10·8
Other	41	11·3
Total	363	100

Table 4 Agreement scores for intra-observer and inter-observer reliabilities

Feature	Agreement	SEM	P-value	95% CI
Intra-observer reliability				
BV	0·979	0·021	< 0·001	0·938–1·00
Paleness	0·836	0·055	< 0·001	0·728–0·944
Flare	0·847	0·106	< 0·001	0·640–1·00
Collagen	0·622	0·080	< 0·001	0·470–0·780
Inter-observer reliability				
BV	0·979	0·021	< 0·001	0·938–1·00
Paleness	0·717	0·070	< 0·001	0·580–0·854
Flare	0·525	0·182	< 0·001	0·170–0·882
Collagen	0·525	0·086	< 0·001	0·356–0·694

CI, confidence interval; BV, branched vessels.

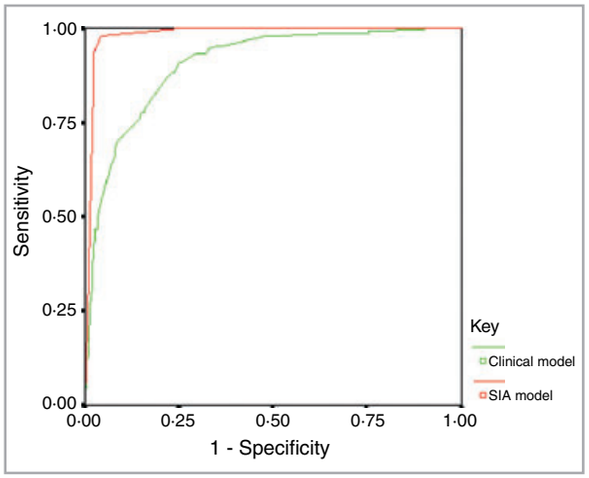

Fig 3. Receiver–operator characteristic curves for the 'SIA' and 'clinical' diagnostic models. The closer a curve is to the upper left corner, the closer it is to perfect accuracy.

Table 5 Accuracy of the 'SIA' and 'Clinical data' diagnostic methods, as determined by receiver–operator characteristic curve generation

Model	Area under curve	P-value	95% CI
SIA	0·982	< 0·001	96·8–99·7
Clinical	0·905	< 0·001	87·4–93·6

CI, confidence interval.

that the area under the SIA curve is 0·982, which is significantly ($P < 0·001$) different from 0·5 (a value of 0·5 indicates that the test is no better than chance alone). Of note is the finding that the 95% CIs for the two curves do not overlap, the SIA model producing values more accurate than the clinical model.

The combining of all the SIA and clinical predictors resulted in a combined model consisting of three features only, these three being the same predictors as for the SIA model. No clinical data were found to add significantly to the diagnostic accuracy of the SIA model.

Discussion

Skin cancer is the commonest form of cancer in humans, with an incidence of over 600 000 cases per year in the U.S.A. and up to 2% of the population per year in Australia.[6] In 2001 over 62 000 new skin cancer cases were reported in the U.K. alone,[7] although under-reporting means that even this figure is likely to be grossly underestimated. The recognition that ultraviolet radiation plays a major role in skin cancer development[6,8] has led to a number of public health campaigns targeted at reducing public exposure to excess sunlight. Despite these campaigns several factors act to thwart such efforts and include the continued social desire for tanning, popularity and ease of travel to high solar risk areas (e.g. Australia, Africa), and a possible increase in terrestrial solar radiation as a consequence of a depleted ozone layer. These, coupled with an ever-ageing population, seem to indicate that the incidence of skin cancer may continue to rise.

Such increasing incidence of skin cancer, mounting pressures arising from a health-conscious and aware public, and tighter restrictions on waiting times call for efficient diagnoses at primary and specialist healthcare levels. The diagnostic accuracy by GPs is, however, reported as relatively poor,[9,10] and although improvements are found in the expert setting difficulties in diagnosis still exist. In the Nambour study, BCC diagnosis by dermatologists produced a sensitivity of 98%, but a specificity of only 45% and an overall accuracy of 59%.[11] In the settings of a renal transplant clinic, the BCC diagnosis results for dermatologists were 66·6%, 85·6% and 40% for the sensitivity, specificity and overall accuracy, respectively.[12]

Although various investigative techniques have been described to aid NMSC diagnosis including fine needle aspiration cytology[13] and ultrasound,[14] they are generally specialist procedures beyond the practical scope of a busy primary care or hospital outpatient setting. SIAscopy, however, has been shown to provide a simple, rapid and practical aid to pigmented lesion diagnosis.[1–3] Images of the melanin, blood and collagen of the lesion, together with a dermatoscopic image, are displayed on the computer screen, the entire scan/image process being completed within approximately 10 s. By examining the images, the clinician is aided in making a diagnosis based on features being present or absent in the scans.

A previous pilot study by our group had investigated the potential for the SIAscope in diagnosing NMSC, with results suggesting that the presence of branched vessels, focal paleness, vascular flare or collagen changes may indicate the presence of NMSC.[15] The present study was therefore performed to assess NMSC diagnosis by the SIAscope formally.

In the assessment of proposed SIA features, any feature should be easily recognized on SIAgraphs, not only by experienced users but also by the novice. The intra-rater reliability assesses the ability for a user to identify features consistently on two separate occasions (i.e. if the user thinks branched vessels are present in a lesion, does he or she still identify the feature at a later date in the same lesion?). Kappa statistics are used to calculate the agreement, whereby a score of '1' indicates perfect agreement and '0' indicates no agreement whatsoever, with various strengths of agreement being assigned according to scores.[4] For the researcher, intra-rater agreements for branched vessels, paleness and flare were classed as 'almost perfect'. The agreement for the feature 'collagen changes' was poorer, however, being classed as 'substantial strength' only, indicating that although the three former features were easily recognizable, collagen changes were less reliably recognized. Inter-rater reliability gave the agreement scores for a novice user, compared against the opinion of the researcher on his first examination of the 100 SIAgraphs; agreement for branched vessels was similarly close to '1', and the agreement for focal paleness was 'substantial'. Flare and collagen changes were less reliably identified, however, with poorer agreement scores. The inclusion of either of these latter two features in a diagnostic model would therefore call for caution due to their suggested poor inter-rater reliability. The 95% CIs for these scores, however, suggest that the true value for these agreements could in fact be greater; this may be explored with larger studies.

The comparison of the ROC curves for SIA and clinical diagnostic models indicates that the SIA model, when used alone, may be more accurate at NMSC diagnosis than by using objective clinical data alone. Indeed, when all the clinical and SIA data were combined to form a single diagnostic model, no clinical data were found to add significantly to the SIA model. The final model, comprising branched vessels, paleness and flare, produced a sensitivity of 98·0% (95% CI 94·3–99·2) and specificity of 95·7% (95% CI 92·1–97·1). The area under the ROC curve for the SIA model was 0·982: this is close to a 'perfect accuracy' score of 1. These results are certainly encouraging and would be consistent with known biological features of NMSC; characteristic telangiectasia can often

macroscopically be seen coursing over the surface of BCCs, and studies involving dermatoscopy,[16] video microscopy[17] and capillaroscopy[18] have served to support such findings. The SIAscope consistently identified such branched vessels in nearly all the NMSCs. Histological studies of the vascular pattern of BCCs have shown an increase in the vascular count at the periphery of BCCs[19] but not in the tumour bodies themselves.[20] This is consistent with the SIA findings of focal paleness in a large proportion of the NMSCs, but the finding was not unique to this group; benign lesions, notably the dermatofibromas, may also occasionally exhibit focal paleness on SIAgraphs. Although this may be due to a biological feature such as dermatofibromas having relatively avascular bodies, it may also be explained by the flat lens of the SIAscope exerting a pressure-induced blanching effect to the surface of the lesion. It may be argued that the pressure effect may also explain the paleness seen in NMSCs, although the inclusion of this feature in the diagnostic model would indicate that if paleness is indeed an artefact, then it is in fact a diagnostic artefact. The finding of vascular flare in the NMSCs was almost exclusive to the superficial BCCs and could indicate either an inflammatory response to the early tumour, or even the first stages of angiogenesis. The numbers of superficial BCCs in the study were small, however, and it cannot be assumed that flare is indeed unique to superficial BCCs. The exclusion of collagen changes from the final model was unsurprising as many benign lesions were found also to exhibit this feature which could be attributed to these lesions causing elongation of the rete ridges, which in turn is interpreted by the SIAscope as collagen changes. Conversely, a number of BCCs did not seem to have collagen changes, which may be due to their noninvasive nature, although this was not formally examined in this study. Refinement of the objective definition of collagen changes may prove to make this feature of significant use in a diagnostic model, either to diagnose NMSC or to differentiate invasive from noninvasive BCCs.

In summary, the model for NMSC diagnosis by the SIAscope included the features 'branched vessels', 'focal paleness' and 'flare' as indicators of NMSC presence. The presence of collagen changes could not, in this study, be included in the model. It should, however, be stressed that this study was conducted in a screened population. Not only had the patient population been screened by their GP, but also by the hospital specialist. Only those then being listed for excision biopsy were included in this study. The reason for this study design was that histological diagnosis was used as the gold standard with which to compare the SIAscope. Ideally, SIAgraphs should be performed in patients in a prescreened setting, although the current lack of a practical, noninvasive, gold standard tool with which to compare the SIAscope makes the design and performance of such study difficult.

It should also be noted that the accuracies found in this study refer to those of the SIA model only. This is produced and tested on the same data and, by definition, the model has been constructed specifically to fit this single population as best as possible. Testing the model on a different population may therefore be expected to produce less favourable results, and such a study is currently underway by our group to compare the SIAscope model with a clinician in diagnosing NMSC. Further studies in this field are also warranted to investigate the ability for the SIAscope to diagnose superficial BCCs and to ascertain if the SIAscope can differentiate BCCs from SCCs.

To conclude, in this study the SIAscope model displayed the ability, through the identification of branched vessels, paleness and flare, to diagnose NMSC with an overall accuracy of 98·2%, with no need for clinical data to be gathered. This is an encouraging result and may implicate the SIAscope to be an efficient, cost-effective adjunct in the diagnosis of NMSC. Further studies are warranted to test the model on separate populations and are currently underway by our group.

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