HGGA, Volume *3*

Supplemental information

Neural network classifiers for images of genetic conditions with cutaneous manifestations

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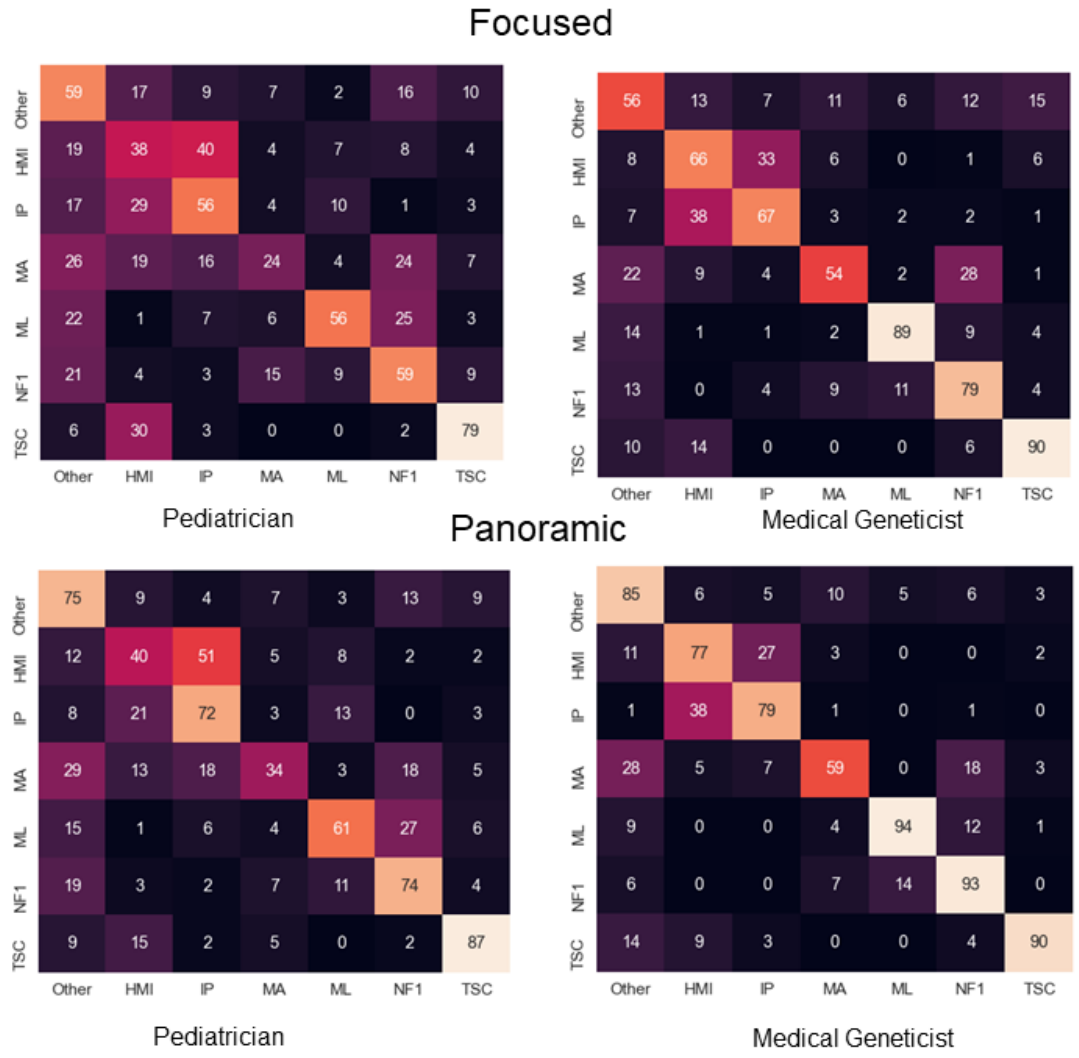
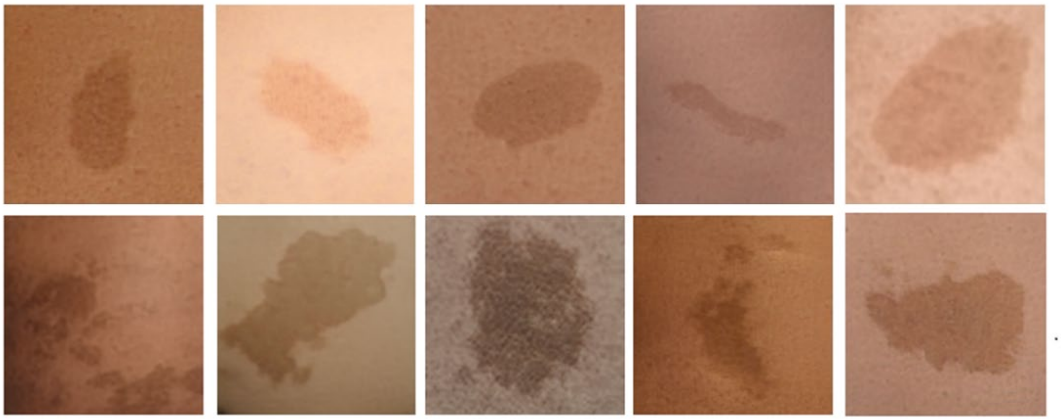
Supplemental material

Figure S1.



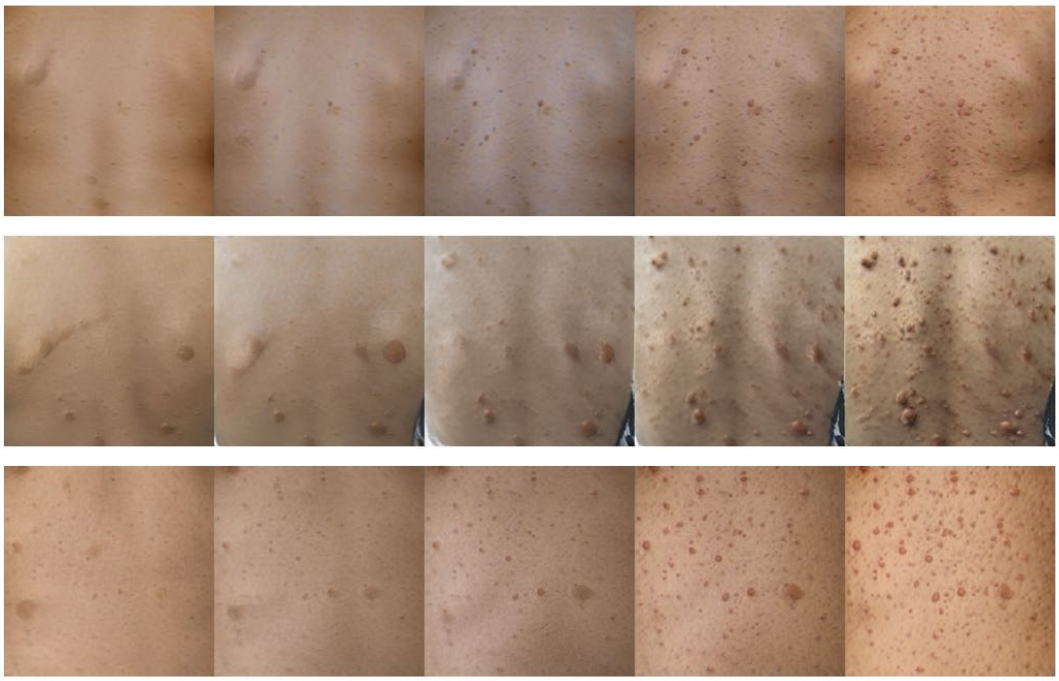
Confusion matrices. Confusion matrices for clinicians, showing absolute numbers (instead of percentages, as shown in Figure 3).

Figure S2.



Images generated via generative adversarial network. Top row: examples of generated images of café-au-lait macules (CALMs) in Neurofibromatosis type 1 (NF1). Bottom row: examples of generated images of CALMs in McCune-Albright syndrome (MA).

Figure S3.



Disease progression images generated via generative adversarial network. Examples of disease progression in Neurofibromatosis type 1 (NF1) generated via a generative adversarial network (GAN).

These images show the accumulation of other features beyond café-au-lait macules (CALMs) such as cutaneous neurofibromas. Other features, such as the scapulae in some images, are also generated, since training images included features such as these.

Table S1.

Syndrome/ condition	**Inheritance pattern**	**De novo rates**	**Gene(s)**	**Prevalence per 100,000[a]**	**Skin manifestations**	**Common extracutaneous features[b]**
Hypomelanosis of Ito (MIM: 300337)[1; 2]	Likely Mosaic	Unknown	Multiple	1.2	Hypopigmentation following the lines of Blaschko[c]; alopecia; patchy depigmentation	Variable depending on underlying cytogenomic cause and affected tissues, but can include developmental delay; seizures; scoliosis; chest wall deformity; digit abnormalities; hemihypertrophy; retinal hypopigmentation
Incontinentia Pigmenti (MIM: 308300)[3]	X-linked Dominant, Mosaic	65%	*IKBKG* (MIM: 300248)	1.2 (birth prevalence)	Blisters (Stage I), Wart-like rash (Stage 2) Swirling macular hyperpigmentation (Stage 3)[c]; Linear hypopigmentation (Stage 4)	Seizures; intellectual disability; male embryonic lethality; leukocytosis
McCune-Albright Syndrome (MIM: 174800)[4]	Mosaic	100%	*GNAS* (MIM: 139320)	0.55	Café au lait pigmentation[c] associated with midline of body, classically described as having jagged and irregular boarders	Fibrous dysplasia; scoliosis; hemihypertrophy; precocious puberty; excessive growth hormone; hyperthyroidism
Neurofibromatosis Type 1 (MIM: 162200)[5-7]	Autosomal Dominant	42%[8]	NF1 (MIM: 613113)	33.3 (birth prevalence)	Café au lait macules (CALMs)[c], classically described as	Plexiform neurofibromas; Lisch nodules; choroidal freckling; optic gliomas

					having smooth borders; dermal neurofibromas; axillary and inguinal freckling; xanthogranuloma; nevus anemicus	
Noonan with Multiple Lentigines (MIM: 151100)[8]	Autosomal Dominant	Unknown	*PTPN11* (MIM: 176876), *RAF1* (MIM: 164760), *BRAF* (MIM: 164757), *MAP2K1* (MIM: 176872)	Unknown	Multiple lentigines[c]; CALMs[c]	Hypertrophic cardiomyopathy; pectus deformity; short stature; hypertelorism; dysmorphic facial features; intellectual disability
Tuberous Sclerosis Complex (MIM: 191100, 613254)[9; 10]	Autosomal Dominant	80%[11]	*TSC1* (MIM: 605284), *TSC2* (MIM: 191092)	10.0	Hypomelanotic macules (white ash leaf spots)[c]; confetti skin lesions; angiofibromas; shagreen patches, fibrous cephalic plaques; ungual fibromas	Seizures; intellectual disability; behavioral disturbances; subependymal nodules, cortical dysplasia, subependymal giant cell astrocytomas; renal disease; cardiac rhabdomyomas; lymphangioleimyo-matosis

Description of genetic conditions studied.

[a] Orphanet. Prevalence and incidence of rare diseases: Bibliographic data, January 2019, Number 01. 2019. https://www.orpha.net/orphacom/cahiers/docs/GB/Prevalence_of_rare_diseases_by_diseases.pdf. Accessed 16 March 2021. Prevalence is given for the population unless otherwise stated.

[b] Features can be highly variable, including because some conditions may have different molecular/genomic etiologies.

[c] Skin manifestation used in study.

Table S2 (version supplied in Excel due to length).

URLs for images used for classifier (links are subject to change). Conditions studied: Hypomelanosis of Ito (HMI), Incontinentia Pigmenti (IP), McCune-Albright Syndrome (MA), Neurofibromatosis Type 1 (NF1), Noonan Syndrome with Multiple Lentigines (ML; formally known as LEOPARD syndrome), Tuberous sclerosis Complex (TSC), and other (other skin conditions). For each row, an asterisk (*) indicates that the corresponding image was used in the testing set. URLs without an asterisk correspond to images that were used in the training set. Results of the comparison of human and ML classification of test set images are shown in Figure 2.

Table S3 (version supplied in Excel due to length).

URLs to images used for disease progression in Neurofibromatosis type 1 (NF1) generated via a generative adversarial network (GAN) (links are subject to change). NF1_early, NF_intermediate, and NF1_late refer to the disease stages, which were based on visual review of cases by both a clinical geneticist and a genetic counselor using per described age-related manifestations.

Table S4.

	Medical geneticists (n = 30)	**Pediatricians (n = 30)**	**All clinicians (n = 60)**
Experience in specialty			
< 1 year	6.7% (2)	10% (3)	8.3% (5)
1-5 years	13.3% (4)	13.3% (4)	26.7% (8)
5-10 years	20% (6)	0% (0)	20% (6)
>10 years	60% (18)	76.7% (23)	68.3% (41)
Practice locations			

North America	96.7% (29)	100% (30)	98.3% (59)
Outside North America	3.3% (1)	0% (0)	1.7% (1)

Clinician demographic information.

Survey. Sample of survey sent to clinicians.

Supplemental methods

Generative adversarial network and morphing

Genetic conditions can have multiple manifestations, which can change over time. In NF1, the earliest observable features are typically café-au-lait macules (CALMs). Later, other features, such as cutaneous neurofibromas, emerge.[7; 12] Our classifier focused on the former finding, since we were interested in identifying the condition in an early stage, when the condition is less obvious. However, we wanted to observe and depict how this and other datasets might be used in related ways. To do this, we trained a GAN to generate new images based on the collected dataset.

After classification, we used a subset of our dataset, and collected new images of later-stage disease to generate new images and to show how "morphing" could illustrate disease progression. We identified and used 107 early, 71 intermediate, and 103 late-stage NF1 images (Table S3). These were collected, labeled, and processed in the same way as the images for the classifier. We trained StyleGAN2-ada on our skin images of the NF1 stages.[13] Stages were assigned by our study team (and reviewed by a genetic counselor and medical geneticist) based on age and clinical features according to the natural history of disease.[12] We loaded the model weights pretrained on Flickr-Faces-HQ (FFHQ) dataset, changed the model objective into conditional GAN, where the labels correspond to the three NF1 stages, and then fine-tuned on our NF1 localized images with the same hyperparameters used for FFHQ dataset.[13] During training, we kept the NF1 images in their original forms and did not apply any preprocessing, such as

cropping and centering the images or background blurring, which are often done to FFHQ dataset. We chose not to preprocess in this way, as we wanted to explore a model that could be more readily applied to image sets without this additional step. Moreover, in many medical cases, all parts of an image may be important, and methods must be developed to analyze the skin findings in conditions like HMI or IP, where cropping and centering will not work since the lesions may not be small or discrete.

In this morphing experiment, we considered only focused images. This was because, with our small NF1 dataset, our exploratory work at generating realistic panoramic images did not produce realistic images, since the GAN not only has to generate the skin lesions but also the body parts where the lesions occur. To generate an image, conditional StyleGAN2-ada takes two key inputs: a random vector z and a 1-hot label vector.[13] The random vector z is responsible for creating a random image from the label specified by the 1-hot vector. For our method, the three 1-hot label vectors are $v_1 = [1, 0, 0]$, $v_2 = [0, 1, 0]$ and $v_3 = [0, 0, 1]$ to denote that the NF1 image is of an early, intermediate or late stage. The 1-hot vector is then multiplied with the label embedding $L \in R^{MxD}$, where M is the number of labels and D = 512 is the default setting. In our running example, we have M = 3, and Lv_1 returns the vector representing the label "NF1 early stage." We set the vector representing NF1 intermediate stage to be the average of the vectors representing NF1 early and late stages, that is $Lv_2 = 0.5(Lv_1 + Lv_3)$. L is a model parameter trained using our NF1 images. To generate later stages of an early stage NF1 image, we computed a linear interpolation between v_1 and v_3, and then passed these interpolated vectors with the same random vector z as inputs to StyleGAN2-ada. Our code is available at: github.com/datduong/stylegan2-ada-MorphNF1.

Examples of images of skin lesions generated by our GAN are shown in Figures S2. Through the GAN, we also generated images to depict disease progression, as shown in Figure S3. All newly generated images, and images obtained by morphing and style-mixing were shown to practicing genetics clinicians, who subjectively endorsed realistic output, providing directions for future studies aimed to objectively quantify the results.

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