# Ablative Fractional Laser Treatment for the Clinical Improvement of Hypertrophic Scars and Scleroderma: a prospective cohort study

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## I. Objective

The objective of this study is to evaluate the efficacy of ablative fractional $CO_2$ laser treatment on the clinical improvement of skin conditions including hypertrophic scars and scleroderma.

## II. Background

Skin conditions such as hypertrophic scars and scleroderma (morphea) are all linked to abnormal collagen production and distribution throughout the skin.

Hypertrophic scars are the result of abnormal wound healing and while poorly understood, they are believed to be triggered by the inflammatory cascade through cytokine dysregulation. The resulting phenotype is a haphazard increase in collagen and abnormal vasculature. TGF-B and PDGF-1 have both been implicated in hypertrophic scar pathogenesis. The second condition, scleroderma (also known as morphea), is an autoimmune disease that causes the formation of stiff scar-like skin lesions that can restrict motion across joints in addition to its aesthetic implications. Scleroderma is characterized by excessive collagen deposition leading to the thickening of the dermis, subcutaneous tissues, or both. The disease is progressive and can often worsen, despite treatment. There is currently no cure to the autoimmune disease and little relief for those suffering from lesional contracture.

Ablative fractional carbon dioxide ($CO_2$) lasers are commonly used to improve the appearance of both conditions, either alone or through laser-assisted drug delivery.[9-11] While the mechanism is not completely understood, ablative fractional laser alone may induce MMPs to help remodel and normalize both collagen and elastin.[11]

In this study, we seek to evaluate the effects of ablative fractional $CO_2$ laser treatment on the redistribution/regeneration of collagen on the clinical, microscopic, and molecular profiles hypertrophic scars and scleroderma.

### Study design

A prospective cohort study of 10 subjects with hypertrophic scars and 10 subjects with scleroderma.

### Analysis of Skin Samples

Optional skin samples will be used to test the hypothesis that fractional laser treatment can improve the clinical appearance of scars and scleroderma.

Skin will be sampled using four 3 mm-punch biopsies. Biopsies will be obtained from the treated lesion (1) and perilesional healthy skin (1) during the first and during the post-procedural visit. Skin biopsies will be optional for scleroderma subjects.

Using histopathological analysis, microscopic and immunohistochemical tissue effects between treatment arms will be compared.

The study will take place at MGH's Clinical Unit for Research Trials & Outcomes in Skin (CURTIS) at 50 Staniford Street, Suite 240 Boston, MA 02114 or Translational Clinical Research Center (TCRC) on the 12th floor of the White Building.

## III. Aims

The aims of this study are:

- To determine the efficacy of ablative fractional laser in clinical improvement of hypertrophic scars and scleroderma.

## IV. Subject selection

Subjects will be screened to determine if they meet all the eligibility criteria specified below.

### a. Inclusion Criteria

1. Subject must be able and willing to provide written informed consent and comply with the requirements of the study protocol;
2. In good general health, based on answers provided during the screening visit;
3. Any gender and any Fitzpatrick skin type;
4. Age equal to or greater than 18 years old;
5. Subjects in the hypertrophic scar branch must have at least one extragenital hypertrophic scar (defined as abnormal proliferation of scar tissue that forms at the site of cutaneous injury and does not regress and grows beyond the original margins of the scar) at least 4cm in length for scar treatment;
6. Subjects in the scleroderma branch must have eligible extragenital lesions; large enough to treat;
7. Willing to sun protect treated area for the duration of enrollment in the study and 1 year after treatment.

### b. Exclusion Criteria

1. Participation in another investigational drug or device clinical trial in the past 30 days;
2. Are pregnant or lactating;
3. Use of any prescription or in-clinic medications or treatments, such as intralesional corticosteroids or excision, on the eligible scars/scleroderma in the previous 3 months;
4. History of allergic reaction to topical or local anesthesia;
5. Regular intake of high doses of anti-inflammatory drugs (aspirin >81 mg/day, ibuprofen, corticosteroids, etc.) or high and/or non stabilized doses of immunosuppressive drugs;
6. Clinically significant abnormal findings or conditions which might, in the opinion of the Investigator, interfere with study evaluations or pose a risk to subject safety during the study;
7. Laser treatment in past six months;
8. History of poor wound healing.

### c. Source and Recruitment of Subjects

The study will be posted on the Partner's clinical research web page (Rally), around the hospital, and outpatient clinics (treating scars, scleroderma, or morphea) to reach an economically and socially diverse population.

## V. Subject Enrollment

### a. Method of Enrollment

All subjects who electronically sign an informed consent form (ICF) and are screened will be documented on a screening log. All subjects who qualify at the screening visit and who are enrolled in the study will be documented on the enrollment log. A note will be made in the source documentation verifying that the subject has willingly signed the ICF prior to participation in any study procedures. All randomized subjects will receive a subject number.

### b. Informed Consent Form (ICF)

A licensed physician investigator or sub-investigator will inform the potential study subject of all aspects of the study and answer their questions. If the subject agrees to be a study subject, they will document consent in electronic form by signing an online ICF via Adobe eSign. Subjects who need more time to decide whether they would like to participate will have access to the electronic consent form and will call if they are interested in participating in the study.

The investigator is responsible for using a consent form that has been

approved by the IRB/Partner's HRC and is the most current version. If a new version of the consent form is approved by the IRB/Partner's HRC while a subject is still participating in the study, then the Investigator will inform the subject of the changes and, if the subject agrees to continue study participation, they should sign the updated form.

Electronic informed consent will be obtained prior to performance of any protocol-specific procedures.

c. Subject selection

Ten subjects with one or more hypertrophic scars and ten subjects with scleroderma will be recruited for this study. Each subject will undergo an biopsy of perilesional normal-appearing skin adjacent to lesion to be treated (scar or scleroderma) and an optional biopsy of the treated side at their final visit. Biopsies will only be optional for scleroderma subjects.

## IV. Study Procedures

### a. Study Visits and Procedures

*Baseline Assessment (Phone Call/In-Person Visit)*
The baseline/consent assessment will be done in-person or phone call upon physicians discretion. At the baseline visit, eligibility criteria, including a review of medical history and medications, and detailed information about the study will be reviewed. Informed consent will be obtained, if the subject desires to proceed with the study.

*Trial treatment Visit 1*
Once consented, range of motion assessment (non-facial scleroderma), Mouth Handicap in Systemic Sclerosis scale (facial scleroderma) and Modified Vancouver Scar Scale (hypertrophic scars)(Appendix 2 ) will be used to assess lesions. Medical photography of the lesions and urine pregnancy test (for female subjects of childbearing potential) will be obtained prior to treatment. OCT imaging and three-dimensional imaging (Cherry Imaging) may also be performed on select consented subjects. The subject will be questioned about itch and pain in the area that will be treated.

Two 3 mm-punch biopsies will be obtained, one from perilesional normal-appearing skin adjacent to treated lesion (scar or scleroderma), and one from skin treated with laser. Biopsies will be optional for scleroderma subjects.

The subject will be anesthetized with 23% lidocaine, 7% tetracaine topical numbing for 30 minutes to one hour, which is standard of care in laser clinic.

Once the subject has been anesthetized, they will undergo laser treatment. The entire lesion will be treated with Ultrapulse $CO_2$ laser DeepFX an energy level between 20 mJ-50 mJ and 5%-10% density, 1-2 passes. The area to be treated will not exceed 20cm. Vaseline will be applied evenly with a gloved hand on the entire lesion following the procedure.

*Trial treatment Visit 2 (1 month after treatment visit 1)*
The treated lesion(s) will be evaluated clinically for any potential adverse events and urine pregnancy test (for female subjects of childbearing potential) will be obtained prior to treatment. Each area of scar or scleroderma will be marked with a surgical marker based on photographs from the previous visit to ensure the treatment area is consistent. Medical photography of the lesion and urine pregnancy test (for female subjects of childbearing potential) will be obtained prior to treatment. OCT imaging may also be performed on select consented subjects.

The subject will be anesthetized with 23% lidocaine, 7% tetracaine topical numbing for 30 minutes to one hour, which is standard of care in laser clinic. Once the subject has been anesthetized, they will undergo laser treatment. the lesion will be treated with Ultrapulse $CO_2$ laser DeepFX, an energy level of 20 mJ-50 mJ and 5%-10% density, 1-2 passes. The area to be treated will not exceed 20cm.Vaseline will be applied evenly with a gloved hand on the entire lesion following the procedure.

*Trial treatment Visit 3 (1 month after treatment visit 2)*
The treated lesion(s) will be evaluated clinically for any potential adverse events and urine pregnancy test (for female subjects of childbearing potential) will be obtained prior to treatment. Each area of scar or scleroderma will be marked with a surgical marker based on photographs from the previous visit to ensure the treatment area is consistent. Medical photography of the lesion and urine pregnancy test (for female subjects of childbearing potential) will be obtained prior to treatment. OCT imaging may also be performed on select consented subjects.

The subject will be anesthetized with 23% lidocaine, 7% tetracaine topical numbing for 30 minutes to one hour, which is standard of care in laser clinic. Once the subject has been anesthetized, they will undergo laser treatment. The entire lesion will be treated with Ultrapulse $CO_2$ laser DeepFX, an energy 20 mJ-50 mJ and 5%-10% density, 1-2 passes. The area to be treated will not exceed 20cm. Vaseline will be applied evenly with a gloved hand on the entire lesion following the procedure.

*Post-procedural visit (final visit, 1 month after treatment visit 3)*
One-month after the last treatment The subject will be questioned about itch and pain in the treated area.  Range of motion assessment (non-facial scleroderma),

Mouth Handicap in Systemic Sclerosis scale (facial scleroderma) and Modified Vancouver Scar Scale (hypertrophic scars) (Appendix 2) will be used to assess lesions. Lesion marked with surgical marker. Additional medical photography and two 3 mm-punch biopsies will be obtained, one from perilesional normal-appearing skin adjacent to treated lesion (scar or scleroderma), and one from lesional skin treated with laser. Biopsies are optional for scleroderma subjects only. OCT imaging and three-dimensional imaging (Cherry Imaging) may also be performed on select subjects.

*Clinical assessment*

Clinical photographs taken pre-treatment and post-treatment will be complied and reviewed in blinded fashion by at least one dermatologist using the Physician's Global Assessment, a widely used scale from the existing literature to determine clinical change from baseline. We will use the Mouth Handicap in Systemic Sclerosis[1] scale for assessing facial scleroderma. For non-facial scleroderma, we will evaluate range of motion of the joint by assessing flexion, extension, supination, and pronation using a goniometer[2]. All scars, facial and non-facial, will be assessed using the Modified Vancouver Scar Scale[3].

*Cherry Imaging Photography*

The Cherry Imaging system is a 3-dimensional photographic imaging system designed to accurately measure aesthetic treatments to deliver objective subject data before and after aesthetic treatments. The handheld camera captures thousands of three-dimensional images of the face and/or body from multiple field views and angles that are analyzed to provide 100-micron accuracy level data of the body and/or face for real-time evaluation of treatment results and traceability over time. The Cherry Imaging device will be used to take images of the scars before the laser treatment takes place and during each subsequent study visit. No special lighting is needed for the imaging device, so the images will be taken and processed directly in the room where the laser procedure will take place.

*Lumenis® Ultrapulse® C02 laser with DeepFX™*

The Lumenis Ultrapulse C02 laser is approved by the U.S. Food and Drug Administration (FDA) for several treatments in dermatology & plastic surgery, podiatry, otolaryngology (ENT), gynecology, and surgery. However, the Lumenis Ultrapulse C02 laser is not FDA approved for scleroderma.The subject will be

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[1] Mouthon L, Rannou F, Bérezné A, et al. Development and validation of a scale for mouth handicap in systemic sclerosis: the Mouth Handicap in Systemic Sclerosis scale. *Ann Rheum Dis*. 2007;66(12):1651-1655. doi:10.1136/ard.2007.070532

[2] Micheletti RG, Chansky PB, Haun PL, et al. Ablative fractional laser resurfacing for treatment of sclerosis and contractures in chronic graft-versushost disease: A pilot study. *J Am Acad Dermatol*. 2020;82(4):984-986. doi:10.1016/j.jaad.2019.07.084

[3] Baryza, M. J., & Baryza, G. A. (1995). The Vancouver Scar Scale: an administration tool and its interrater reliability. *The Journal of burn care & rehabilitation*, *16*(5), 535-538.

anesthetized with 23% lidocaine, 7% tetracaine topical numbing for 30 minutes to one hour, which is standard of care in laser clinic. Once the subject has been anesthetized, they will undergo laser treatment. The lesion(s) will be treated with the laser at an energy level of 20 mJ-50 mJ and 5%-10% density, 1-2 passes. Protective eyewear will be worn by subjects and study staff in accordance with standard laser safety procedures. Subjects will then be instructed to perform post-procedural care.

*Optical coherence tomography (OCT) imaging*

This device is not FDA approved. However, it's been safely used in over 1000 research participants so far. OCT imaging is performed spectral-domain OCT scanner TELESTO II (Thorlabs Inc., Newton, New Jersey). It operates at a central wavelength of 1,300 nm with an output power of 2.2 mW with continuous wave exposure of approximately 30 seconds per image, non-pulsed. Using a lens with an optical lateral resolution of 13 μm (LSM03, Thorlabs Inc.), we acquire images with an oversampling factor of 2× leading to voxel sizes of 6.5 × 6.5 × 3.5 μm3 and a field-of-view (FOV) of 6 × 6 × 3.5 mm3 (length × width × depth), acquired at an A-Scan rate of 76 kHz.

The imaging data is further processed and analyzed by custom made software tools implemented in MATLAB 2016b (MathWorks Inc). All OCT image data files will be labeled with the study subject number assigned to each subject upon consent. No identifying information will be used in labeling the image data files and the files will be stored on Partners OneDrive.

The OCT imaging system will be cleansed with 70% isopropyl alcohol wipe in the subject's presence prior to perform any imaging procedure. The subject's lesion at the intended OCT imaging sites will be cleansed with 70% isopropyl alcohol prep and allowed air dry thoroughly. A z-spacer (OCT-Imm03, ThorLabs, Inc., Newton, NJ) will be attached to the OCT probe and glycerol will be utilized for optical coupling (immersion) between the OCT spacer and the skin. The acquisition and saving time per image will be less than 1 minute. If study staff operating the OCT imaging device decide the images are of too low quality or contain artifacts that would affect analysis, this procedure may be repeated on an area of the skin within close proximity to the original imaging location but at least 2-3 cm away from the original location. After finishing the OCT imaging procedures, the z-spacer will be detached and cleansed with 70% isopropyl alcohol wipe then allowed to air dry thoroughly prior to next use.

*Skin biopsies*

Two skin biopsies will be obtained at visit 1 and at the post-procedural visit of perilesional normal-appearing skin adjacent to treated lesion (scar or scleroderma) and laser treated lesional skin. This will result in up to four biopsies per subject over the course of this study. Biopsies are optional for scleroderma patients only.

The areas to be biopsied will be cleansed with a 70% isopropyl alcohol prep. The area will then be anesthetized with lidocaine HCl 1% and Epinephrine 1:100,000 (approximately 1 cc to each site). 3 mm punch biopsies will be performed similar to that performed in the dermatology clinic. Biopsy sites will be closed with two absorbable sutures (5.0 or 6.0 fast absorbing gut) or with gel foam. Vaseline and band-aid will be applied.

*Tissue handling*

All specimens will be manually bisected with a 15-blade. One-half of each specimen will be placed in formalin and sent for pathological analysis for H/E and immunohistochemical staining. The other half of the specimen will be evaluated using electron microscopy.

*Histopathological analysis*

Specimens be will be fixed in zamboni and sectioned. Immunohistochemical staining to using Masson's trichrome stain, elastin and CD31 will be used to evaluate collagen, elastic fibers and vasculature in each specimen. Immunohistochemical staining for nerve fiber density will be done as well.

**b. Remuneration**

Subjects will be reimbursed up to $ 500 dollars for participation and completion of this study. They will receive, $50 for each second and third treatment visit (visit 2-3) and $200 for completing the first and the final visit if biopsies are taken(visit 1 and 4) .If biopsies are not taken, subjects will be paid $50 for completing the first and the final visit each. If the subject does not complete the study, they will be paid in accordance to the number of visits ($50 per treatment visit, $50 per biopsy). We will also provide a parking voucher at MGH main campus for each visit upon request.

We may use subject samples and information to develop a new product or medical test to be sold. The Sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay subjects if samples or information are used for this purpose.

We will be using an approved, outside vendor (Forte Research) to make these payments via a reloadable credit card-based system, called Forte Payments. This secure system is similar to a gift card or credit card. If subjects are paid by this system, they will be given a Forte Payments Via card (which is just like a debit card) when subjects enroll in the study. Once the card is activated, the study team will add a payment after each paid visit completed by the subjects. The payment should be available within one (1) business day. Research staff will not know where subjects spend the money. Subjects may use the card anywhere Visa cards are accepted, such as at a grocery store.

We will need to collects subjects' Social Security number in order to make these payments, and it will be shared securely with the company that runs the card-based system. Payments like this are considered taxable income. If subjects receive more than $600, the payment will be reported to the IRS as income by the hospital.

## VII. Biostatistical Analysis

In order to detect a difference of one point assuming a standard deviation of one point on the primary clinical outcome measure, Physician's Global Assessment of Clinical Condition (PGA) scale (a numerical scale from 0-6), a sample size of 10 subjects per condition (10 for scars, 10 for scleroderma, 20 total) is required to achieve a power of 0.8. A student's t test, one sample, two-sided, will be used to determine if any significant statistical difference is present between the clinical response of each treatment arm using the absolute difference between the pre- and post-treatment PGA. A p-value of less than 0.05 is considered statistically significant.

## VIII. Risks and Discomforts

There is a potential risk of loss of privacy. We will protect privacy by labeling samples and information only with a code, and keeping the key to the code in a password protected database.

Potential risks of the skin punch biopsy include allergic reaction to the anesthetic, bleeding, infection, poor wound healing, pain, hyper or hypopigmentation and scarring.

Possible risks of fractional laser surgery include pain, scarring, infection, abnormal wound healing, hyper or hypopigmentation.

Possible side effects of topical 23% lidocaine, 7% tetracaine include redness, mild burning sensation, tingling, itching or swelling. Rare side effects include an allergic reaction, which may manifest as dizziness or drowsiness.

## IX. Potential Benefits

### a. Potential Benefits to subjects

Subjects who participate in this study may benefit by having improvement in the appearance of their skin lesions.

### b. Potential Benefits to Society

Information gathered from this study may improve the understanding of disorders of collagen metabolism.

## X. Monitoring and Quality Assurance

### a. Independent monitoring of source data

Experienced study personnel (study monitor) who are not assigned to complete procedures of this study will conduct monitoring after the first subject is enrolled and periodically thereafter. The monitor will be responsible for confirming the completion and correctness of the study procedures as well as record collection and keeping.

### b. Safety monitoring

Prior to enrollment, subjects will be screened for eligibility; at which time a complete medical history, including a baseline assessment of the subject's skin in the area of interest will be done. Evaluations will be ongoing throughout the study to detect adverse events and changes in existing medical conditions.

At any time after enrollment, a subject may be discontinued. Reasons for discontinuation of a subject from the study will include, but may not be limited to, the following:

1. Subject is found to be intolerant to a required study procedure at any time point.
2. Subject is noncompliant with protocol restrictions and requirements.
3. Subject develops an intercurrent illness that would, in the judgment of the investigator, affect assessments of clinical status to a significant degree.
4. Subject becomes pregnant while participating in the study.
5. Subject enrolls in another investigational study.
6. Subject requests to withdraw from the study.
7. The study Sponsor decides to suspend or terminate the study.

If possible, a final set of assessments will be performed on all subjects who end their participation prior to study completion.

### d. Outcome monitoring

The study will be conducted in accordance with applicable regulations and Good Clinical Practice Guidelines. Keeping files locked with access limited to study staff will ensure confidentiality and data integrity.

### e. Adverse Event Reporting

*Definition*

Adverse Event (AE) is any untoward medical occurrence in a subject that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Serious Adverse Event (SAE) is any untoward medical occurrence that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is another medically important condition

*Reporting and Documenting Adverse Events*

All untoward medical occurrences that occur after the subject signs a consent form will be documented as an AE. The Investigator will ensure that all events that occur during the study period are recorded on an Adverse Events Tracking Log. We will report any adverse events that are experienced by subjects during their participation, even those determined to be unrelated to the study. All AEs will be followed until resolution or until, in the Investigator's judgment, they are chronic and stable. If an emergency situation should occur, appropriate medical measures should be taken to stabilize the subject.

Documentation of AEs includes: date and time of onset and resolution of AE, intensity, frequency, seriousness, related interventions and outcome. The Investigator will also evaluate the probability of a causal relationship of the AE to the study treatment as being: "definite, probable, possible, unlikely, or unrelated." Intensity of adverse events will be graded as mild, moderate, or severe according to the following criteria:

- Mild: symptoms that are easily tolerated and transient in nature with minimal or no impairment of normal activity
- Moderate: symptoms that are poorly tolerated, are sustained, and interfere with normal activity
- Severe: symptoms that are incapacitating and render the subject unable to work or participate in many or all usual activities

All SAEs will be reported to the IRB according to the IRB's requirements. They will also be reported to the study Sponsor.

Adverse events will be reported to the PHRC as described in the PHRC policy on Unanticipated Problems Involving Risks to Subjects or Others Including Adverse Events, which can be found on the Research Navigator website.

## XII. Data Management

### a. Data collection

Study data will be collected during all visits. Study data to be collected includes clinical photography, OCT imaging, biological analysis of skin biopsies, cherry imaging, PGA, range of motion assessment, Mouth Handicap in Systemic Sclerosis scale and Modified Vancouver Scar Scale (Appendix 2) assessments, and qualitative subject responses to treatment. All physical documentation and IRB correspondence will be stored in study binders maintained in restricted lab space only accessible by study staff and members of the Manstein Lab. Digital data including photographs will deidentified and stored on Partners computers and EPIC. All study documents containing PHI will be password encrypted, including the enrollment log and identification key. An encrypted external hard drive will be used to store the data as a backup.

### c. Record retention

The Investigator or designees will retain all study records in accordance with MGB Human Subject Research Recordkeeping and Record Retention Requirements Policy and clinical trials regulations.

## XIII. IRB Review and Approval

The study will not begin prior to the receipt of written confirmation of approval by the IRB and any relevant regulatory authority. It is the responsibility of the Investigator to obtain the IRB approval (per the U.S. Code of Federal Regulations, Title 21, Part 56 and applicable ICH guidelines) for the protocol, amendments, informed consent, subject information sheet, questionnaires, and advertising materials used to recruit study subjects, if appropriate.

## XIV. References


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| Score | | Description |
|---|---|---|
| 0 | Completely Clear | No evidence of disease, 100% improvement |
| 1 | Almost Clear | Very significant clearance (≥90% to 100%); only traces of disease remain |
| 2 | Marked Improvement | Significant improvement(≥75% to < 90%); some evidence of disease remains |
| 3 | Moderate Improvement | Intermediate between slight and marked improvement (≥50% to <75%) |
| 4 | Slight Improvement | Some improvement (≥25% to <50%); significant evidence of disease remains |
| 5 | No Change | Disease has not changed from baseline (+ or - <25%) |
| 6 | Worse | Disease is worse than at baseline by ≥25% or more |

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**Appendix 1: Physician's Global Assessment (PGA) of Clinical Condition**

**Appendix 2 : Vancouver Scar Scale**

| Skin characteristics | Parameters |
|---|---|
| Pliability | |
| 0 | Normal |
| 1 | Supple |
| 2 | Yielding |
| 3 | Firm |
| 4 | Ropes |
| 5 | Contracture |
| Height | |
| 0 | Flat |
| 1 | <2 mm |
| 2 | 2–5 mm |
| 3 | >5 mm |
| Vascularity/erythema | |
| 0 | Normal |
| 1 | Pink |
| 2 | Red |
| 3 | Purple |
| Pigmentation | |
| 0 | Normal |
| 1 | Hypo-pigmented |
| 2 | Mixed |
| 3 | Hyper-pigmented |