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New Advancements in Refractive Surgery:

Supplement to EyeWorld Asia-Pacific March 2021

The ZEISS Live Webinar on June 15, 2020 was a continuation from the June 9, 2020 webinar on Small Incision Lenticule Extraction (SMILE). Experts came together to provide new clinical perspectives on diagnostic technologies, molecular markers, and biomechanics as well as management and prophylaxis during refractive surgery in the COVID-19 environment.

SMILE Lenticules and Stem Cells as a Treatment for Corneal Blindness

Dr. John Males first presented the use of stem cells as a treatment for corneal blindness. Dr. Males began by discussing human tissue as a precious resource and that the WHO estimates 10 million people worldwide would benefit from corneal transplantation for issues such as corneal blindness or reduced vision from corneal disease. Availability of corneal tissue is relatively poor in many parts of the world. Dr. Males eventually wondered what SMILE lenticules could offer to patients with corneal pathology. When SMILE procedures are performed, what happens to the corneal tissues and what proportion of lenticules are discarded after surgery? In corneal blindness, a significant proportion of these cases are due to limbal stem cell failure, which can be caused by chemical injuries, burns, ocular surface neoplasia, or surgery.

In Dr. Males' work, he investigated the use of SMILE lenticules as a scaffold to grow and proliferate limbal stem cells. With this project, patients undergoing ReLEx SMILE procedures were offered to participate in the study and there was a 70% acceptance rate in this entirely voluntary study. From the initial results, epithelial cell proliferation could be seen on the surface of the lenticules 8 days after removal. Another method that was utilized to image the stem cell growth was through embedding confetti corneal cells into the surface of the lenticules and Dr. Males saw that the cells would migrate across the surface. This study offered potential applications of treating ocular surface disorders and limbal stem cell failure. Additionally, if lenticules can be preserved, perhaps this method can be a gift to other patients in need of corneal tissue.

Managing Astigmatism Correction in SMILE

In the next presentation, Dr. Shreyas Ramamurthy discussed astigmatism correction in SMILE procedures. Starting with a background on astigmatism in refractive surgery, Dr. Ramamurthy explained that cyclotorsion, if not corrected, can induce under correction and aberrations especially in patients with high astigmatism. Average cyclotorsion is about 3 degrees, and a 7 degree rotation could reduce efficacy by about 25%. Currently, cyclotorsion compensation in SMILE procedures is perfrormed by manual marking and rotation. There is no automated tracking or registration feature available yet.

In one study, Dr. Ramamurthy conducted a prospective interventional case series to compare visual outcomes following cyclotorsion compensation versus no compensation in SMILE for high astigmatism. Patients had manifest cylindrical refraction of 1.5 D or more and bilateral high myopic astigmatism in addition to cyclorotation of > 5 degrees. Patients underwent SMILE and a slit lamp marking was made at 7mm of the central cornea and intraoperative cyclotorsion was measured. The results showed that intraoperative cyclotorsion was lower in the compensation group compared to the no compensation group, though the difference was not significant. Alpins criteria were also determined with no differences in either group.

COVID Times: Do We Have Any Reason to Smile?

Dr. Gaurav Luthra presented next on SMILE procedures during the COVID-19 pandemic. In late March, refractive surgery procedures suddenly came to a standstill due to the lockdown. At this point in time, the demand for refractive surgery began to lean towards the younger population due to their lower health risks. In addition, patients who are working from home have more time to recuperate if they choose to undergo surgery, and colleges have closed, meaning more time for students to recover. Thus, LASIK procedures have increased in May. So, which procedures are safe to perform during this time? One has to consider a variety of factors: ocular virus load and infectivity, COVID-19 status of the patient and surgeon, the operating environment, aerosol generation, and tissue fluid exposure.

Dr. Luthra presented results from an aerosol generation benchmark study performed at Narayana Nethralya showing droplets spreading up to 11 inches during microkeratome incision. Therefore, microkeratome may not be the best procedure moving forward. In Trans PRK, however, the procedure is completed in a single step with no tissue waste and minimal movement. Manual PRK, on the other hand, produces potential aerosols with Amoil's brush. For both Trans and Manual PRK, contact lens wear is not the best option during the COVID-19 pandemic due to the contact lens coming in contact with the ocular tissue. Intent care must also be taken for postoperative care and multiple office visits after surgery.

Dr. Luthra explained that the best way forward is the SMILE procedure due to its single step procedure with no aerosol generation, no plume, and no tissue waste. The patient is also facing away from the surgeon during the procedure and most of the procedure can be done watching a screen. From the patient's perspective, there is minimum time in the operating room, faster recuperation, fewer precautions, and fewer hospital visits.

In Dr. Luthra's own experience in the operating room, he performed COVID-19 testing in patients during the month of May. Surgeons, staff, and patients wear an N95 mask. Surgeons additionally wear protective glasses and knee length shoe covers. At the end of the procedure, all disposables are discarded as safely as possible. Another precautionary technique is to perform a betadine gargle and nasal spray before procedures as it kills all the germs in the mucosa, even in COVID-19 positive patients.

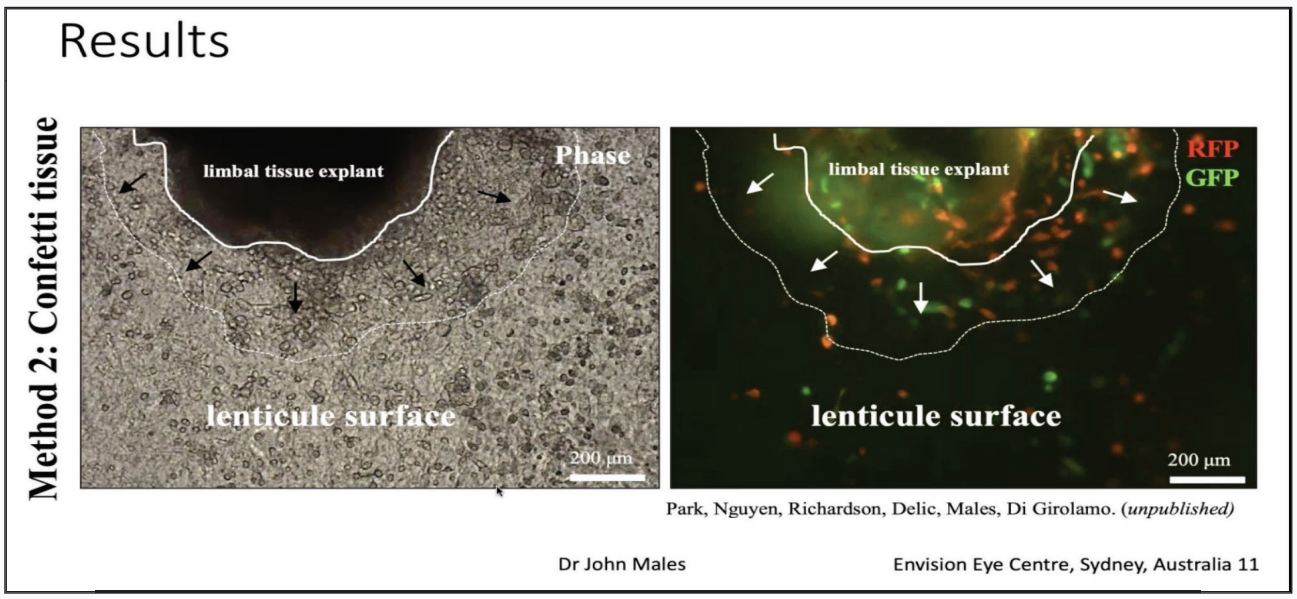

Figure 1. Embedding confetti corneal cells into the surface of the lenticules allows for visualizing the cells proliferating and migrating across the surface. Source: Park, Nguyen, Richardson, et al. Unpublished.

A Fresh Perspective on SMILE in the time of COVID-19

"Another precautionary technique is to perform a betadine gargle and nasal spray before procedures as it kills all the germs in the mucosa, even in COVID-19 positive patients."

Dr. Gaurav Luthra

Optical Quality and Intraocular Scattering after Femtosecond Laser SMILE

Dr. Xingtao Zhou presented next on optical quality and intraocular scattering after SMILE procedures. In his study, Dr. Zhou assessed the development of the continuous curvilinear lenticulerrhexis (CCL) technique for SMILE. Out of 31 eyes (20 patients), the CCL technique was utilized in 16 eyes while the traditional technique was used in 15 eyes. CCL depends on laser scanning quality and is performed by using forceps to separate both the anterior surface and posterior surface of the lenticule from the cap. Then, the forceps are used to extract the lenticule without irrigation. Follow-up was performed at one day and one month following surgery. The results showed that CCL technique exhibited excellent safety and efficacy for myopia correction compared with the traditional technique.

In a different study, Dr. Zhou studied 66 eyes with stable refraction for 2 years undergoing SMILE. Dr. Zhou utilized the optical quality analysis system (OQAS) to obtain retinal image quality and intraocular scattering parameters. At 3-month follow-up, the results showed that the objective scattering index (OSI) initially increased, but decreased significantly over time. Modulation transfer function (MTF) cutoff also improved at 3 months.

From Dr. Zhou's research, he discussed that since the high order aberrations (HOAs) and the scatterings are two independent factors affecting retinal image quality, an assessment of optical quality after refractive surgery needs to take into consideration the influence of intraocular scattering. Additionally, patients with lower intraocular scattering tend to get higher MTF cutoff scores and a lower OSI value after SMILE. OSI actually is a reliable parameter in predicting MTF cutoff scores, and thus a similar result was also reported in LASIK.

Mathematical and Predictive Modeling in SMILE Surgery

The next presentation was given by Dr. Abhijit Sinha Roy, who discussed predictions of the biomechanical status of the cornea after surgery. The OCULUS Corvis® ST combines an air pulse tonometer with an ultra-high-speed Scheimpflug camera allowing clinicians to visualize in-vivo corneal biomechanical index (CBI) and the stress strain index (SSI). However, it is currently still not possible to predict post-operative biomechanics using these parameters.

Dr. Roy's research has been focusing on predicting post refractive surgery biomechanics in the last few years. If one builds a mathematical model using OCULUS Corvis® and OCULUS Pentacam® using both of the data sets, one can derive the corneal biomechanical properties. Additionally, Dr. Roy can use the preoperative biomechanical status of the cornea to perform virtual SMILE on patients and in turn predict the postoperative deformation curve.

Although SMILE and LASIK are structurally two different surgeries, acute biomechanical effects of flap and cap cuts did not influence 1-week and 1-month measurements in both surgeries. However, visualizing the biomechanical response of the cornea using OCULUS Corvis® intraoperatively, the LASIK-flap caused more weakening than the SMILE-cap.

In an ongoing study conducted by Dr. Roy, predicted postoperative corneal stiffness was compared to in-vivo measurements and showed an intra-class correlation coefficient of 0.91 with LASIK, SMILE, and PRK. Including artificial intelligence adjusted predicted corneal stiffness resulted in an even higher intra-class correlation coefficient of 0.95. In application, if postoperative outcome does not match the parameters that the computational model provides, there may be an indication of ectasia or other abnormality.

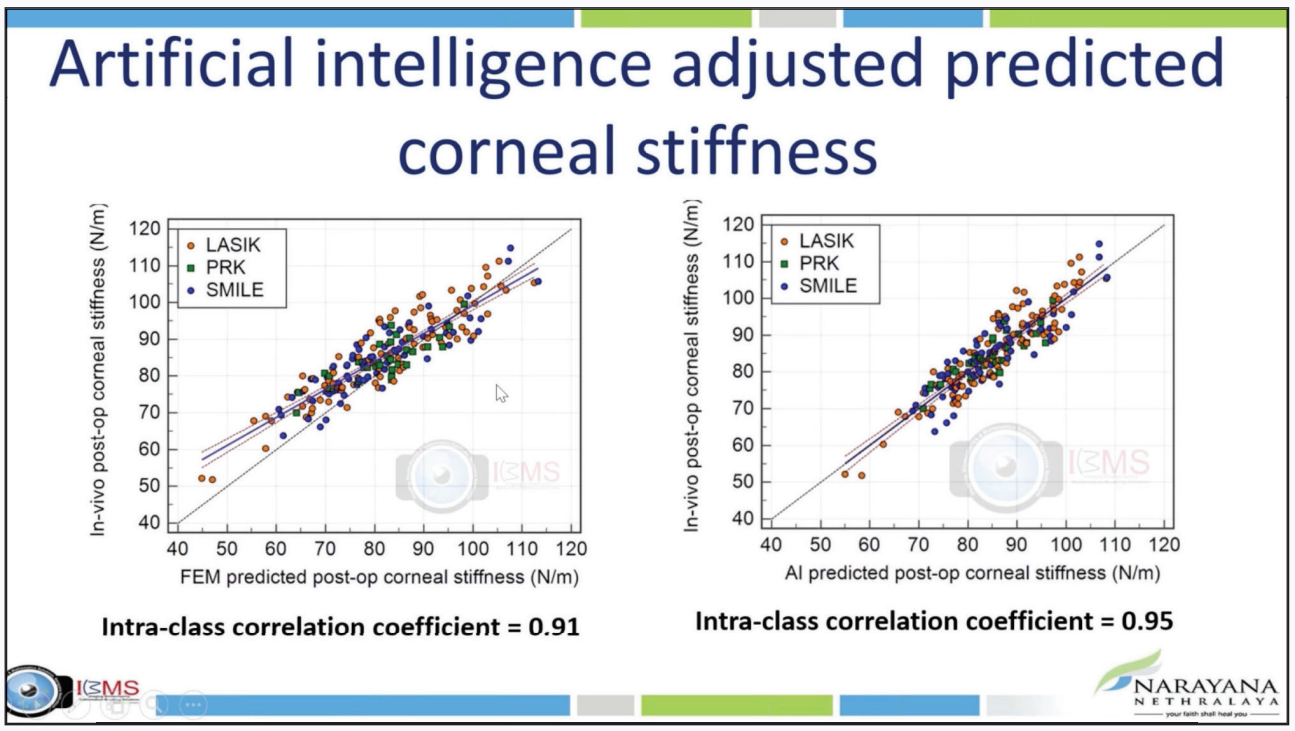

Figure 2. Intra-class correlation efficient of predicted postoperative corneal stiffness compared to artificial intelligence (AI) predicted corneal stiffness shows higher correlation with AI.

Source: Francis M et al. Invest Ophthalmol Vis Sci 2018.

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New Advancements in Refractive Surgery:
A Fresh Perspective on SMILE in the time of COVID-19

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"We are already scratching the epigenetic role in modulating post refractive outcome. This is a new field which is going to have a very useful impact."

Dr. Swaminathan Sethu, India

Story of the Epithelium

Dr. Naren Shetty discussed the need for studying the healing pattern of epithelium. Just like how bone has its own mechanism for healing, epithelium has its own way of healing after refractive surgery. In Dr. Shetty's research, he studied whether artificial intelligence can be used to improve surgery outcomes as well as determining differences in epithelial remodeling between flap and flapless procedures.

In order to build an AI model, Dr. Shetty took the epithelial thickness difference pre- and post-operatively, converted these values to Zernike Indices, and incorporated the values into the AI program. With the help of AI, one can see a significant difference between corneal epithelial thickness among SMILE, LASIK, manual PRK, and trans PRK procedures. Thus, using AI and machine learning, we can predict and choose the most appropriate refractive surgery procedure for specific types of eyes (i.e. early ectasia or epithelial regression). In early ectasia, AI can help with early detection of post-LASIK ectasia much earlier than without the help of AI. In refractive regression, AI can help predict how the epithelium changes during SMILE procedures.

Wound Healing Model in Post SMILE and its Relation to Dry Eyes

Dr. Pooja Khamar next discussed how wound healing differs between SMILE and LASIK. Specifically, Dr. Khamar's research looked at the immediate modulations occurring in the corneal tissue in eyes undergoing either SMILE or LASIK compared to eyes that did not undergo any type of surgery. In this study, the corneal stroma was extracted 14 hours after surgery, and protein from the stroma was extracted. With quantitative proteomic analysis using mass spectrometry, Dr. Khamar found that the lysozyme C enzyme showed less inflammation in SMILE procedures compared to LASIK. There was also better intracellular calcium signaling and homeostasis as well as less extracellular matrix remodeling in post SMILE procedures. Additionally, there was enhanced cell differentiation and quick restoration of corneal epithelium post SMILE surgery compared to LASIK.

Dr. Khamar was also interested in whether these results would hold up in patient eyes, since the previous study was performed on donor eyes. What Dr. Khamar found was that different markers including galectin-3-binding protein and interleukin-1 receptor antagonist protein regulated inflammation while lactoperoxidase and peroxiredoxin-5 proteins aided in wound healing. With this data, Dr. Khamar concluded that lysozyme C and the other protein markers found in the corneal stroma has inflammatory functions and a role in dry eye after refractive surgery.

Epigenetics of Healing in SMILE & LASIK & Implications on Post-LASIK Ectasia

In the next presentation, Dr. Swaminathan Sethu began by describing that a surgeon's precision along with technology and tissue response is necessary for successful refractive surgery. Tissue response, particularly, has been the most researched,

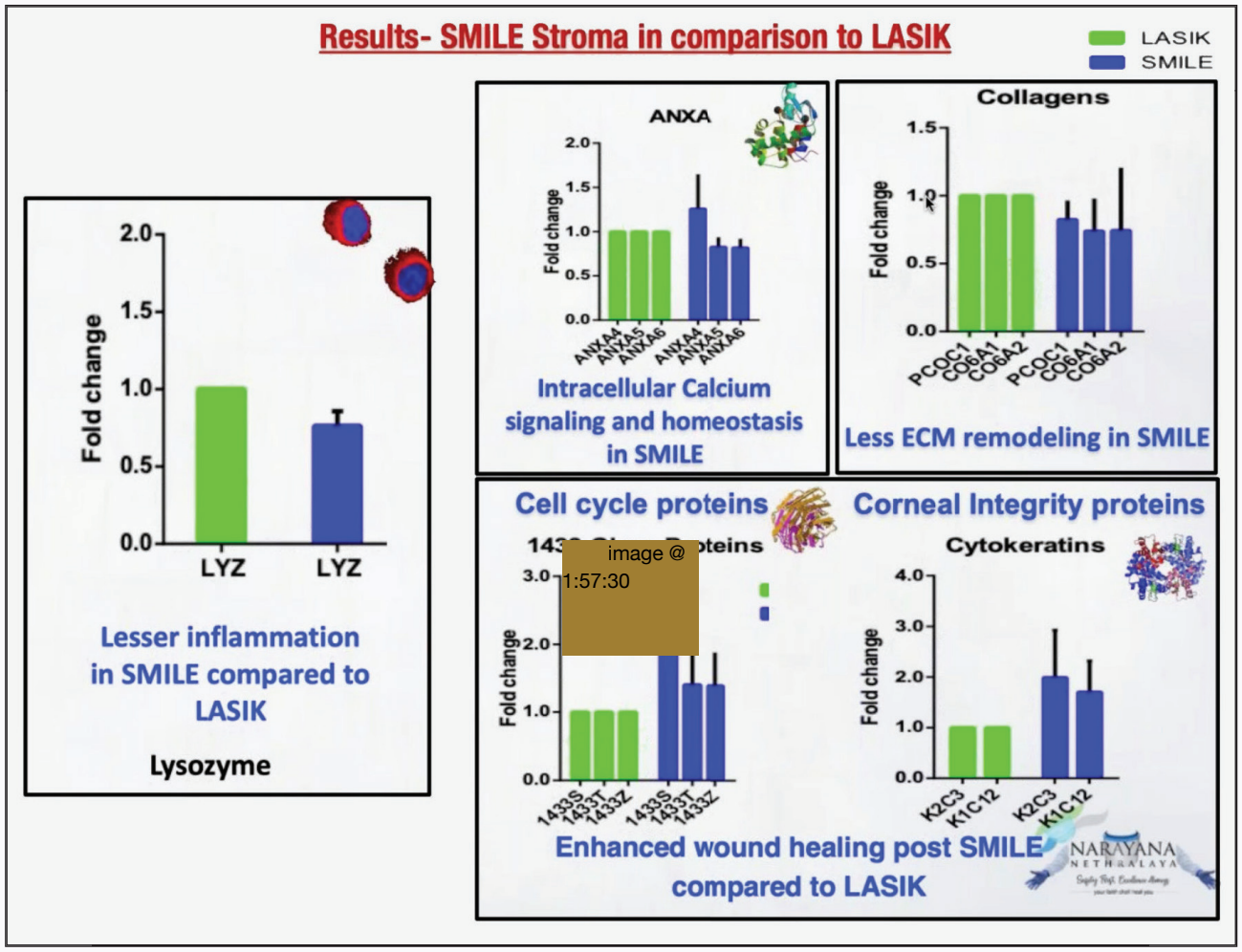

Figure 3. SMILE procedures showed less inflammation, better intracellular calcium signaling and homeostasis, less extracellular matrix remodeling, and enhanced wound healing compared to LASIK.

Source: Khamar P et al. Exp Eye Res 2020.

and if the risk factors associated with tissue response, ultrastructural changes, cellular functions, and gene expression are understood well, then clinicians may be able to modulate wound healing and provide favorable clinical outcomes.

The foundational question to ask first when researching tissue response is: how are these proteins regulated? It begins with messenger RNA (mRNA) taking information from the DNA to produce these proteins. However, there is also some sort of orchestration occurring with the switching on and off of these genes. During refractive surgery, what is the importance of a switch on or switch off of a certain gene? This is where epigenetics comes in. Epigenetics refers to a variety of processes which regulates gene expression programs without changes in DNA sequence.

Dr. Sethu provided a nice analogy of epigenetics to an airplane on a runway. If the runway represents the DNA, the aeroplane represents chromatin or co-factors, the passenger represents gene-specific transcription factors, and the runway lights represents the epigenetic modifications, then the landing decision, either "go" or "no go," guides whether epigenetic modifications are made, allowing the gene to switch on or off. Many factors can cause genes to switch on or off including development and aging, environmental toxins, diet, stress, pathogens, and even surgery.

In terms of wound healing after refractive surgery, epigenetics plays a very critical factor. As Dr. Sethu explained, "Methylation is one of the critical chemical modifications of the DNA which happens and that is what we saw in the research."

From the research, after 3 days of surgery, either SMILE or LASIK, one can see a difference in site level methylation. At 14 days, however, much more is going on. There are more genes that are switched on after 14 days post-SMILE or post-LASIK with functions of immunomodulating, ECM regulating, and cellular signaling. The biggest question that comes from this epigenetic work is whether

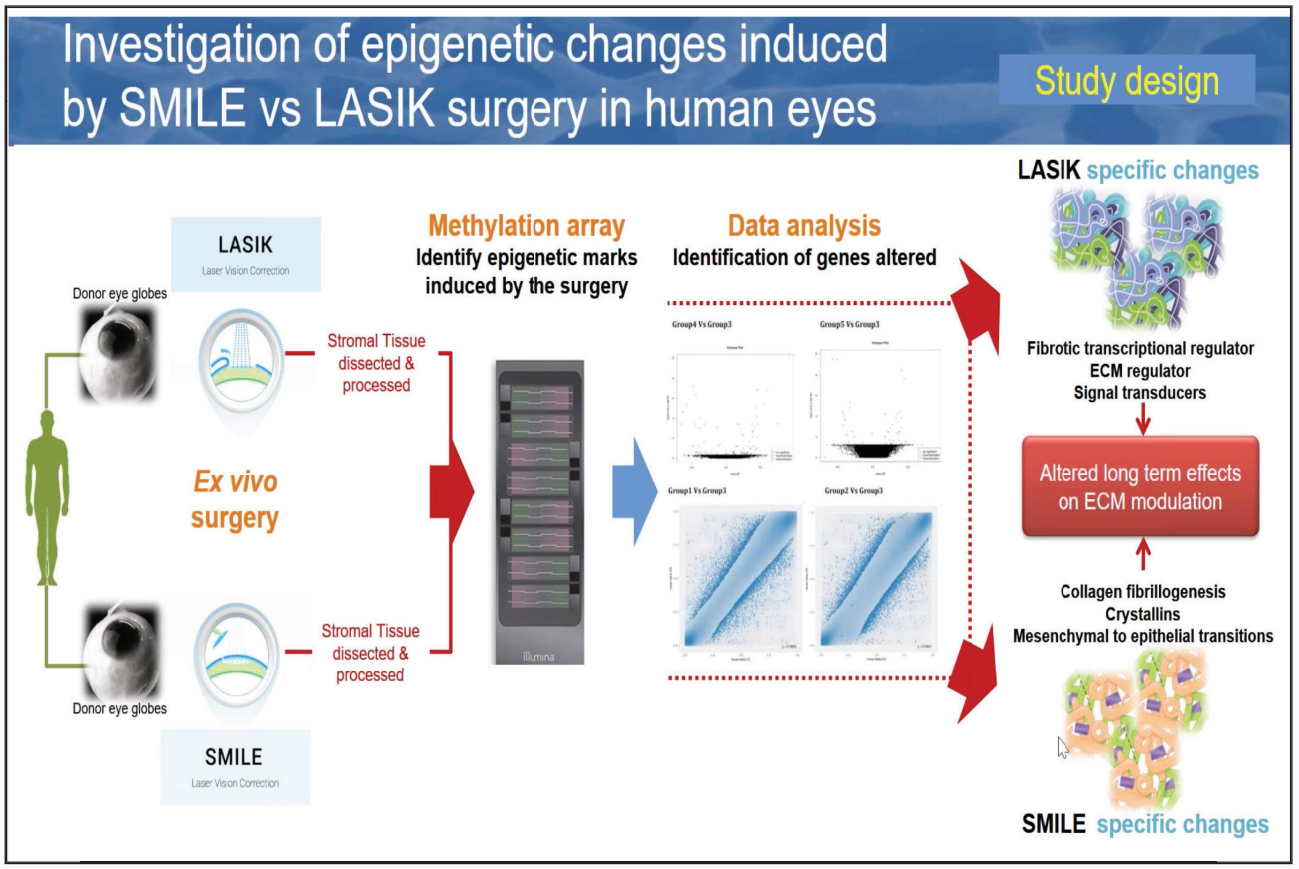

Figure 4. Epigenetic markers can be identified through methylation after both SMILE and LASIK procedures, resulting in altered genes.

Source: Sethu, Swaminathan

any of the clinical risk factors such as corneal thickness or topography will alter methylation. Currently, this question is being researched. Dr. Sethu finally emphasized that "epigenetic biomarkers have a future because different people will have different epigenetic profiles and may respond differently. This is the future."

Tear Optics in SMILE Surgery

Dr. Sheetal Mahuvakar began her presentation on tear optics by discussing the importance of a proper initial work-up of dry eye in any of her patients due to the fact that dry eye status impacts the quality and outcome of refractive surgery. In understanding tear optics, two machines are important in Dr. Mahuvakar's practice: LipiView and OQAS HD Analyzer. The LipiView provides reliable lipid layer thickness measurements in both normal eyes and dry eyes. The OQAS HD Analyzer provides an objective view of vision quality by measuring the scattering of light in the optical pathway. The clinician is able to view what the patient is able to perceive in terms of a clear image compared to a blurry image. Additionally, the OQAS HD Analyzer provides a modular transfer function, indicating whether the tear film is affecting vision.

As for the impact of refractive surgery on tear optics, Dr. Mahuvakar precluded her surgery experience by stating that SMILE procedures result in a higher preservation of corneal nerves whereas LASIK damages more corneal nerves. In her experience, she saw, with LipiView, slightly better lipid layer thickness in an eye that had undergone SMILE at 3 months compared to a LASIK eye. Ocular surface index (OSI) and visual break-up time was also better in the SMILE eye than the LASIK eye. Better outcomes in SMILE compared to LASIK were also seen with ocular surface inflammation, Meibomian gland drop-out, corneal nerve regeneration, and normal epithelial healing.

Dr. Mahuvakar emphasized in her take home points that patients should be evaluated preoperatively using any evaluative machines that are available for use in the clinic. Second, it is important to customize the surgery to the patient's specific conditions and symptoms in order to improve dry eye outcomes. Postoperatively, patients should again be evaluated using the same available machines and treated for dry eye if necessary.

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